National Institute on Drug Abuse

RESEARCH

MONOGRAPH SERIES

Problems of Drug Dependence 1998: Proceedings of the 60th Annual Scientific Meeting

The College on Problems of Drug Dependence, Inc.

179

U.S. Department of Health and Human Services • National Institutes of Health

Problems of Drug Dependence, 1998:

Proceedings of the 66th Annual Scientific Meeting, The College on Problems of Drug Dependence, Inc.

Editor:

Louis S. Harris, Ph.D.
Virginia Commonwealth University

NIDA Research Monograph 179
1998

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

National Institute on Drug Abuse
6001 Executive Boulevard
Bethesda, MD 20892

ACKNOWLEDGEMENT

The College on Problems of Drug Dependence, Inc., an independent, non-profit organization conducts drug testing and evaluations for academic institutions, government, and industry. This monograph is based on papers or presentations from the 60th Annual Scientific Meeting of the CPDD, held in Scottsdale, Arizona, June 12-17, 1998. In the interest of rapid dissemination, it is published by the National Institute on Drug Abuse in its Research Monograph series as reviewed and submitted by the CPDD.
Dr. Louis S. Harris, Department of Pharmacology and Toxicology, Virginia Commonwealth University was the editor of this monograph.

NIH Publication No. 99-4395
Printed March 1999

NIDA Research Monographs are indexed in the Index Medicus. They are selectively included in the coverage of *American Statistics Index, BioSciences Information Service, Chemical Abstracts, Current Contents, Psychological Abstracts, and Psychopharmacology Abstracts.*

BOARD OF DIRECTORS

Linda A. Dykstra, Ph.D., President
Billy R. Martin, Ph.D., President-elect
Stephen G. Holtzman, Ph.D., Past-president
George E. Bigelow, Ph.D., Treasurer
Warren K. Bickel, Ph.D.
Richard Bonnie, L.L.B.
Kathleen T. Brady, M.D., Ph.D.
Linda B. Cottler, Ph.D., M.P.H.
Harriet de Wit, Ph.D.
Avram Goldstein, M.D.
Dorothy Hatsukami, Ph.D.
John Hughes, M.D.
M. Ross Johnson, Ph.D.
Michael J. Kuhar, Ph.D.
Edythe D. London, Ph.D.
Scott E. Lukas, Ph.D.
Frank Porreca, Ph.D.
Beny J. Primm, M.D.
Peter Reuter, Ph.D.
Sidney H. Schnoll, M.D., Ph.D.
Charles R. Schuster, Ph.D.
William L. Woolverton, Ph.D.
Alice M. Young, Ph.D.

EXECUTIVE OFFICER

Martin W. Adler, Ph.D.

SCIENTIFIC PROGRAM COMMITTEE

Thomas R. Kosten, Ph.D., Chair
Scott Lukas, Ph.D., Co-Chair
Martin W. Adler, Ph.D.
Linda Cottler, Ph.D., M.P.H.
Howard Deutsch, Ph.D.
Toby Eisenstein, Ph.D.
Ellen B. Geller, M.A.
Kathryn Gill, Ph.D.
Chris-Ellyn Johanson, Ph.D.
Mary J. Kreek, M.D.
Horace Loh, Ph.D.
S. Steven Negus, Ph.D.
James Zacny, Ph.D.

The following organizations have generously supported the work of the College on Problems of Drug Dependence during the past year:

Astra

Bristol-Myers Squibb

Cephalon

Eli Lilly

Hoffman-La Roche

Immunologic Pharmaceutical Corporation

Institut de Recherche Pierre Fabre

Interneuron Pharmaceuticals

Merck & Co., Inc.

Pfizer

Pharmacia & Upjohn

The Purdue Frederick Company/Purder Pharma

Reckitt Colman

Schering Plough

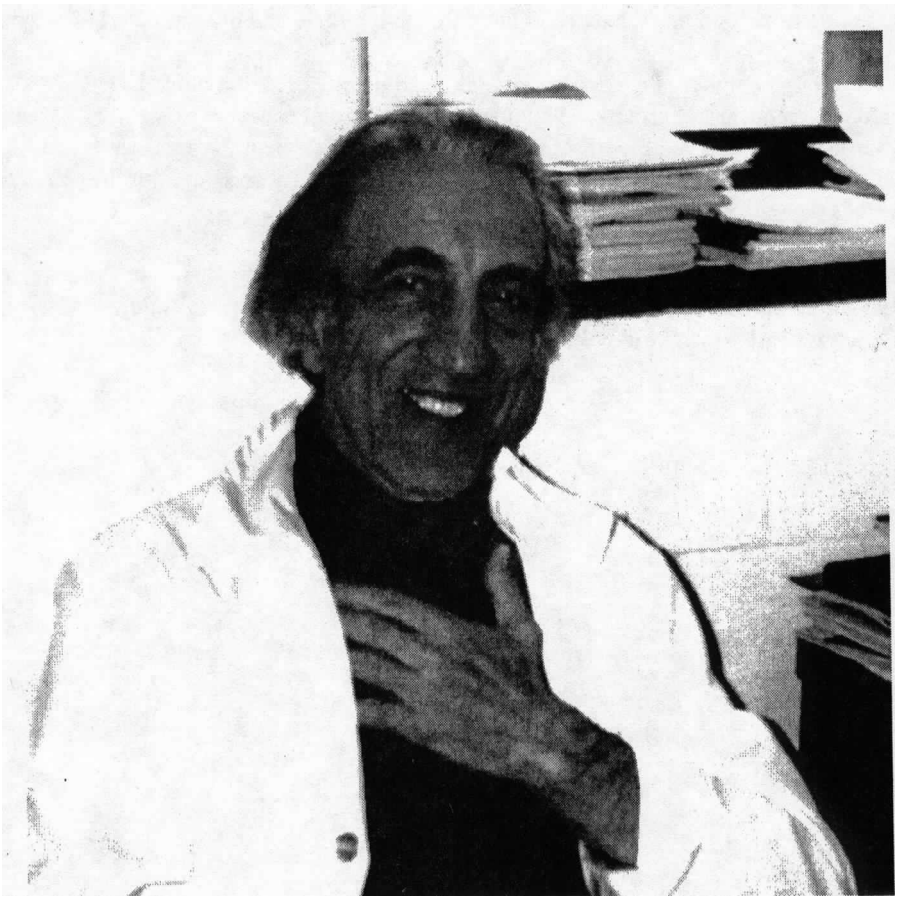
Searle

Synthelabo Recherche

Wyeth-Ayerst

Zeneca Pharmacueticals

TABLE OF CONTENTS



IN MEMORIAM

LEO G. ABOOD
(1922-1998)

On January 18, 1998, three days after his seventy-sixth birthday, Dr. Leo G. Abood died suddenly of a massive heart attack in New York City.

Leo Abood was a distinguished biomedical scientist whose studies on the mechanisms of action of abused substances contributed significantly to the field of drug dependence. Leo was born in Erie Pennsylvania on January 15, 1922. After earning his undergraduate degree in chemistry, at Ohio Sate University, he received his Ph.D. in pharmacology at the University of Chicago. He began his academic career as Instructor of Physiology at the University of Chicago. In 1952, he moved to the University of Illinois College of Medicine, where he rose through the ranks to Professor of Neurophysiology and Biochemistry and Director of Research of the Neuropsychiatric Institute. In 1965, he left Illinois to assume the post of Professor of Brain Research and Biochemistry at the University of Rochester School of Medicine. In 1987, he assumed the title of Professor of Pharmacology and Biochemistry at Rochester, where he continued an active program until his death.

Dr. Abood's research contributions focused on the biochemistry and pharmacology of synapses and excitatory membranes of three classes of abused substances, nicotine, the psychotomimetic anticholinergics and the opioids. The major effort of his research group was "devoted to the purification and molecular characterization of the nicotinic and muscarinic receptors in mammalian brain and elucidation of their functional nature." In collaboration with a number of synthetic chemists, they developed a number of agonists, agonists and affinity ligands for the

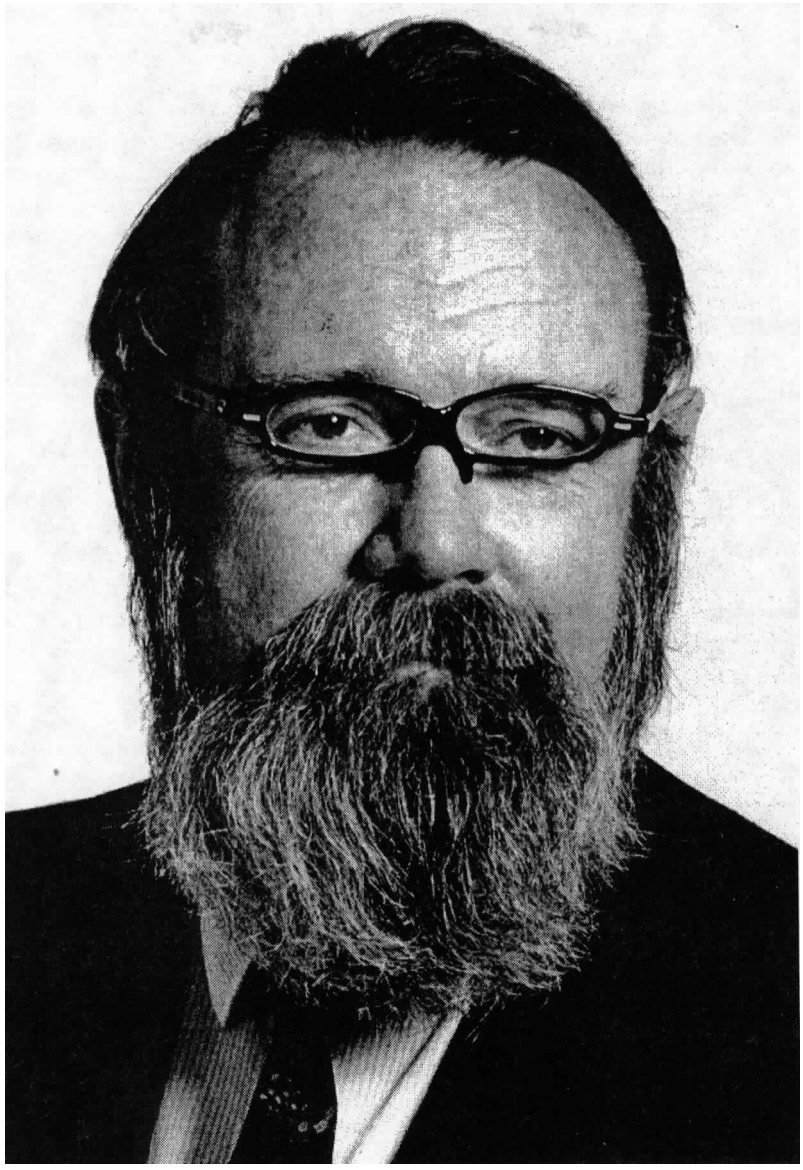
cholinergic and opioid systems which were used in receptor purification and characterization techniques of molecular biology to study the role of second messengers and ionic flux in nicotinic and muscarinic cholinergic receptors.

Dr. Abood served on a large number of national committees and boards. These included several NIH study sections, the NINCDS Board of Scientific Counselors, and a number of important National Academy of Sciences committees. He was on the editorial board of several journals, was a member of the scientific advisory board of the Council for Tobacco Research and chaired the Scientific Advisory Board of the Tobacco Health Research Institute of the University of Kentucky.

In addition to his scientific contributions, Leo was also a kind and caring individual with widespread interest in the arts and humanities. We express our heartfelt condolences to his wife, Lois and his children, Mary and George. We will miss him as a scientifically insightful colleague and friend.

Respectfully submitted,

L. S. Harris, Virginia Commonwealth University, Richmond, VA



IN MEMORIAM

KEITH F. KILLAM, JR.
1927 - 1998

On January 2, 1998, we lost a dear colleague. Keith F. Killam, Jr., Ph.D., to a massive heart attack. Although Keith was known to all of us as a distinguished researcher and teacher, he will also be remembered as a devoted husband, father, grandfather, and friend. It is a privilege to acknowledge his contributions to science and to celebrate his life. He will be missed, both personally and professionally, for his enthusiastic and humanitarian approach to research and research policy issues which have provided answers to problems worldwide and improved the quality and quantity of life.

In 1948, Keith received his B.S. degree in engineering from Tufts College. Upon graduation, he was employed as a Junior Research Pharmacologist by Smith, Kline & French Laboratories in Philadelphia. His devotion to science

and his thirst for knowledge inspired him to return to school where he obtained his masters in 1953 and his doctorate in 1954, both in pharmacology from the University of Illinois. Keith then rejoined Smith Kline & French as a Senior Research Pharmacologist.

In 1959, Keith continued his academic career at Stanford University as an Associate Professor and was promoted to Full Professor in 1967. He continued his professional career by embracing the opportunity to join the University of California at Davis as their first Chairman of the Department of Pharmacology in 1968 and served in that capacity until 1993. Although retired as Chair, he remained an active faculty member continuing his life long passions - research and teaching. Keith was regarded as an excellent teacher and mentor whose compassion and excitement of discovery in the laboratory permeated his teaching.

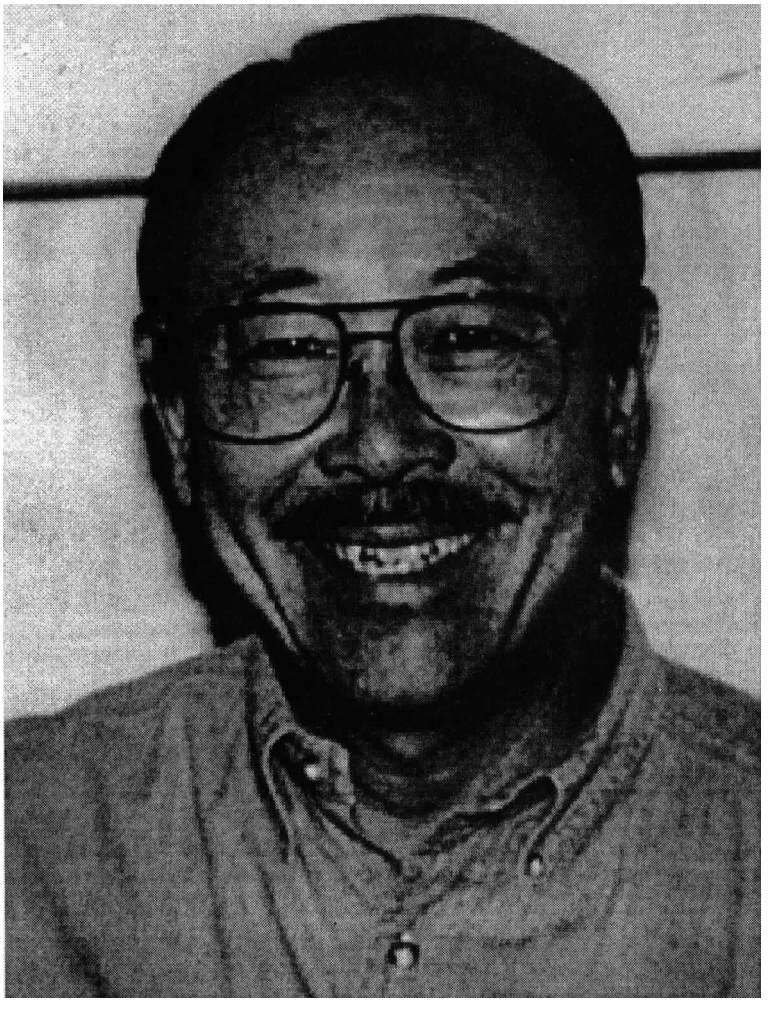
Keith's desire, leadership and breadth of expertise knew no boundaries to bring research and its benefits to the attention of society. He was a very outspoken person and strong advocate for the humane use of animals in research. He served the scientific community well as a leader of numerous scientific societies. He chaired many important independent committees, served on editorial boards, national and international committees as well as advisory committees to the National Institutes of Health, National Institute on Mental Health, National Institute on Drug Abuse, and National Science Foundation. He was an excellent President of the American Society for Pharmacology and Experimental Therapeutics (ASPET) in 1980-1981, the Western Pharmacology Society in 1972 and the American College of Neuropsychopharmacology (ACNP) in 1976-1977. Keith served on the Boards of Directors of the Federation of American Societies for Experimental Biology (FASEB) and the Committee on Problems of Drug Dependence (CPDD). He had a very pronounced positive effect on world wide issues related to drug use and abuse in his capacity as Councilor of the International Union of Pharmacology (IUPHAR) from 1984-1990 and Vice President from 1990-1994.

Those of us who were lucky enough to work closely with Keith will remember his ultimate commitment to science, his wonderful sense of humor and his ability to always get the job done efficiently and effectively. Thankfully, all the memories are not limited to work related issues but include challenging philosophy of science, conversations and enjoying good music, food and libations. Long work hours were always followed by Keith's contributions to the good times which deserve appreciation and fond memory. His hard work, his scientific contributions, his total commitment to health related issues and his enjoyment and fulfillment of life have earned him our highest respect and our enduring affection.

Keith is survived by his wife Eva of 43 years, three daughters, four grandchildren and one brother. The many scientific contributions of this husband and wife team are only overshadowed by their total commitment and devotion to each other. Keith will be remembered as a visionary with the wisdom and leadership to attain his personal and professional goals. The breadth and diversity of his expertise and dedication to the advancement of knowledge enriched the lives of all who knew him. Keith will be missed by his family and his extended family of friends, colleagues and students.

Respectfully submitted,

W. L. Dewey, Virginia Commonwealth University, Richmond, VA



IN MEMORIAM

AKIRA E. TAKEMORI
(1929-1998)

CPDD lost a founding member who was richly rewarded during his career by students and peers for his distinguished contributions in teaching, research and public service. Akira E. Takemori (Arkie) died unexpectedly after a valiant struggle from complications of surgery for esophageal cancer. Born in Stockton, CA, his early youth was spent in an internement camp during World War II with other Japanese Americans. Subsequently, he earned an A.B. in 1951, at Cal Berkeley and a M.S. at UCSF in 1953. He served in the U.S Army Medical Service Corp from 1951 to 1953, and then obtained his Ph.D. in 1958 at Wisconsin, remaining there for postdoctoral training at the Enzyme Institute. His first academic appointment was at SUNY, Syracuse, NY, where he served from 1959 to 1961, as Instructor and Assistant Professor in Pharmacology. He then moved to Minnesota, where he rose through the ranks in the Department of Pharmacology to the full professorship in 1969, and retired in 1994.

Takemori became renowned for his major innovations on the basic mechanisms involved in opioid effects. His pioneering research in the sixties and seventies on morphine and its surrogates provided early evidence for the existence of multiple opioid receptors. By application of PA_2 concepts for studying agonist and antagonist action, he and his associates demonstrated that different types of opioid receptors were involved in mediating its many varied responses. He also established that an alteration in receptor sensitivity occurs after tolerance development by demonstrating that mice treated chronically with morphine became sensitized to the antagonistic action of naloxone

due to enhancement in binding affinity for naloxone at receptor sites. The conceptual implications of this finding stimulated other laboratories to apply the approach to study receptor functions in tolerance development.

Later, Arkie collaborated with Portoghese in a fruitful relationship that provided major tools for studying opioid effects. Their efforts culminated in the development of several opioid antagonists, which by virtue of their preferential selectivity for different opiate sensitive sites, provided definitive proof of the existence of several opioid receptors. One of the most important, β-FNA, an irreversible antagonist, was used to identify μ effects of various opiates and to localize their loci of action in the central nervous system. Other antagonists were applied for discriminating κ and δ receptor subtypes, δ1 and δ2. Making these antagonists available to others contributed to tremendous advances in the understanding of pharmacology of the opioids. In recognition of these seminal innovations, the Nathan B. Eddy Award for outstanding contributions in drug dependence was given to the team in 1991.

Among other notable honors Arkie received were Teacher of the Year in 1979, at Minnesota, and the presidency of American Society of Pharmacology and Experimental Therapeutics (ASPET) in 1992. He was called upon to serve on NIH peer review committees for NIDA and NIGMS, as well as on many editorial boards. He trained many graduate students and postdoctoral fellows from all parts of the world who later became leaders and notable contributors in pharmacology and drug dependence.

Arkie was a natural athlete who displayed skill and competitiveness in many sports. He was more than ordinary in baseball, basketball, handball, tennis and judo. Later he became an avid golfer, who despite his small stature out drove most of his more physically endowed opponents. After his retirement, he became a certified golf club maker but sadly he ran out of time to practice his new vocation. He is survived by his wife Valerie, who shared closely his professional and social interests in pharmaceutics, skiing, dancing and devotion to their children Tensho, Rema and daughter-in-law Martha. The Akira E. Takemori Memorial Fund for graduate students has been established at ASPET to honor one who has given much in his lifetime to pharmacology and pharmacologists.

Prepared by: J. M. Fujimoto and E. L. Way, University of CA-San Francisco, San Francisco, CA

NATHAN B. EDDY AWARD LECTURE

J. Lewis

University of Bristol, Bristol, London

"In Pursuit of the Holy Grail"

I have attended every CPDD meeting since the Nathan B. Eddy Memorial Award was established and each year I've been interested to find out who was to he the recipient without ever dreaming that in could be me. This is without doubt the greatest moment of my career and I am honored that the College has bestowed on me its premier award. We all owe an enormous debt of gratitude to the great man whom I was privileged to meet, for he, more than any other individual, laid the foundations for the field of drug abuse research.

My surprise that I am now in the company of some of the giants of this field probably relates to my position outside the mainstream of drug abuse research as a non-American medicinal chemist with a career spent largely in industry. For though I have worked in the University of Bristol for six years, for the previous 27 years Reckitt and Colman paid my salary and gave me the opportunity to develop a career among the opioids. My Reckitt and Colman career of course had a focal point in buprenorphine. It is given to relatively few scientists in the pharmaceutical industry to be involved in the discovery of a drug but to be involved in the discovery and then to be allowed to be responsible for its development was a stroke of good fortune: for which I am deeply grateful. I hope you will not to be too bored with these personalized reminiscences particularly of the early days of the odyssey which has been the story of buprenorphine.

The research and development activity in industry is very much a learn effort; I am conscious that I will not have the opportunity to acknowledge by name a great many Reckitt people who made enormous contributions to the development of buprenorphine. But in the best traditions of the Oscar ceremony, there are individuals whom I must mention because their influence on the progress of buprenorphine and on my career have been so fundamental.

The first of these is Kenneth Bentley, who established the chemistry of Diels-Alder adducts of thebaine and had the vision in the 1950's that opioids with structures substantially more complex than morphine could selectively retain the desirable actions whilst shedding undesirable side effects. Though this was a simplistic view, it was nevertheless borne out to a substantial extent with the orvinols. Ken Bentley laid the chemical foundations upon which we were able to build a successful development program.

I first met Ken Bentley in 1950, in my first term as a freshman at Oxford. The Oxford tutorial system is based on a weekly one to one meeting between the student and his tutor. Ken Bentley was my designated tutor for that first term's tutorials in organic chemistry. I remember the first tutorial to this day. The question was: how many methods did I know for the preparation of aldehydes? I managed two, or was it three? Ken then proceeded to write down two dozen other methods! He made so much of an impression on me that fifteen years later when he was Head of Chemistry at Reckitt and Colman, I jumped at the opportunity to join him as his deputy.

In those intervening years, I graduated and completed my D.Phil. in natural product organic chemistry. After a two year stint in the chemical industry, I moved back to academia as a lecturer at Loughborough and established a research program in organic synthesis methodology but at that time, Loughborough was in transition from technical institute to university and the opportunity to join Ken Bentley was too good to turn down. My career in drug abuse research was thus not planned and I owe it primarily to Ken Bentley.

Loughborough continued to be involved from time to time in my career. In 1973, Bentley left Reckitt to become Professor and Chairman of the Department of Chemistry at Loughborouph, giving me the opportunity to succeed him as Research Director. The Loughborough connection was renewed live years ago, after my move to Bristol. I started a collaboration with John Traynor which has continued, now that he is ensconced with Jim Woods at Ann Arbor.

How did Reckitt and Colman, a consumer product company whose main business is in grocery stores get involved in opioid research? It happened because among their consumer product lines, the company had some over the counter pharmaceutical products including two dispersible aspirin formulations - Disprin® and Codis®. Codis is a combination product containing 300 mg aspirin and 8 mg codeine. In fact, Codis was the key to Reckitt's venture into discovery research. To find an improvement on codeine was the rationale for the opioid program and to replace aspirin we set out to discover new non-steroidal anti-inflammatory drugs.

Reckitt set up a joint research program with McFarlan-Smith, a long-established producer of opium alkaloids. Bentley started working on Diels-Alder adducts of thebaine as a lecturer at Aberdeen University and was hired with his research program by McFarlan Smith on behalf of the joint venture. In 1964, Reckitt took over the program and Bentley moved to Hull; I joined a year later.

By then, not only had Bentley assembled a group of about twenty organic chemists of varying levels, but they had synthesized about 200 orvinols and thevinols and filed patents. Inevitably, in such a situation, pharmacological evaluation lagged behind the synthesis but some fantastically potent morphine-like opiates including etorphine had already been identified. These orvinols were several thousand times more potent than morphine in the rat tail pressure test (Bentley and Hardy, J Amer Chem Soc, 1967, 89: 3281-3292). The popular scientific press were excited by news that doses of a few milligrams of etorphine could immobilize an elephant or rhinoceros. This turned out to be very bad publicity for etorphine for it convinced the World Health Organization (WHO) that etorphine was extremely dangerous and therefore should be controlled in Schedule 4 of the Single Convention, the most restrictive level of control. At about that time, fentanyl, a synthetic opiate of not dissimilar potency to etorphine was being developed by Paul Jannsen as an intravenous anesthetic for human use. Fentanyl and its analogs have been huge commercial successes whereas etorphine, which I'm sure could have been an equally successful clinical anesthetic, has had very 'modest sales as a veterinary anesthetic. I think we must conclude that etorphine arrived too early for the consumer marketing people of Reckitt to appreciate how it should be commercialized.

When I joined Bentley, the group was starting to explore the effect of replacing the N-methyl group in the orvinols particularly with allyl and cyclopropylmethyl (CPM) groups. This structural manipulation had been shown to be an important step in the conversion of opioid structures into analogs of lower abuse liability. The pharmacology of nalorphine was becoming understood and pentazocine and cyclazocine had been disclosed by the Sterling group directed by Lou Harris and Syd Archer. The first N-CPM orvinol to attract attention was M320 which was discovered by my new colleague Alan Boura who was in charge of the pharmacology group. M320 produced very potent antinociceptive activity but was also a powerful CNS depressant. These effects could not be reversed by nalorphine which was the only morphine antagonist available at that time. This pharmacological profile of M320 was described in detail in a paper published in 1966 (Boura and Fitzgerald, Brit J Pharmacol, 26: 307-321).

If you read this paper you will realize that the profile described is that of a full kappa agonist. This report predates by nearly ten years the descriptions of ketazocine and ethylketazocine by Bill Martin as the first kappa agonists. Later, when the full battery of isolated tissue tests, guinea pig ileum, mouse vas deferens, rat vas deferens and rabbit vas deferens were available, so that mu and kappa affinity and efficacy could be evaluated, we were able clearly to show the high efficacy kappa agonism of M320. It also has some mu efficacy and substantial affinity for mu and delta receptors so that its opioid receptor profile is quite similar to that of ketazocine and EKC. Just after I arrived, M5050, or diprenorphine was synthesized. It was our best morphine antagonist at that time though it was later shown also to have kappa partial agonist effects. It has proved a very useful pharmacological tool and is still the preferred "universal opioid ligand."

The orvinols provided not only exciting opportunities for opioid pharmacologists, but for the organic chemist the chance to observe some spectacular molecular acrobatics as these complex molecules rearranged themselves simply by treatment with acids or bases. After a year or so of self indulgence with the exciting chemical toys I had been given, I decided that we had to get down to the serious business of finding candidates for development.

A number of N-CPM derivatives had been selected by the pharmacologists for clinical evaluation. Soon after I arrived in Hull, we received a report from Arthur Keats on his evaluation of two orvinols in a small number of patients with post operative pain. These candidates, designated M278 and M285 were administered to patients after

only acute toxicity tests. How time has changed! Since both candidates showed signs of the dysphoria and psychotomimetic effects which had first been seen with nalorphine, neither candidate was seriously followed up. The company was thus spared further development costs but one might ask whether the patients were exposed to significant risk by the lack of multiple dose toxicity studies? Clinical studies without such toxicity data could not take place today but in truth, it was extremely unlikely that a single low dose of an opioid with good acute safety would cause any conceivable harm. When I think of how much of my subsequent career was involved with regulatory authorities over the minutiae of safety issues, the procedures of the early sixties seems light years away.

At that time the pharmacological screening of new opioids was almost totally based on rodent antinociceptive tests. Morphine was active in tests which used heat or pressure as nociceptive stimulus, but nalorphine was inactive in these tests though it had been proven to be an analgesic in man. It was argued that any compound having antinociceptive activity in the heat and pressure tests would display the full range of morphine-like effects including the main unwanted effects - respiratory depression and physical dependence. Our primary screen was the tail pressure test in rats which was used to eliminate candidates which would be too morphine-like. We were looking for morphine antagonists in the tail pressure test and an antinociceptive response in the anti-writhing test, which we now call the abdominal stretch test. Our other priority was good oral activity because we particularly wanted to compete in the codeine and oxycodone markets. At that time, oral morphine was not established as the analgesic of choice for advanced cancer pain.

After M278 and M285, the first candidate which appeared to satisfy all these criteria was M5205. It was put through a preclinical safety program and after brief Phase I evaluation it was tested in a single dose study in post-operative patients. It was not particularly effective and produced some dysphoric effects. A further blow for M5205 came when in studies in rhesus monkeys at the University of Michigan, Deneau and Seevcrs showed that it substituted for morphine in withdrawn morphine-dependent monkeys and in a direct dependence study gave rise to a withdrawal syndrome that was morphine-like.

At this point around 1968/9, our corporate masters were getting distinctly cold feet. I had succeeded Ken Bentley as Head of Chemistry and assumed responsibility for the orvinol project. The pharmacology group was then joined by a bright young Ph.D. from Strathclyde who became the second key influence in my opioid career - Alan Cowan. I quickly discovered that Alan shared my commitment and enthusiasm for the orvinols. He was given responsibility of the analgesic testing program and together we set out to select what we realized would be the last candidate - we had one last throw of the dice and we had to win.

Our strong feeling was that among the many orvinols rejected earlier because of their activity in the pressure test some, particularly those having the N-CPM substituent, must have morphine antagonist activity which would indicate that their abuse liability might be lower than that of morphine. If they had such activity it had been missed possibly because the pressure test had been relatively insensitive to antagonist activity. Some of the orvinols had been tested in the rat warm water tail withdrawal test and of these a small group of N-CPM derivatives had shown bell shaped dose response curves. Though we weren't sure how to interpret this effect, we associated the descending arm of the curve with an antagonist effect and concluded that the tail withdrawal test may be more sensitive to morphine antagonist activity than tail pressure. This proved to be the case and we showed that this group of orvinots indeed' were antagonists of morphine in the tail withdrawal test.

So the breakthrough we had been seeking was made. We had found that this group of orvinols were relatively weakly active as agonists in the thermal antinociceptive tests so that their antagonist actions could be identified. We recognized that the activity of our candidates in the pressure model could give them a distinct edge as clinical analgesics but might be associated with unacceptable abuse liability. Thus, the primary criterion for choosing our single candidate had to be the assessment of abuse liability which at that time effectively meant physical dependence. Though the significance of reinforcing effects was becoming recognized, tests involving self administration and discriminative techniques were in the early stages of development.

Alan set up mouse and monkey models of physical dependence and evaluated the leading candidates. His primate model using groups of three patas monkeys housed in large cages was perhaps slightly less sophisticated than the established model of Deneau and Seevers at the University of Michigan but it allowed Alan to differentiate the morphine abstinence syndrome from the cyclazocine syndrome - what nowadays we would call mu and kappa. We

decided to characterize the primary physical dependence associated with each of our candidates. We would reject those that showed significant morphine-like abstinence and hoped that any cyclazocine-like effects would be mild.

The results of Alan's study showed that we now had two serious contenders M6007 and M6029. M6007 produced a mild, delayed cyctazocine-like abstinence syndrome whereas for M6029, there was no evidence of abstinence either precipitated by naloxone or on abrupt withdrawal. This convinced us that M6029 was our candidate and from then on most of our effort was concentrated on this exciting compound which later we named buprenorphine. Incidentally, the first indication the buprenorphine was a kappa-opioid receptor antagonist was obtained by Alan from his dependence studies in those patas monkeys. He showed that buprenorphine could precipitate the characteristic abstinence syndrome in cyctazocine as well as morphine dependent monkeys (Cowan, Advances in Biochemical Psychopharmacology 1974, 8:427-438)

The first disclosure of the pharmacological profile of buprenorphine, subtly designated as RX6029-M was made by me at the 1972 Scientific Meeting of CPDD at Ann Arbor. In this report, we detailed the performance of buprenorphine in a battery of antinociceptive tests, physical dependence in mice and monkeys, cardiovascular gastrointestinal and behavioral tests. In addition, we reported acute toxicity data; the LD50 values in mice and rats are many thousand times higher than the ED50 values in the antinociceptive tests showing how incredibly safe buprenorphine is in acute overdosage. This continues to be one of its most important benefits.

The preclinical safety studies with buprenorphine caused no particular problems and so in 1971 came the next moment of truth - the first administration of buprenorphine to humans. It was quite customary at that time for the people involved in the discovery of a drug to be the first volunteers and so Alan and myself together with Peter Crocker, our development chemist, went to the Western Royal Infirmary in Glasgow to receive buprenorphine administered intravenously by the senior Consultant Anesthetist Donal Campbell. The chosen doses were 50 µg, 100 µg and 200 µg in ascending order. Peter and Alan received the tower doses and experienced no very marked effects either subjective or on any of the vital signs that were measured. When my turn came, things were a little different - after a few minutes, not immediately; I was very aware of a drug effect. I had previously never received morphine so I couldn't describe it as morphine-like but it obviously was. There were no dramatic changes in vital signs and no signs of dysphoria. This was encouraging because we knew that nalorphine, cyclazocine and pentazocine all showed some level of dysphoric effects in patients. But we were still at a relatively tow dose equivalent to about 10 mg morphine and higher doses might show these effects. My problems started when the test was thought to be over and I got up to join the others for lunch. I felt dizzy and over the next several hours felt very nauseated and vomited several times. It quite took the edge off our stay in a splendid hotel on the banks of Loch Lomond. After a good night's sleep, I felt fine the next morning but we had had the first glimpse of buprenorphine's Achilles heel as an analgesic - the rather high incidence of nausea and vomiting.

Though our scientific objective was to find a replacement for morphine, the market we were primarily aiming at was the oral opiate market held by codeine and its derivatives. So we needed an oral preparation of buprenorphine. Unfortunately, our volunteer studies of oral buprenorphine did not look promising. We estimated that at least ten times as much drug needed to be administered orally to achieve the effect of an intravenous dose. The problem associated with this low oral bioavailability would be variability of effect and in particular potential overdosage in patients with compromised metabolism. So, we looked for alternatives and turned to the sublingual route because a few years earlier a study of sublingual etorphine in cancer patients had given very encouraging results. Since I was regarded as susceptible to the nausea and vomiting effects, I was required to take part in the trials of all the formulations of buprenorphine; though I never experienced anything quite like that first intravenous dose, our commitment to the cause was certainly put to the test.

The clinical testing program was conducted in patients with post-operative pain or in chronic pain from cancer. Both the injection and the sublingual preparation showed good efficacy with a relatively low incidence of morphine-like side effects in the post-operative pain group. The side effects were somewhat more pronounced in ambulatory patients treated with the sublingual preparation which gave 50-60% bioavailability and was otherwise well tolerated.

By the time buprenorphine reached the market first in the UK in 1978 in injection form, I had been elevated to the post of Research and Development Director. One of the advantages of working in a small pharmaceutical company like Reckitt and Colman was that I could continue to take a direct part in the key activities involving the

development of buprenorphine. These increasingly became the issues of abuse liability and national and international controls.

Buprenorphine's launch in the UK was at about the same time as the arrival in the US market of butorphanol and nalbuphine. The evaluation of the abuse potential of these mixed agonist-antagonists and pentazocine occupied the attentions of drug abuse researchers as the WHO and national control authorities tried to decide whether or not they should be controlled and if so, whether the level of control should be like morphine and the other opiates, or at some lower level.

Among the many people who studied the abuse potential of buprenorphine and provided perspective for the control authorities, two were of crucial importance - Bill Martin and Don Jasinski, who at that time were at the Addiction Research Center in Lexington.

I realized that studies in prisoner post-addicts at Lexington would provide the most relevant data in the evaluation of the abuse potential of buprenorphine. When the drug was sent to Lexington in 1974, Bill Martin was using his chronic spinal dog assays to characterize opioids in his two receptor model - which he designated mu and kappa in 1975. At that time, I believed or maybe just hoped that buprenorphine was only quantitatively different from the other mixed agonist / antagonists. In a brilliant study of buprenorphine he showed that it was qualitatively different, a mu partial agonist without significant kappa agonist properties.

The studies in the prisoner post addicts were delayed for two reasons. One was relatively trivial - the sponsors of the study were to be French's Mustard - the Reckitt and Colman US subsidiary. The other which was much more serious, was the increasing opposition to the use of prisoners as subjects for drug evaluations. This had an important consequence for the future of buprenorphine. Don Jasinski responded to the pressure on the use of prisoners by pointing out that the pharmacology of buprenorphine made it an attractive candidate as a treatment for opiate dependence which had been a major factor leading to the incarceration of the volunteers. Thus. Don's studies aimed not only to determine the human abuse potential of buprenorphine but also to investigate its possible use as a treatment drug. The story of the development of buprenorphinc as an addict treatment thus started in 1975. Even by the prolonged time scales of drug development, this one is really long, but I am pleased that buprenorphine is now marketed in Europe for this indication and the NDA in this country is, we hope, not far off.

The problems of international control of the mixed agonist-antagonists ran in parallel with the issue of the status of buprenorphine in this Country under the Controlled Substance Act. In the control of opiates, the Act uses the term derivative of an opiate in order to cover substances of similar pharmacological profile which can be prepared from opiates. Thebaine, which is a constituent of opium and therefore defined as an opiate in the Act, is the starting point for a great number of opioid drugs including oxycodone and oxymorphone, which are opiates, but also naloxone and naltrexone which plainly aren't opiates. Because they are prepared from thebaine. they were controlled in Schedule 2 and subject to all the restrictions of the act covering their use, handling, distribution and export. These restrictions applied for several years until their formal exemption from the Act was secured.

This interpretation of the word derivative as "anything prepared from" is unique to the Controlled Substances Act. It meant that every compound we synthesized in our program because thebaine was the starting material, was automatically in Schedule 2 and when we wanted to send them to this country, an Import Permit had to be raised which would usually take about three months. Since we sent more than a dozen compounds for abuse liability testing at the University of Michigan and Medical College of Virginia and many batches of buprenorphine both as drug substance and as formulations, the burden of this control was considerable.

When the NDA for buprenorphine injection was approved at the very end of 1982, the issue of its control status had to be resolved before it could be marketed. In the scheduling process, FDA are required to make a recommendation to DEA on the basis of their assessment of the scientific evidence. We were informed of their provisional decision, fortunately before it was sent to DEA. It was that buprenorphine should be rescheduled to Schedule 3 and classified as a "narcotic drug." This label had previously only been applied to Schedule 2 opiates like codeine and hydrocodone in certain oral preparations which are exempt from Schedule 2 and controlled in Schedule 3-5 with the "narcotic drug" label. With pentazocine in Schedule 4 and without the narcotic drug classification and nalbuphine and butorphanol uncontrolled. buprenorphine appeared to have been harshly treated particularly with respect to the

narcotic drug issue. A hastily arranged meeting at FDA with Frank Vocci and others allowed me to convince them that Schedule 3 was unjustified by the comparative abuse liability data. But they felt they could not remove the narcotic drug label and this lead to the formal proposal by DEA to reclassify buprenorphine to Schedule 5 - narcotic. We were invited to seek a review of the decision before an Administrative Law Judge. After discussion within the company and with our US attorneys we decided that the potential damage to the international status of buprenorphine was sufficient to justify the cost of delaying the US marketing of buprenorphine. Since the narcotic drug designation would have no relevance if buprenorphine was exempt from control, we decided to appeal against any control of buprenorphine though our primary motivation was to avoid narcotic drug status.

The process starting in mid 1983 and lasted a year during which period I spent a great deal of time with our attorneys Tom Henteleff and Peter Mathers. We became quite close and I believe were a pretty formidable team. The review was based on written testimony by nearly thirty expert witnesses called by us, DEA, or a third party Johnson and Johnson who decided to try to muddy the waters; they certainly did not intervene to lend us their support! The DEA's case was that there had been reported abuse of buprenorphine particularly in Germany and New Zealand so that this proved that it was a narcotic like morphine. They produced local witnesses to corroborate these reports, so that when it came to the cross examination the Judge decided that it was unfair to require these witnesses to come to Washington. Thus, two of the cross examination sessions took place outside Washington - one in Hawaii for the New Zealand witnesses and one in London for those from Europe; the opening and closing sessions were in Washington for a total of about twelve days of court room activity. This sort of hearing is not exactly Perry Mason, but there were some almost dramatic moments. These moments seemed to come when a witness had been backed into a corner by skillful questioning and then would come the one question too many, perhaps the one to which the attorney did not know the answer, and the witness would be off the hook. But I have to say that our witnesses were superb - we had lined up some of the real heavy weights of this field, among them several past winners of this award.

The definition of a derivative was of course, a central issue in the hearing. As organic chemists, we understand that a derivative is a product prepared from a compound by essentially a single simple chemical step. Moreover, since the Controlled Substances Act also controls the immediate precursors of synthetic opiates, it seems logical that for the purpose of control, the normal organic chemist' definition of derivative should apply. The alternative "prepared from" definition which had been used to control every compound prepared from thebaine, however many and however complex were the chemical steps involved, seemed totally unjustified. It lead me to think how we might be able to illustrate just how inappropriate was this definition. I recalled that thebaine had been degraded to a single ring aromatic compound and when I looked this up, I realized that this degradation product could fairly easily be converted to aspirin, which we then proceeded to do in the lab. Thus, aspirin could be prepared from thebaine and therefore fulfilled the derivative criterion of a narcotic drug. Of course, no one believes that aspirin is a narcotic but the point was made. To complete the picture, I discussed with Kenner Rice whether his total synthesis of morphine could be modified to allow the synthesis of buprenorphine without involving an opiate intermediate. He assured me that this was the case so that we could justifiably claim that the synthesis of buprenorphine from thebaine was a matter of convenience and cost effectiveness, not necessity.

Our efforts were rewarded when the Administrative Law Judge ruled that buprenorphine should not be controlled under the Controlled Substances Act. It was remarkable that the Judge, whom I believe had his salary paid by DEA, ruled against the Agency but we soon found out that we had won a battle not the war because the Administrator of DEA proceeded to ignore the Judge's recommendation and after our appeal was rejected, issued the rescheduling of buprenorphine to Schedule 5 narcotic. Out of this frustrating experience came some good - the notice of rescheduling stated that buprenorphine is a narcotic drug because it is a derivative of an opiate and has proven abuse potential. This means that those research products for which abuse potential has not been proved should not be automatically controlled. Interestingly, the WHO control process a few years later resulted in control of buprenorphine in Schedule 3 of the Psychotropic Convention. The narcotic drug classification in this. country did not trigger international control under the Single Convention for which we were relieved and control of buprenorphine has not in itself been a deterrent to its further development.

The narcotic drug classification does become a problem when it comes to the marketing of buprenorphine in this country for the treatment of opiate addicts. As a designated narcotic drug there is a requirement for new regulations covering the use of buprenorphine in addicts, as there are for methadone. It is to be hoped that the formulation of

buprenorphine with naloxone to prevent diversion will be made exempt from such regulations. When Don Jasinski described the clinical pharmacology of buprenorphine after his study in Lexington in 1975, he concluded it had a very attractive profile for a treatment for opiate abuse. Why has it taken so long to convert this potential into a marketed treatment? I suppose there are several reasons but they are largely commercial and financial. Reckitt and Colman was naturally reluctant to get involved in addict treatment while the market for sublingual buprenorphine as an analgesic was being developed. The other major problem was the attitude of Reckitt's US licensees who were fundamentally opposed to the prospect of buprenorphine being used in addicts. In 1986, the situation changed when Bob Schuster was appointed Director of NIDA. Bob had a good understanding of the pharmacology of buprenorphine from his membership of WHO Expert Committees which several times in the preceding years had considered the control of the mixed agonist-antagonists. He was largely responsible for ensuring that pentazocine and buprenorphine were controlled under the Psychotropic Convention and not the Single Convention. One of the goals Bob set for NIDA was to provide new pharmacotherapies for opiate abuse and he identified buprenorphine as the prime development candidate. I managed to convince my commercial colleagues that this was now in Reckitt's best interest. There were still licensee problems but these were finally resolved not long before I retired when the US license expired and Reckitt decided to go it alone. That turned out to be a very beneficial decision for buprenorphine because it lead to the appointment of Charles O'Keefe to run the operation and he has proved the ideal person to ensure the Reckitt-NIDA partnership achieves a successful NDA.

I am pleased to report that there has been life for me after buprenorphine. Quite some time before I retired, it became clear that Reckitt was going to abandon discovery research. That finally happened when I retired. I was fortunate to be allowed to spend my pre-retirement years with a small CNS research group I set up with Reckitt sponsorship in the Bristol University Medical School under David Nutt. David's scientific skills and qualifications range from basic pharmacology to psychiatry so we had both preclinical and clinical groups. Our program included some opioid work but was largely based on the alpha-2 / imidazoline receptor ligands which had been discovered by the last generation of Reckitt medicinal chemists lead by Chris Chapleo.

As my retirement approached, I decided I wanted to go back to my medicinal chemistry roots. I was too old a dog to learn new tricks so I looked to NIDA for support in the exploration of the orvinol series for alternatives to buprenorphine. NIDA succumbed and in 1991, I set up a small group in the School of Chemistry. My first graduate student was Andy Coop who taught me some of the organic chemistry that had been going on during my twenty years of doing other things. I am pleased that Andy is still in the field working with Kenner's group in NIDDK. Having got started, it was not long before I was talking to Jim Woods about collaboration in the field of irreversible antagonists into which we had an entree with clocinnamox and methoclocinnamox which we had discovered at Reckitt and Colman in the late 1980's and Jim had evaluated as part of the CPDD program. So, Jim and I got together and landed a second grant in 1992; I then recruited a fresh post-doc, Steve Husbands, who has also remained in the field. After three years with me and a successful spell with Amy Newman, he is now a confirmed drug abuse researcher back with me in Bristol. It has given me great pleasure to see Andy and Steve grow in this field.

I very much enjoy collaborating with Jim Woods and John Traynor. It has lead to the discovery of a very interesting possible candidate as a successor to methadone. BU72, which we are talking about at this meeting, is a high efficacy mu agonist of long duration and potency about 1000 times morphine. Yet after 18 hours when its agonist effect has subsided, it becomes a profound non-competitive antagonist lasting up to a week. This kind of discovery ensures that there is continued excitement in my involvement in this field.

My response to the tremendous honor the College has bestowed on me is to dedicate it to buprenorphine, and to all those who have contributed to its development and to my career in opioid research which has given me so much pleasure and enjoyment. And finally to my family and particularly my wife Joy, who has experienced the emotional highs and lows of my career and given me unwavering support.

Thank you.

SYMPOSIUM I

DR. SYDNEY ARCHER MEMORIAL SYMPOSIUM ON MEDICINAL CHEMISTRY IN DRUG ABUSE RESEARCH

J. M. Bidlack

Department of Pharmacology and Physiology, University of Rochester, School of Medicine and Dentistry, Rochester, NY

Summary

This symposium focused on the role of medicinal chemistry in drug abuse research, highlighting the contributions made by the late Dr. Sydney Archer. Dr. Bidlack gave an overview of Dr. Archer's extensive research career. Dr. Archer received his Ph.D. in Organic Chemistry at Penn State University. From 1943 to 1973, Dr. Archer rose from Group Leader to Associate Director and Vice President at Sterling-Winthrop Research Institute. In 1973, Dr. Archer left Sterling to become Research Professor of Chemistry at Rensselaer Polytechnic Institute, a position he held to the time of his death on August 22, 1996. During his comprehensive career, Dr. Archer synthesized numerous opioids, including pentazocine and cyclazocine. A charter fellow and former board member of CPDD. Dr. Archer served on a wide range of public service committees, including NIDA's Biochemistry Study Section, and he was chair of the Medicinal Chemistry Study Section at NIH. Dr. Archer will always be remembered for his keen intellect and endless enthusiasm.

Dr. Louis S. Harris at the Medical College of Virginia of Virginia Commonwealth University worked with Dr. Archer at Sterling-Winthrop. Dr. Harris summarized the importance of mixed agonist/antagonist analgesics, such as pentazocine and cyclazocine. The initial pharmacological characterization of benzomorphans was discussed by Dr. Harris. The contribution that the benzomorphans have had in understanding the pharmacological properties of the opioid receptor was emphasized in Dr. Harris' presentation. Dr. John Lewis, at the University of Bristol, UK, discussed irreversible opioid agonists and antagonists. Both Drs. Lewis and Archer had synthesized a number of cinnamoylamino-containing opioids. They often had vigorous discussions on the mechanism of action of these compounds. The pharmacological properties of a number of 14β-cinnamoylamino-containing opioids was presented by Dr. Lewis. Dr. Kenner Rice, at NIDDK at NIH in Bethesda, MD, discussed novel ligands for the dopamine transporter and opioid receptors. Dr. Rice presented an extensive overview of drug addiction and the approaches that medicinal chemists are using to selectively target compounds to the dopamine transporter and opioid receptors. Dr. F. Ivy Carroll, at the Research Triangle Institute, NC, new compounds for both opioid receptors and the dopamine transporters. He presented a number of novel compounds that acted at the opioid receptor. This part of the symposium made the transition from opioids to cocaine. The last speaker, Dr. John L. Neumeyer. at McLean Hospital, Harvard Medical School, Boston, MA, discussed designing compounds directed at targeting the dopamine receptor or the kappa opioid receptor. He presented data, suggesting that kappa agonists, may be effective in treating cocaine abuse.

SYMPOSIUM II

NONHUMAN PRIMATE MODELS FOR STUDYING NEUROBIOLOGICAL SUBSTRATES AND COGNITIVE PROCESSES AFFECTED BY DRUGS OF ABUSE

Advances in Nonhuman Primate Neuropharmacology: *In Vivo* Microdialysis and PET Neuroimaging

L. L. Howell

Departments of Psychiatry, Pharmacology, Emory University, Yerkes Regional Primate Center, Atlanta, GA

Recent technological developments in *in vivo* neurochemistry and brain imaging have been applied toward understanding the neuropharmacology of cocaine. In this context, nonhuman primates represent an unique animal model because microdialysis studies can directly quantify drug-induced changes in brain neurochemistry, providing critical information to support and validate PET neuroimaging studies. Once developed, neuroimaging protocols can be extended directly into clinical studies of drug addiction. Because nonhuman primates are a valuable resource. the effective use of *in vivo* microdialysis requires special considerations. Magnetic resonance imaging (MRI) is currently being used to derive stereotaxic coordinates for accurate probe placement and to verify the location of the implant site. Multiple probe placements in the same guide cannulae are being used in order to maximize the amount of information obtained in individual animals. These protocols are part of ongoing self-administration studies characterizing acute tolerance and sensitization, and medication effectiveness in reducing cocaine use. In PET neuroimaging studies, a number of useful ligands have been developed to target presynaptic and postsynaptic mechanisms associated with the acute and chronic effects of cocaine. These studies have demonstrated long-term down regulation of dopamine D_2 receptors associated with cocaine self-administration that persists for months during drug abstinence. Similarly, dopamine transporter ligands are being used to characterize neuroadaptive responses during chronic cocaine use, and to evaluate medications for the treatment of cocaine addiction. Cerebral blood flow studies are being conducted in awake. behaving monkeys in order to characterize the pattern of brain activation induced by cocaine. Results demonstrate a reliable and robust change in the pattern of blood flow that has a time course consistent with drug-induced euphoria reported in clinical studies. Moreover, prominent effects observed in frontal regions could underlie the perfusion deficits associated with chronic cocaine use in humans. Nonhuman primates are ideal subjects for neuroimaging studies due to their neuroanatomical similarity to humans, sufficient brain size for accurate spatial resolution, and the ability to control for drug history.

ACKNOWLEDGMENTS: Supported by DA10344 and RR00165.

Drug Effects on Computerized Neuropsychological Test Performance

L. H. Gold, M. A. Taffe, and M. R. Weed

Department of Neuropharmacology, The Scripps Research Institute, La Jolla, CA

A computerized behavioral test battery based on human neuropsycholopical tests has been developed to assess cognitive behavior in rhesus monkeys. The battery (CANTAB, CeNes Ltd., Cambridge, UK) addresses memory (delayed non-matching to sample, DNMS; spatial working memory using a self-ordered spatial search task, SOSS), attention (intra-/extra-dimensional shift, ED/ID), motivation (progressive-ratio, PR), reaction time (RT) and motor coordination (bimanual task). As with human neuropsychological batteries, different tasks are thought to involve different neural substrates and therefore performance profiles should assess function in particular brain regions. Monkeys reliably perform multiple tasks providing longitudinal assessment of changes in a number of behaviors for a given animal. Data from acquisition and long-term performance (1.5-3 years) was presented. Acute doses of scopolamine (0.003-0.024 mg/kg, im) impaired SOSS performance in a difficulty-dependent manner, disrupted choice accuracy in the DNMS across all conditions, decreased the final completed ratio attained in the PR procedure and slowed RT and bimanual motor performances. The effects of acute amphetamine (0.03-0.56. mg/kg, im) were

highly variable with respect to dose. SOSS and DNMS performance in general was not altered except for individual subjects at high doses. In PR, moderate doses of amphetamine tended to increase, and higher doses decrease, the last completed ratio. Release latencies in the RT task were faster with high doses and bimanual motor performance was speeded, except for high doses which disrupted performance in some subjects. Throughout a repeated high-dose treatment with MDMA (10 mg/kg, im, twice daily for 4 days) the amount of time spent sleeping during the night was markedly reduced and performance on all tasks was disrupted. Performance returned to baseline levels between 1 and 2 weeks post-treatment. Demonstration of control norms and sensitivity to pharmacological manipulations are important validations of this test battery for use in characterizing performance following CNS manipulations such as infection with SIV and long-term drug toxicity.

ACKNOWLEDGMENTS: Supported by DA09111, MH47680, and DA05831.

Cognitive Deficits and Cortical Dopamine Dysfunction after Long-term Administration of PCP

J. R. Taylor and J. D. Jentsch

Department of Psychiatry, Yale University School of Medicine, New Haven, CT

There is now strong evidence that drug abuse is associated with deficits in memory, learning and attention, cognitive functions dependent on intact dopamine (DA) innervation of the frontal cortex (FC). Little is known, however, about how drug abuse may alter cognitive functions associated with 'impulsivity', a process which could be critical in craving and reward-seeking behavior. The Object Retrieval Detour task, which measures response inhibition, is known to depend on intact FC function. In this task, the subject has to retrieve a reward from a transparent box with one open side. The open side can be directed towards the monkey, and thus the subject can simply reach along its "line-of sight". In contrast, when the open side is directed laterally, reaching directly at the transparent barrier must be inhibited and instead "negotiating" the barrier is necessary to obtain the reward. To investigate the hypothesis that chronic administration of PCP would alter the neural circuitry associated with cognition and reward, monkeys were given PCP (0.3 mg/kg BID 14 days) or saline. All subjects performed well on the line of sight reaches, both groups retrieving the reward on the first reach ("success") on 80% of the trials. When subjects needed to inhibit direct reaches, because the opening was displaced laterally, PCP-treated subjects performed significantly worse than controls -- never achieving more than a 60% success rate up to 28 days after drug treatment. Thus, the performance of "difficult" trials requiring response inhibition and planning (as opposed to solely sensory-guided responding) were selectively impaired in PCP treated monkeys. Post-mortem regional brain neurochemistry revealed that significant reductions in DA utilization (homovanillic acid (HVA):DA ratio) in the dorsolateral prefrontal cortex, prelimbic cortex and frontal eye fields correlated with successful performance. Subcortical regions were not affected and there were no changes in the other metabolites and transmitters examined. Further studies in rodents demonstrated that long term exposure to PCP or cocaine causes mesolimbic DA hyperactivity and impulsivity associated with potentiated responding for reward-related stimuli. Repeated exposure to drugs of abuse may produce dysfunction of corticolimbic circuits associated with inhibitory control and reward -- functions that may be critically involved in impulsive behavior that may contribute to craving and relapse.

ACKNOWLEDGMENTS: Supported by DA11717, MH57483, and DA11026.

The Role of the Amygdala in Learning about Reward

E. A. Murray

Laboratory of Neuropsychology, National Institute of Mental Health, NIH, Bethesda, MD

Neuropsychological studies in nonhuman primates have led to the view that the antygdala plays a critical role in three broad areas of cognition: stimulus memory, stimulus-reward association. and emotion. Recent studies employing selective lesions of the amygdala made with the excitotoxin ibotenic acid suggest a revision of this view. First, stimulus memory functions formerly attributed to the amygdala can now be attributed instead to another, neighboring region within the ventromedial temporal lobe, the rhinal cortex (i.e. entorhinal and perirhinal cortex; Murray, 1996, Sem Neurosci, 8: 13-22). Second, with respect to stimulus-reward association. recent research in rhesus monkeys has demonstrated a double-dissociation of function of the amygdala and the neighboring rhinal cortex. Selective lesions of the amygdala yield significant impairments on a test of reinforcer devaluation. which requires the association of objects with the value of a particular reinforcer, but not on tests of visual discrimination learning for secondary reinforcers (Malkova *et al.,* 1997, J Neurosci. 17: 6011). Conversely, lesions of the rhinal cortex yield deficits on tests of discrimination learning for secondary reinforcers (Baxter. Hadfield and Murray, unpublished data) but fail to disrupt the effects of reinforcer devaluation (Thornton. Malkova and Murray. Behav Neurosci, in press). Taken together, these data suggest that there are two reward mechanisms operating in the medial temporal lobe, one mediated by the amygdala and another by the rhinal cortex. Thus. contrary to the prevailing view. the amygdala is not required for learning whether an object is rewarded or not; however, the amygdala is necessary for associating objects with the values of particular reinforcers. By contrast. the rhinal cortex may represent part of a neocortical system specializcd for object-information proccssing that registers the history of reinforcement of an object. Third, selective amygdala lesions, like larger aspiration lesions, significantly disrupt the emotional responses of' monkeys (Meunier *et al.,* 1996. Soc Neurosci Abstr, 22: 1867), a finding consistent with the idea that the amygdala is critical for eliciting appropriate emotions to environmental stimuli.

ACKNOWLEDGMENT: Supported by the NIMH-IRP.

Comparing Neuronal Responses in the Ventral Striatum to Cocaine and Juice Reward

T. G. Aigner, E. M. Bowman, M. Shidara, and B. J. Richmond

Division of Basic Research, National Institute on Drug Abuse, Rockville, MD

The ventral striatum is considered to be a brain region important for processes related 10 motivation and reward. Indeed, this region may hold the key to providing explanations about how drugs of abuse can come to exert such powerful influences over the behavior of humans and animals. We electrophysiologically recorded from single neurons in various sites in the ventral striatum in rhesus monkeys who had been trained to release their grasp on a bar in a simple cue-reaction time task that required 1, 2, or 3 correct responses to obtain reward. In some cases the reward was orally delivered juice and in some cases the reward was intravenously delivered cocaine (4-16 µg/kg/infusion). On correct, but unrewarded trials the reward apparatus was activated with the delivery valve turned off (sham reward). When the reward was juice and the progress through each of the trials was indicated by a stimulus light that brightened, the animals appeared more motivated as the rewarded trial approached (they responded more quickly and accurately). In addition, neuronal activity coded the state of the cue; i.e. the neurons carried information about how the monkey was progressing through the schedule. When the brightness cue no longer indicated progress, but rather was illuminated randomly with each trial, this differential neuronal activity disappeared, indicating that the monkeys were associating the meaning of the cue. When cocaine was the reward. the neuronal responses were different from those for juice, even though the sensory parameters were the same in both conditions. And, even though the brightness cue indicating progress toward reward was the same for both. the neuronal responses failed to indicate proximity to cocaine reward. The neurons tended to respond similarly to both cocaine and sham rewards. These results suggest that the ventral striatum is important for the planning and persistence in a stepwise behavioral sequence that leads to reward, and that this capability is lost when that reward is cocaine.

SYMPOSIUM IV

ENDOGENOUS CANNABINOIDS: RELEVANCE TO MARIJUANA ABUSE

J. L. Wiley', S. R. Childers[2], R. K. Razdan[3], D. Piomelli[4], and B. R. Martin[1]

[1]Department of Pharmacology and Toxicology, Medical College of Virginia of Virginia Commonwealth University, Richmond, VA; [2] Department of Physiology and Pharmacology, Bowman Gray School of Medicine, Wake Forest University, Winston-Salem, NC; [3]Organix, Inc., Woburn, MA; and [4]The Neurosciences Institute, San Diego, CA

Dr. Childers discussed recent advances in cannabinoid phamacology. Within the last decade, a number of scientific breakthroughs have occurred in the cannabinoid area, including [1] synthesis of a potent and selective binding ligand, CP 55,940; [2] cloning of the brain cannabinoid (CBl) receptor; [3] discovery of an endogenous cannabinoid, arachidonyl ethanolamide (anandamide) in porcine brain; and [4] synthesis of SR 141716A, a selective antagonist of CBl receptors. This symposium focused on recent research with anandamide and selected synthetic analogs and on the relevance of research findings to understanding the neural basis for marijuana abuse and the possible physiological functions of the endogenous cannabinoid system. The cannabinoid CBl receptor has been shown to be a G-coupled protein receptor. Although anandamide differs in chemical structure from prototypic tricyclic and bicyclic cannabinoids and aminoalkylindoles, recent studies have shown that, like these classical cannabinoids, anandamide binds competitively to the cannabinoid CBl receptor and inhibits adenylate cyclase and N-type calcium currents. As might be expected of a short-acting neuromodulatory substance, the metabolism of anandamide differs from that of long-acting natural constituents of the marijuana plant and synthetic analogs.

Dr. Piomelli discussed recent research into the biochemical mechanisms for synthesis, release and inactivation of two endocannabinoids that have been identified in brain and periphery: anandamide and 2-arachidonylglycerol. Anandamide is released from neurons upon demand by an activity- and receptor-dependent mechanism that may involve phosphodiesterase-mediated hydrolysis of the phospholipid precursor, N-arachidonyl phosphatidylethanolamide. Extracellular anandamide may be inactivated by high-affinity uptake into neurons or astrocytes, followed by hydrolysis catalyzed by anandamide amidohydrolase. Uptake is the rate-limiting step in anandamide inactivation, and is selectively blocked by the compound AM404. AM404 effectively protects anandamide from inactivation *in vivo,* and may help reveal the elusive physiological functions of this lipid signaling molecule. 2-Arachidonyl-glycerol is also produced in brain by an activity- and receptor-dependent process. 2-Arachidonylglycerol formation may be mediated by sequential stimulation of PLC and diacylglycerol lipase activities. The mechanisms of 2-arachidonylglycerol inactivation are still unknown, but they may involve uptake into cells and/or hydrolytic cleavage to arachidonate and glycerol. Hence, the endogenous cannabinoid system appears to be composed of two novel arachidonate derivatives with corresponding endogenous mechanisms for release and inactivation of these substances. The unique biological properties of the endocannabinoids suggest that they may play a role in the control of movement, pain and cognition.

Dr. Razdan discussed similarities and differences in the pharmacology and structure-activity relationships (SAR) of the anandamides as compared to the prototypic classical cannabinoid, Δ^9--tetrahydrocannabinol (THC). Given the mechanisms for controlling the amount of endocannabinoids present in the synapse (as examined earlier), exogenously administered anandamide is rapidly degraded. Hence, although anandamide and THC share a similar profile of pharmacological activities, there are some differences, particularly in their time course. Attempts to synthesize unique anandamide analogs which are more stable and less susceptible to degradation by amidases has resulted in a series of anandamide analogs designed to incorporate salient features of the known SAR of THC; e.g., manipulation of the length of the ethanolamide portion of the anandamide molecule compared to manipulation of the length of the lipophilic side chain of THC. Examination of the synthesis and pharmacology of these anandamide analogs reveals an orderly SAR with similarities to that of THC.

Dr. Wiley discussed recent behavioral research with anandamide and its analogs and the relevance of this research to understanding the neural basis of marijuana abuse and dependence. One hypothesis of how marijuana produces its intoxicating effects is that it interacts with brain cannabinoid receptors and mimics the actions of arachidonylethanolamide (anandamide) and/or other endocannabinoids, in a manner similar to the way in which

poppy seed products imitate the actions of endogenous opioids. Drug discrimination is an animal model of the subjective effects of psychoactive drugs in humans. In this procedure, animals are trained to press one of two levers when they receive an injection of THC and to press a second lever when they receive an injection of vehicle or another non-cannabinoid substance. Anandamide and some of its analogs produce THC-like effects in this procedure; however, the cannabimimetic effects of endocannabinoids and most synthetic analogs tend to occur only at high doses that suppress overall responding. In chronic dosing studies, precipitated withdrawal in THC-dependent rats has been induced by injection with SR141716A, but, as yet, precipitated withdrawal has not been demonstrated following chronic dosing with anandamide. In conclusion, although pharmacokinetic factors can explain some of the differences in the pharmacology of anandamide and THC, pharmacodynamic factors may also be operational. Dr. Martin concluded with an overall summary of the current status of cannabinoid research and discussed areas for future research.

ACKNOWLEDGMENTS: Cannabinoid research at Virginia Commonwealth University and Organix, Inc. was supported by NIDA grants DA-03672 (BRM and JLW), DA-09789 (BRM, RKR, JLW). and DA-08904 (RKR).

SYMPOSIUM V

DRUG ABUSE PHARMACOTHERAPY DEVELOPMENT IN THE PRIVATE SECTOR

W. K. Schmidt[2], C. W. Gorodetzky[2], N. L. Teti[3], F. Vocci, Jr.[4], S. A. Grossman[5], and R. S. Mansbach

[1]NorthStar Research & Development, Newark, DE; [2]Hoechst Marion Roussel, Kansas City, MO; [3]The DuPont Merck Pharmaceutical Co., Wilmington, DE; [4]NIDA Medications Development Division, Rockville, MD; [5]Hill & Knowlton, Washington, DC; and Pfizer Central Research, Groton, CT

This symposium was designed to raise issues pertinent to the role of industry in the discovery and development of medications for substance abuse. Although several past symposia and workshops have touched on this issue, the unique challenges and hurdles inhibiting widespread industry involvement have never been fully addressed. Speakers were challenged to address the following issues:

- To what extent does the perception of (un)profitability or stigma play into corporate decisions?
- What is the minimum rate of treatment success that will sustain a product?
- How is such a product marketed?
- What incentives or information would stimulate new programs?

Dr. Schmidt began the symposium with a review of the economics of drug addiction, current products used for alcohol, opioid, and nicotine dependency, and recent advances in developing new products. The experience of bringing addiction medications to FDA approval was discussed by Dr. Gorodetzky and Mr. Teti who intertwined preclinical and clinical data with additional remarks on agency interactions and post-launch experience. The perspective of NIDA was discussed by Dr. Vocci who related how the intramural drug discovery program is modeled on industry principles and how a comfortable collaboration between industry and government has been achieved. Mr. Grossman, a former deputy assistant secretary at HHS, discussed market forces which govern industry involvement in addiction therapy and explored possible legislative developments that may alter perceptions within the private sector toward pharmacotherapy development. Finally, Dr. Mansbach discussed various hurdles that industry faces in developing new products for drug abuse pharmacotherapy and opportunities and action items for accelerating the process. These presentations were intended to highlight the issues which the drug industry faces in developing pharmacotherapeutics for addictive disorders and to stimulate further interest in substance abuse medication development within the pharmaceutical industry.

Schmidt: Introduction, current medications, and recent advances in therapeutics. A recent Institute of Medicine study estimated that the total annual economic cost of drug addiction (illicit drugs, alcohol, nicotine) was $257 billion *(Dispelling the Myths About Addiction,* IOM, 1997). Of this, $53 billion involves to *direct costs* (dominated by nicotine), $134 billion involves *morbidity and mortality costs* (dominated by illicit drugs and nicotine), and $134 billion involves *indirect costs* (e.g. social and property losses, dominated by alcohol). Surprisingly, the greatest overall costs related to addictive disorders involve legal drugs (alcohol, $99 billion, and nicotine, $91 billion) vs. illicit drugs ($67 billion). This places the economic cost of drug addiction ahead of mental disease, diabetes, heart disease, cancer, stroke for the total impact on U.S. society. The prospective patient population is large (11 million heavy drinkers, 61 million current smokers, 13 million illicit drug users during the past month) and is similar in magnitude to the population size for other chronic diseases (diabetes, 16 million; congestive heart failure, 5 million; hypertension, 50 million). Industry statistics show 2.7 million physician visits in 1997 for tobacco, alcohol, and drug-related disorders (National Disease & Therapeutic Index, IMS America, 1997). These statistics should give considerable incentive to the pharmaceutical industry to develop and market new drugs to treat addictive disorders. However, substance abuse pharmacotherapies represent less than 1% of the $94 billion U.S. market (1997) for prescription and OTC drugs with estimated market values of $53 million for alcohol and opioid abuse medications, $700 million for nicotine replacement therapy, $52 million for non-nicotine treatment of tobacco dependence, and $0 for cocaine dependence (no marketed pharmacotherapy). Current therapies involve substitution therapy (oral methadone and LAAM for opioid dependence; nicotine patches, gum, nasal spray for tobacco dependence), pharmacologic antagonism, reward reduction, or anti-craving effects (bupropion for tobacco

dependence; naltrexone for alcohol & opioid dependence), or the pharmacologically-reinforced threat of adverse physiological responses with continued drug usage (disulfiram for alcohol dependence). Newer and more selective therapies may be possible with more recent developments in neurochemistry, neuroanatomy, and molecular biology coupled with a better understanding of social and psychological rehabilitation and comprehensive treatment programs, much as is currently used to treat other chronic medical diseases. While many advanced products in clinical development represent a continuation of previous pharmacological strategies, others are novel (e.g. an mGLUR-II antianxiety medication in phase I development for smoking; GABA and CCK-B related drugs for alcoholism; buprenorphine + naloxone sublingual wafers for opioid dependence; dopamine transport inhibitors, sigma antagonists, and therapeutic vaccines or antisera for cocaine dependence). True innovation is being shared by larger and smaller companies in association with NIDA's Medication Development Division. Much more innovation would result if advances in current or future medical treatment and insurance reimbursement of substance abuse disorders would expand the pharmacotherapy market to more closely represent the impact of substance abuse on the U.S. economy.

Gorodetzky: Nicotine replacement therapy: Lessons learned. This talk reviewed the author's experience over more than 10 years in the development of nicotine replacement medications for the treatment of nicotine dependence. The following lessons were identified, with some general applicability to the area of medications development for treatment of substance abuse:

1. Initial Steps in Transdermal Nicotine, 1986-90
   - Lesson 1 - Ethical and Public Relations Issues Are Not Easy - These issues revolved around the marketing of a drug for the maintenance of dependence (at least initially) and the perceived potential stigma of association with addiction.
   - Lesson 2 - Patent Issues Aren't Easy Either - What might be patentable or enforceable, especially with an older drug marketed for another indication, is not always obvious.
   - Lesson 3 - Multi-company Collaborative Development - Although at times difficult, it can be very beneficial and is often necessary.
2. The Patch Wars, 1990-93
   - Lesson 4 -Labeling Issues - Labeling a replacement medication must account for relative toxicity and potential abuse liability.
   - Lesson 5 - The Power of the Media: DTC Advertising; Unrealistic Expectations; Safety Issues; Supply Problems - The media can be a very powerful force for positive communication, but it can also lead to misunderstanding, confusion and problems. Handle with great care!
3. The Rx/OTC Race, 1993-96
   - Lesson 6 - Thinking Out-of-the-Box: The Naturalistic Trial - Medications development for substance abuse will often require creative thinking, not "development as usual".
   - Lesson 7 - FDA/Industry Partnership - This can be a very effective and important relationship.
   - Lesson 8 - The Public Health - Development of treatments for substance abuse provides unique opportunities to impact both the individual and the public health.

In the development of medications for treatment of drug abuse, there are new and increasing opportunities, unquestionable unmet medical need, and a chance to influence both personal and public health. The industry needs to sharpen its thinking about evaluating potential new therapeutic candidates, perhaps by considering a "benefit x profit" product, as well as a "benefit/risk" ratio.

Teti: Development of naltrexone, the first FDA-approved medication for alcoholism in three decades. Mr. Teti focused on the magnitude of the problem of alcohol addiction in the United States and the associated societal costs of the disease. The 1995 introduction of ReVia™ (naltrexone HCl) was an important breakthrough with the potential to help millions of people. Mr. Teti discussed the clinical effectiveness of ReVia including the reduction of the craving felt for alcohol and increasing abstinence rates. Despite a solid launch for ReVia, including a massive public relations campaign and intense focus on sales and marketing through direct to consumer ads and full sales force details, ReVia sales never fully met market or company expectations. Through market research, it was discovered that the majority of physicians surveyed said they would write ReVia prescriptions if appropriate, but felt they had not had any occasion to. Mr. Teti concluded by saying, "Alcoholism

takes a toll on American society and affects every person in some way. Although ReVia is a small product to our company financially, it is our largest product in terms of the impact it can have on our society."

Vocci: MDD / industry interactions in the search for medications for substance abuse disorders. The National Institute on Drug Abuse formed the Medications Development Division in 1990. The purpose of MDD is to facilitate the development of medications for substance abuse disorders, primarily those associated with increased risk of HIV transmission, namely opiate and cocaine dependence. MDD is organized along the lines of a pharmaceutical development organization and can facilitate projects by consultation and preclinical testing, clinical testing and cooperative development projects on medications of mutual interest. Recently, a market assessment analysis was performed of the potential size of the market for a pharmacotherapy for the treatment of cocaine dependence. Although there are over two million cocaine users in need of treatment, concerns exist regarding the size and uncertainty of the market and reimbursement mechanisms. The analysis showed the possibility of a cocaine dependence pharmacotherapy having peak annual revenues of $200-400 million. Despite the potential size of the market it is believed that additional incentives may be necessary to engage large pharmaceutical firms to work in this area of medications development. Such incentives may involve a guaranteed minimum sales volume, i.e., Federal Government purchase of medications for cocaine dependence treatment, or a legislative approach, i.e., transferable credit of a one year delayed generic approval for a drug of choice in exchange for approval and marketing of a cocaine pharmacotherapy.

Grossman: Policy and market incentives for private sector development of anti-addiction medications. Government policies and regulation strongly influence business investment in the pharmaceutical industry. The long R&D timeframes required for new drug development increase the uncertainty of developing all classes of medications. However, societal interests in promoting research may lead to improved quality of life, a strengthening of the economy, and increased productivity. Drug abuse has a significant and often devastating impact on productivity, health, and social well-being. This provides a compelling justification for providing incentives to encourage development of pharmacotherapies for treating social drug use problems. The Federal Government can provide three types of incentives to stimulate pharmacotherapy research: (a) *ordinary incentives,* e.g. R&D tax credits, CRADAs, patents and trademarks; (b) *upgraded incentives,* e.g. Orphan Drug Act marketing exclusivity, pediatric patent extension; and (c) *extraordinary incentives,* e.g. a one year patent extension on any drug of choice for the company sponsoring innovation of new anti-addiction medications. The latter is justified since there has been a lack of private sector investment in new anti-addiction medications. Factors include: uncertainties about the market size, questions about whether the government and insurance companies will reimburse for anti-addiction medications, no organized constituency for anti-addiction research, complexities of the biological processes involved in drug addiction, ethical and logistical problems with clinical trials, and questions about intellectual property protection. Ordinary incentives have not been enough; most "new" products represent "old" science. Market exclusivity alone may not be a good fit for the anti-addiction market. Thus the enormous potential for societal benefits may justify extraordinary incentives for anti-addiction medications, but the potential for windfalls must also be examined. Extraordinary incentives appropriate for this market are: (a) patent extension on a drug other than the one being encouraged; (b) advanced special purchase agreements with the Federal Government; (c) a significant "bounty" of tax incentives or a cash prize to paid to the first company succeeding in development of a cocaine abuse pharmacotherapy; (d) indemnity protection for clinical research and assumption of patient treatment risk during and after development of new anti-addiction medications. This will require Congressional interest (e.g. through IOM reports or through further development and support for incentives outlined in the Biden bill, S. 2015, New Medications to Treat Addiction Act of 1998). The right policy and market incentives are not yet clear. Further action requires a coalition of efforts to support anti-addiction research and new drug development.

Mansbach: Discussion and comments. It is clear from this symposium that many factors play a role in the prospects for successful drug development for addiction disorders. Historically there have been several daunting hurdles for industry involvement with addiction despite an unquestioned unmet medical need for effective therapies. Among these hurdles are: 1) perceived weakness in the ultimate commercial opportunity of such an enterprise; 2) scheduling and other regulatory issues; 3) resistance on the part of patients and providers to accept addiction as a medical disorder; 4) unrealistic efficacy expectations; 5) the potential need to treat not one, but several aspects of the disorder with different medications; and 6) a reluctance of the pharmaceutical industry to partner with government agencies because of restrictive collaborative agreements.

Despite these challenges, several recent developments have provided hope and opportunity for an enhanced role of corporate research and development in addiction therapy. For example. the appearance of transdermal nicotine as a multi-million dollar product has demonstrated that tremendous underlying demand for a medicinal adjunct accompanies serious attempts at smoking cessation. With the explosion of new insights into the cellular basis of drug dependence and a solid foundation of validated animal models, more opportunity exists now than ever before for de novo, mechanism-based approaches to treatment based on well-defined molecular targets. Further opportunities exist in exploiting the ever-growing pipeline of selective drugs being developed for other CNS disorders. As many compounds under clinical investigation for depression or psychosis are directed at the same neurochemical pathways which influence drug-mediated reward, some of these may also benefit sufferers of addictive disorders, thus bringing added value to a product for which the critical early investments have already been made. Industry also has the option of submitting compounds to the NIDA/MDD testing program, which eliminates the need for establishing labor-intensive screening procedures yet permits companies to maintain confidentiality and proprietary interests.

Further inroads are possible in energizing the corporate community to invest in new addiction therapies. It is imperative that drug discovery scientists and managers be made aware of scientific developments in drug dependence, and reminded of options that exist to test novel agents without exposing the company to undue financial risk. Additional momentum can be gained from clarifying the standards for efficacy that must accompany FDA approval. Finally, creative legislation to establish truly compelling monetary incentives would transform the competitive landscape for addiction therapy, and bring the enormous expertise and resource of the pharmaceutical industry to bear on this serious unmet medical need.

SYMPOSIUM VI

MOTIVATING BEHAVIOR CHANGE AMONG COCAINE ABUSERS THROUGH INTENSIVE CONTINGENCY MANAGEMENT INTERVENTIONS

K. Silverman[1], S. T. Higgins[2], R. A. Rawson[3], J. B. Milby[4], and C. R. Schuster[5]

[1]Johns Hopkins University, Baltimore, MD; [2]University of Vermont, Burlington, VT; [3]Matrix Center, Los Angeles, CA; [4]University of Alabama, Birmingham, AL; and [5]Wayne State University, Detroit, MI

Cocaine abuse continues to have devastating consequences on the U.S. public health. Unfortunately, relatively few treatments have been shown effective in addressing this problem. Among the most fundamental challenges in the treatment of cocaine abuse is identifying methods to motivate users to change their behavior. Contingency management procedures are motivational interventions which have been effective in producing substantial behavior change among cocaine abusers. These interventions arrange for the systematic application of environmental consequences contingent on therapeutically important behaviors. The procedures are ethical, humane, and effective in motivating cocaine abstinence and other therapeutic behavior change among illicit drug abusers. This symposium described contemporary research on the use of intensive contingency-management interventions designed to address the problem of cocaine abuse from four independent research groups. The four presentations in this symposium showed that contingency management procedures can promote cocaine abstinence in a range of populations (primary cocaine dependent patients, cocaine abusing methadone patients, and cocaine abusing homeless adults). Data were also presented showing that a particular type of contingency management intervention, voucher-based reinforcement of cocaine abstinence, can produce long-term effects on cocaine abstinence (i.e., effects that can be detected 1 year after treatment is discontinued); as well as effects that appear superior to another commonly used drug abuse treatment (i.e., Relapse Prevention treatment). Finally, two presentations reported promising data on practical applications of contingency management interventions suggesting that it may be possible to utilize existing public and private financial resources (i.e., housing in ongoing public housing programs or salary for work) in contingency management procedures to promote important behavior change and cocaine abstinence. Overall, the studies showed that contingency management interventions can promote cocaine abstinence in a variety of populations who have been difficult to treat by other means. Novel applications of this technology are under development and may allow for its wide scale application.

Improving Cocaine Abstinence During Outpatient Treatment and One Year of Follow-up with Contingent Reinforcement

S. T. Higgins

During the past eight years our group has been assessing the efficacy of an outpatient behavioral treatment for cocaine dependence that integrates the Community Reinforcement Approach (CRA) with contingency management. The efficacy of this treatment has been supported in four controlled clinical trials conducted in our clinic. This presentation focused on a recent clinical trial that assessed whether contingent incentives reinforce cocaine abstinence in dependent outpatients (N=70), and whether that effect is sustained during one year of follow-up. All patients met DSM III-R criteria for cocaine dependence and received 24 weeks of treatment and one year of follow-up assessments. The treatment provided to all patients combined counseling based on the Community Reinforcement Approach with incentives in the form of vouchers exchangeable for retail items during treatment weeks 1-12 and state lottery tickets during weeks 13-24. In one (contingent group) of two groups, incentives were delivered contingent on cocaine-free urinalysis results, while in the other group (noncontingent group) incentives were delivered independent of urinalysis results. In addition to urinalysis monitoring during treatment, drug use and related areas of functioning were assessed at intake and 6, 9, 12, 15, and 18 months after treatment entry. Significantly more patients in the contingent group than the noncontingent group achieved 10-13 weeks of continuous cocaine abstinence during treatment ($p<05$); percentages of patients who were cocaine abstinent during the latter weeks of treatment were significantly greater in the contingent group than the noncontingent group ($p<.05$); and point prevalence and continuous cocaine abstinence during the one-year follow-up period were significantly greater in the contingent group than the noncontingent group ($p<.05$). Contingent incentives can

directly reinforce sustained cocaine abstinence in dependent outpatients, and this effect remains discernible during the year after treatment termination.

ACKNOWLEDGMENTS: Supported by NIDA grant R01 DA06113 and DA08076.

Relapse Prevention and Contingency Management of Cocaine Abuse in Methadone Patients

R. A. Rawson

Cocaine abuse is a serious and widespread problem in methadone patients. This presentation described a clinical trial that evaluated two promising approaches, relapse prevention (RP) and contingency management (CM), for the treatment of cocaine abuse in methadone maintenance patients. The RP condition consisted of three RP sessions per week for 12 weeks. The CM program involved an identical schedule of clinic visits as the RP condition. The CM procedure established a graduated system of positive reinforcement vouchers delivered to Ss upon achievement of cocaine negative urine samples. The design in this study was a 2x2 (RP by CM). Cocaine abusing methadone patients (N=120) were randomly assigned into one of 4 groups with either a RP procedure (n=30); a CM procedure (n=30); a combination of RP and CM procedure (n=30); or a condition which involved methadone maintenance treatment as usual, with no specific intervention for cocaine abuse (n=30). The study showed that the contingency management procedure significantly increased cocaine abstinence ($p<.01$), whereas relapse prevention failed to produce any significant effects either alone or when combined with contingency management.

ACKNOWLEDGMENT: Supported by NIDA grant R01 DA09419.

Effective Treatment for Homeless Substance Abusers: Contingencies Enhance Outcomes

J. B. Milby

Behavioral day treatment with special interventions for homelessness were described that include transportation to and from shelters, noon meal, abstinence contingent housing, work therapy and low rent housing access. The 1991 research demonstration (Homeless I) day treatment successfully engaged homeless substance abusers and produced positive outcomes of reduced cocaine and alcohol use, increased employment, and improved homeless status in a randomized, controlled trial. Results for alcohol and drug abuse, homelessness and employment showed significant differences favoring day treatment over usual care at 2, 6, and 12 months. In another randomized controlled trial, (Homeless II), both groups received improved day treatment but one additionally received abstinence contingent housing during day treatment and work and housing access used in Homeless I aftercare. Improved contingency management and isolation of abstinence contingent housing effects in Homeless II were described. Results comparing day treatment alone (DT) to day treatment plus (DT+) showed similar significant improvements at the same follow-up intervals from pre to post treatment in homelessness, employment and ASI outcomes, with most trends favoring DT+, but robust differences favoring DT+ in abstinence. Though Homeless II was not designed to determine the role of improved contingency management, since both groups experienced all contingencies except for housing, work and housing access, investigators believe improved contingency management was at least partly responsible for observed outcomes. Implications for future research and development of cost effective treatment for this dysfunctional population were discussed.

ACKNOWLEDGMENT: Supported by NIDA grant R01 DA08475.

A Reinforcement-Based Therapeutic Workplace for Drug Abusers

K. Silverman

Voucher-based reinforcement of drug abstinence has been effective in promoting abstinence from cocaine and from opiates in chronic drug abusers in methadone treatment. Recent research has shown that the efficacy of this intervention can be increased by increasing the magnitude of voucher reinforcement and the duration of the intervention and that increasing the duration of the intervention can prevent relapse, at least as long as the intervention is in effect. However, the need for high magnitude reinforcement and long duration interventions raises a practical problem: How can high magnitude reinforcement and long duration interventions be supported? This presentation described a novel application of this abstinence-reinforcement technology, the Therapeutic Workplace, designed to address this problem. The Therapeutic Workplace involves the integration of abstinence reinforcement contingencies into a model employment setting, using salary that drug abusers earn for work to reinforce drug abstinence. Drug abuse patients are hired and paid to work each day in the Therapeutic Workplace to perform data entry jobs. To link salary to abstinence, participants are required to provide a drug-free urine sample to gain access to the workplace each day; drug abstinent patients then receive a monetary voucher after completing each work-shift. In this way, participants can work and receive voucher-based salary only when they are abstinent from drugs. Patients are also given intensive academic and job skills training. The efficacy of the Therapeutic Workplace intervention was evaluated in heroin and cocaine abusing methadone patients in a treatment program for pregnant and postpartum drug abusing women (N=40). Patients were randomly assigned to a Therapeutic Workplace group or to a no-treatment control group. All patients could receive standard drug abuse treatment during the study. Analysis of urine samples collected 3 times per week during the first 3 months of treatment showed that the Therapeutic Workplace intervention significantly increased patients' longest duration of sustained abstinence from opiates and cocaine (P=.04) and significantly increased the percent of drug-free urines (P=.04). This study demonstrated the feasibility and effectiveness of the Therapeutic Workplace intervention and suggests that employment may serve a valuable role in the treatment of drug abuse as a vehicle for funding, implementing, and sustaining abstinence reinforcement contingencies.

ACKNOWLEDGMENTS: Supported by NIDA grants R01 DA09426.

Discussion: Motivating Behavior Change Among Cocaine Abusers Through Intensive Contingency Management Interventions

C. R. Schuster

The papers presented in this exciting symposium demonstrate that the application of the principles of behavior analysis continue to produce innovative, clinically significant approaches to solving the multiple problems faced by people seeking help for their drug dependence problems. The papers clearly demonstrate the efficacy of vouchers, which are exchangeable for goods and services, as reinforcers for providing drug-free urine specimens. Of great importance is the report by Higgins that the voucher-based intervention group continued to show significantly greater levels of abstinence one year after the end of the intervention in comparison to controls. Thus, although many clients relapse to drug use after abstinence-contingent voucher-based reinforcement is discontinued, many do not. Clearly more research is needed to determine how best to preserve the gains made during the voucher intervention period, but the Higgins report are heartening. Rawson reported. the results of an important study that provided a comparative assessment of the efficacy of the voucher-based abstinence reinforcement intervention relative to another commonly used drug abuse treatment intervention, Relapse Prevention. Although the contingency management intervention significantly increased abstinence, the Relapse Prevention counseling intervention did not appear to affect abstinence, either alone or when combined with contingency management. The comparison to this widely used counseling approach provided striking evidence of the efficacy of the contingency management approach. The reports by Milby and Silverman are heartening in that they point out ways that contingency management procedures can be employed in a manner that may make them adaptable to community drug abuse treatment programs. This technology transfer is essential if these demonstrated efficacious behavioral interventions are going to become available to the drug dependent persons struggling to become drug-free in our community drug abuse treatment programs. These studies show that contingency management interventions hold great promise for

the treatment of drug dependence, but further development of the technology is still needed. We are currently conducting research on the use of vouchers for reinforcing complete abstinence in heroin dependent cocaine abusers. Research volunteers in this study are maintained on buprenorphine, have counseling sessions once weekly and receive vouchers for drug-free urines using the same parameters as described in the Higgins presentation. To date we have been unsuccessful in getting our experimental research volunteers to stop taking both heroin and cocaine in comparison to a yoked control group. We are modifying our approach to these poly-drug abusers such that the requirements for earning a voucher will be sequential to determine whether targeting one drug first and later both drugs will improve the successfulness of this approach. We must continue research designed to adapt the proven contingency management programs to non-research settings and determine how best to insure their wide scale application for problems where research has shown them to be effective and useful. It is also important to recognize the limitations of the voucher based contingency management approach to poly-drug abusers and determine how best to employ it with this group of clients.

SYMPOSIUM VII

MAGNETIC RESONANCE APPLICATIONS IN SUBSTANCE ABUSE

M. J. Kaufman, L. Chang, T. Ernst, D. J. Meyerhoff, P. F. Renshaw, E. A. Stein, and J. Frascella

Harvard Medical School, Belmont, MA; Harbor-UCLA Medical Center, Torrance, CA; University of California San Francisco, San Francisco, CA; Medical College of Wisconsin, Milwaukee, WI; and the National Institute on Drug Abuse, Rockville, MD

Introduction

Magnetic resonance (MR) technology is becoming an important contributor to substance abuse research. Its noninvasive nature, the increased availability of MR scanners. and the development of sophisticated imaging protocols, are facilitating tremendous growth in the number of studies of mechanisms and sequelae of drug abuse.

An Overview of Magnetic Resonance Techniques Used in Substance Abuse Research (Dr. Ernst)

Structural MRI

Magnetic resonance imaging (MRI) measures radio signals from nuclei in a strong magnetic field. Image contrast is dependent on the proton density and two tissue parameters, the relaxation times T_1 and T_2. MRI yields superior soft tissue contrast. High-resolution MR images (morphometry) can be used to detect abnormal brain morphology.

Functional / physiologic MRI techniques

MR Angiography (MRA) generates images of larger blood vessels, and may quantify blood flow or velocity. Most MRA techniques use MRI sequences in which the signal from flowing blood is much brighter than the MRI signal from stationary material. Perfusion MRI measures regional cerebral blood volume and flow. It is usually based on tracking of a bolus of contrast agent (gadolinium) during first pass through the brain. High speed imaging is necessary; typically, the entire brain is scanned every few seconds for a period of 1-2 minutes (using echo planar imaging, EPI). Magnetic resonance spectroscopy (MRS) measures brain chemistry in vivo; proton (^{1}H) MRS and phosphorous (^{31}P) MRS are most commonly used. The major brain metabolites detectable in vivo with ^{1}H MRS are: N-actetyl-aspartate (NA), a neuronal marker; creatine plus phosphocreatine (CR), involved in high energy phosphate metabolism; choline containing compounds (CHO), involved in cell membrane metabolism; and myo-inositol (MI), a glial marker. Also observable are glutamine and glutamine, and, if present, lactate, ethanol, and lipids. The major brain metabolites in ^{31}P MRS are: ATP, phosphocreatine (PCr), and inorganic phosphate (Pi) (involved in high energy phosphate metabolism), and phosphomonoesters (PME) and phosphodiesters (PDE). The tissue pH may also be assessed with ^{31}P MRS. Functional MRI (fMRI) is a tool to study brain activation. Activated brain regions show a local increase in oxygen consumption and perfusion, causing a change in the MRI signal. Activation may be observed during sensory, motor or cognitive tasks, but also by injection of drugs (e.g. cocaine). The difference between images acquired during the activated state and during rest shows which brain regions are activated. A typical fMRI scan for a particular task lasts only a few minutes. However, one of the disadvantages of fMRI is its susceptibility to motion.

Magnetic Resonance Spectroscopy and Functional MRI Studies of Heroin and Cocaine Abusers (Dr. Renshaw)

Recently, transient increases in ^{1}H MRS metabolite resonance intensities have been reported by two independent laboratories following intravenous cocaine administration to humans. Christensen et al. (1996) have noted dose and time dependent increases in the basal ganglia NAA and the Cho resonances. Similarly, Li and colleagues (1998) have observed increases in the NAA/Cr ratio in spectra obtained from the basal ganglia. Further studies will be needed to determine whether these changes reflect increases in the concentration of metabolites or, more likely,

alterations in the relaxation times of these compounds, which are confined to the intracellular space.
Phosphorus (^{31}P) MRS studies of cocaine dependent subjects have demonstrated a characteristic pattern of altered cerebral metabolism, consisting of increased phosphomonoesters (phospholipid precursors) and decreased nucleoside triphosphate (largely adenosine triphosphate) levels. These biochemical alterations are not observed in opiate dependent subjects and are similar to results obtained in studies of animals exposed to repetitive partial ischemia. Based on these observations, we have hypothesized that treatment with CDP-choline may be of therapeutic benefit to stimulant-dependent individuals.

fMRI methods provide a means of observing regional changes in cerebral hemodynamics following focal activation with a temporal resolution of seconds. Recently, cocaine-induced signal changes have been observed in man (Breiter *et al.* 1997). The interpretation of these results is confounded by the fact that cocaine dramatically increases cardiac output, constricts cerebral arteries, elevates hematocrit, and produces restlessness, all of which independently alter image signal intensity. Importantly, it has recently been demonstrated that cocaine and cocaine methiodide (which does not enter the central nervous system) produce similar changes in MR image signal intensity in rats (Zhang *et al.* 1998). As an alternative to drug studies, we have recently demonstrated that fMRI provides a noninvasive means to detect cue-induced changes in cerebral activity (Maas *et al.* 1998; Stein *et al.* 1998), which may be directly relevant to the process of addiction.

Cerebral Metabolite Abnormalities in Cocaine and Methamphetamine Users with HIV (Dr. Chang)

Localized ^{1}H MR spectroscopy allows measurement of the concentration of certain neurochemicals in specified brain regions. Compared to normal subjects, asymptomatic cocaine users (abstinent for more than 6 months) showed significantly elevated total creatine (+7% in the temporoparietal white matter; +6% in the frontal white matter) and elevated myoinositol (+18% in the temporoparietal white matter and 6-12 % in the frontal regions). Decreased N-acetyl compounds (-5.1%; p=0.02) were observed only in the frontal brain regions, especially in the male users.

To study the interaction effects between HIV and drug abuse on brain metabolites and function, we evaluated HIV-infected individuals with a history of cocaine or methamphetamine use and found that they had more severe abnormalities in cerebral metabolites than HIV patients who did not use any illicit drugs. A significant interaction effect between HIV and cocaine use also was observed with functional MRI (fMRI) for a battery of tasks specific for the evaluation of choice reaction time (requiring decision making and working memory).

The Effects of Acute and Chronic Nicotine on Human Brain Activity (Dr. Stein)

Nicotine is one of the most addictive substances in humans. However, little is known about the neuropharmacology and sites of action of nicotine in the human brain. Such knowledge may help in the development of new behavioral and pharmacological therapies to aid in treating nicotine dependence and improve smoking cessation success rates. Functional magnetic resonance imaging (fMRI), a real-tirne imaging technique, was used to examine the acute CNS effects of intravenous nicotine in a population of 16 active cigarette smokers. Three doses of nicotine (0.75, 1.5 and 2.25 mg/70 kg) and saline were each administered IV over a 1 min period in an ascending, cumulative dosing paradigm while whole brain gradient-echo, echo planar images were acquired every 6 seconds during consecutive 20 min. trials on a GE 1.5 Tesla Signa scanner.

Nicotine induced a dose-dependent increase in several behavioral parameters including rush, high and liking. In addition, nicotine induced a dose-dependent increase in neuronal activity in brain regions including the nucleus accumbens, amygdala, cingulate and frontal lobe. These structures are consistent with nicotine's behavioral arousing and reinforcing properties in humans, and have been previously shown to participate in the reinforcing. mood elevating and cognitive properties of other abused drugs including cocaine, amphetamine and opiates, suggesting that nicotine acts similarly in the human brain to produce its reinforcing and dependence properties.

Nicotine produces alterations in mood, and may increase attention and cognitive performance. However the effects on cognitive processing are not well understood. We therefore compared brain activation patterns induced by two cognitive tasks in smokers and age matched control subjects using fMRI. Chronic smokers (mean duration of smoking - 14.5±7.0 years) performed a working memory and a concept formation task while undergoing whole brain FMRI scanning one to two hours after each subject's last smoking episode. There was a decrease in task

performance on the concept formation but not the visuospatial working memory task in the smokers when compared to control subjects. Both tasks produced activation in frontal cortex including dorsolateral prefontal cortex and strong activation in parietal and visual cortical areas. The extent of activation was significantly greater in controls than in smokers in most activated regions. We are now determining the mechanism underlying differences in task activation; specifically whether chronic cigarette smoking alters neuronal activity or vascular responsivity.

Metabolite Abnormalities in Abstinent Drug Abusers Detected with MR Spectroscopic Imaging (Dr. Meyerhoff)

While PET and SPECT studies have implicated cerebral cortical involvement in addiction, almost all magnetic resonance spectroscopy (MRS) studies of the acute and chronic effects of abused substances such as cocaine and/or alcohol on brain metabolites have been limited in their ability to evaluate cortical brain regions. Recent improvements of ^{1}H MR spectroscopic imaging (^{1}H MRSI) methodology have enabled measurement of brain metabolites in brain cortex close to the skull surface without significant "contamination" of spectra with resonances from skull lipids. Two recent brain ^{1}H MRSI studies will be presented: 1) a Point Resolved Spectroscopy (PRESS) ^{1}H MRSI study of 9-months abstinent heavy drinkers compared to light/non-drinking controls; and 2) a multi-slice ^{1}H MRSI study of recently abstinent cocaine-only dependent subjects and of recently abstinent cocaine/alcohol co-dependent subjects compared to controls. These studies show metabolite abnormalities in the brain of abstinent substance abusers that are consistent with neuronal damage in prefrontal cortex and, in some cases, reactive gliosis in the frontal lobe. Metabolite abnormalities were associated with measures of drug use and dependence. Results of MRI segmentation studies show that tissue contribution to the analyzed MRSI voxels is not different between groups, ruling out effects of atrophy on the detected metabolite differences between groups. Metabolite changes in subcortical white and gray matter of chronic substance abusers have been controversial. These prefrontal cortical metabolite changes, however, are consistent with other neuroimaging findings and with the notion of long-lasting cortical involvement in chronic substance abuse.

Cocaine-Induced Cerebral Hemodynamic Changes: Angiography and Functional MRI Studies (Dr. Kaufman)

Cocaine is known to acutely induce cerebral blood flow abnormalities, presumably as a result of its vasoconstrictive properties. Since the brain can be easily damaged by disruptions in blood flow, it is important to develop techniques that can characterize cocaine-induced cerebrovascular changes and determine whether prophylactic medications protect cocaine users from cerebrovascular dysfunction. Magnetic Resonance Angiography (MRA) and Dynamic Susceptibility Contrast MRI (DSC MRI) can be used to evaluate cocaine's acute effects on cerebral hemodynamics.

MRA detects signal from flowing blood and clearly visualizes large cerebral vessels. MRA detects vasoconstriction because at the point of and distal to constriction. blood flow velocity is reduced, thereby causing signal loss. MRA studies of men administered low doses cocaine revealed a high incidence of cerebral vasoconstriction. Moreover, a dose-effect relationship between cocaine and vasoconstriction was detected. This relationship was statistically strengthened when stratified by the amounts of lifetime cocaine use reported by study subjects. This suggests that small cocaine doses are sufficient to induce large cerebral artery vasoconstriction in healthy humans, and that the degree of vessel narrowing may be enhanced in individuals with heavier cocaine use histories.

DSC MRI utilizes intravenous administration of a contrast agent (gadolinium) to detect cerebral hemodynamic changes. When gadolinium enters a tissue, it disrupts the local magnetic field in proportion to its concentration. Using high speed echo planar imaging, it is possible to visualize the transit of gadolinium through brain blood vessels, and with tracer kinetics to calculate cerebral blood volume (CBV). In studies conducted in men administered cocaine, CBV was reduced by 20% compared to baseline, indicating vasoconstriction. In women, a smaller reduction in CBV was noted (-13%) than found in men, with no CBV reduction found during the follicular menstrual cycle phase. This suggests that gonadal steroid hormones may modulate the vasoconstrictive effect of cocaine. These gender differences are consistent with prior studies documenting that in subjects with comparable chronic cocaine abuse histories, women develop fewer SPECT perfusion defects than men.

Summary and Comments (Dr. Frascella)

The study of the clinical neurobiology of substance abuse and addiction is advancing rapidly by the rich array of MR methods. Several aspects of brain structure and function are now possible, and afford new insights into underlying neural mechanisms altered by drugs of abuse. For example, important research using MRS is emerging on how cerebral metabolites are altered by cocaine, methamphetamine, and alcohol; these changes also are being assessed in drug abusers with and without HIV. Similar to recent craving studies using PET, fMRI is being used successfully to detect cue-elicited changes in brain activity. In addition to determining acute effects of drugs such as nicotine, cocaine and alcohol, brain changes following chronic exposure are being investigated with MR techniques. These changes are being effectively associated with neurobehavioral outcomes, such as mood and cognitive performance. Furthermore, brain changes are now being studied following extended periods of abstinence, and this work will have tremendous implications for treatment. Finally, MRA has shown for the first time in humans the direct effects of cocaine on the cerebral vasculature, and importantly, how vasoconstriction is enhanced in individuals with heavy cocaine histories, thus rendering these individuals more vulnerable to the vascular damage. In sum, neuroimaging techniques, particularly those employing MR technology, hold enormous promise for elucidating how drugs of abuse and the addiction process alter human central nervous system anatomy and processing. The challenge remains to reveal how these changes, in turn, affect human behavior.

References are available from senior author upon request.

ACKNOWLEDGMENTS: Supported by NIH grants DA00280, DA00329, DA08365, DA09448, DA09465. DA10214, MH51358, and AA10788.

SYMPOSIUM VIII

THE DRUG EVALUATION COMMITTEE OF THE CPDD: HISTORY AND CURRENT STATUS

^C. P. France, *L. S. Harris, **A. E. Jacobson, [#]J. H. Woods, and [§]W. L. Woolverton

^Louisiana State University Medical Center, New Orleans, LA; *Medical College of Virginia of Virginia Commonwealth University, Richmond, VA; **NIDDK, National Institutes of Health, Bethesda, MD; [#]University of Michigan, Ann Arbor, MI; and [§]University of Mississippi Medical Center, Jackson, MS

Since its origin as the Committee on Problems of Drug Dependence of the National Academy of Sciences, abuse potential testing of novel compounds has been a major function of CPDD. Most recently, this effort has been fulfilled by a group of laboratories (University of Michigan, Medical College of Virginia of Virginia Commonwealth University, University of Mississippi Medical Center, Louisiana State University Medical Center) known as the Drug Evaluation Committee (DEC). DEC laboratories have established programs for evaluating the abuse potential of opioids, stimulants and depressants. Compounds are submitted by academia, industry and government. The program includes in vivo assays of reinforcing and discriminative stimulus effects in non-human primates, as well as their capacity to establish and maintain physical dependence of the opioid or depressant type. *In vitro* assays to help establish mechanism of action complement in vivo assays. The data are used to predict abuse potential of novel compounds and are available to the scientific community, as well as to national and international agencies involved in the regulation of drugs of abuse. In the symposium, members of the DEC elaborated on the history, scientific and regulatory role, and current research of the DEC.

The History of the Drug Evaluation Committee

A. E. Jacobson

DEC is sponsored by the CPDD. We act as honest brokers, determining abuse potential and physical dependence potential of analgesics, stimulants, and depressants for pharmaceutical industry, governmental organizations, and university researchers. DEC's precursors have been part of CPDD since CPDD's inception in 1929 as a committee of the National Research Council, National Academy of Sciences (NRC, NAS). In the beginning, drug evaluation was the quintessence of CPDD. The 1929 NRC, NAS committee was established to study narcotics in animals and man, and did so by determining appropriate pharmacological assays and attempting to synthesize non-dependence-producing analgesics. The chemistry was assigned to Dr. Lyndon Small and his colleagues at the University of Virginia. A year later, pharmacological work began under Dr. Nathan Eddy at the University of Michigan. The clinical work, under Dr. Clifton Himmelsbach, began in 1934. Small and Eddy moved to NIH in the 1940's; the contemporary Laboratory of Medicinal Chemistry in NIDDK, NIH, can trace its history to their groups. NIDA's intramural research program can, in some measure, trace its history back to Himmelsbach's Clinical organization. The University of Michigan's pharmacology group has continued, as modified by Dr. J. Woods, and DEC expanded its pharmacology efforts in 1973, adding a group at Virginia Commonwealth University under the direction of Drs. L. Harris and M. Aceto. By 1951, Small's group had prepared hundreds of new compounds, and many of them were evaluated at the University of Michigan under the direction of Dr. M. Seevers. Single dose suppression and primary physical dependence techniques were explored in monkeys at Michigan, and Eddy established a mouse hot-plate antinociceptive assay at NIH. Initially, the DEC only offered antinociceptive and physical dependence evaluation of analgesics. Current procedures for are summarized by Woods, and by Woolverton (see below). DEC work is published in refereed journals, in the NIDA Monograph, and on-line in the CPDD's home page on the web (http://views.vcu.edu/cpdd/), under the "Drug Evaluation Committee" heading. DEC started as a function of an NRC, NAS committee and was committed to scientific investigation of opioids. We have evolved into a multi-university consortium of researchers who perform a public service function, free of charge, and conduct double-blind assays with well-established protocols to obtain essential data on several classes of drugs potentially subject to abuse; the CPDD can take great pride in this accomplishment.

Identification and characterization of novel opioids

J. H. Woods, G. Winger, and J. R. Traynor

The opioid drug evaluation unit for the DEC includes Drs. Woods, Winger, and Traynor, at the University of Michigan, and Drs. Harris, Aceto, May, Bowman, and Beardsley at the Medical College of Virginia, Virginia Commonwealth University. At the present time, in vitro assays consist of opioid receptor binding at various membrane preparations including monkey brain homogenates and opioid receptor clone preparations. *In vivo* mouse analgesia assays include heart induced tail-withdrawal measures and writhing assays; both agonist and antagonist actions are assayed in these preparations. In the rat, physical dependence studies are carried out using continuous infusion techniques. In the normal rhesus monkey drugs are evaluated for their analgesic, discriminative and reinforcing stimulus, and respiratory effects. Observational measures of drug effects are made as well in the monkey. In the morphine-dependent monkey, observational procedures allow the assessment of drug-induced suppression or precipitation of the morphine withdrawal syndrome; occasionally, primary physical dependence studies are carried out in the monkey. The findings that are associated with these assays are reported each year in the annual reports from the participating institutions. Over 1700 compounds are a part of the data base with significant information available on a variety of opioid agonists and antagonists that act a mu, kappa, and delta opioid receptors. A variety of other pharmacological agents have, as well, been described by the group.

Recently obtained data on novel opioid agonists and antagonists including include reports on zipeprol (Aceto et al., 1996) and mirfentanil, a fentanyl analog with a complex mode of action (France *et al.,* 1992). The current set of procedures can classify the vast majority of drugs that are submitted to the DEC and allows the assessment of abuse liability of submitted compounds. These procedures also provide a rich set of biological data for the identification of novel opioid actions. Current research interests of the group include assessing potential therapeutic alternatives to those currently available for opioid abuse and identification of compounds with selective actions as analgesics, such as compounds that act selectively in the peripheral nervous system.

Abuse potential assessment of stimulants and depressants: Evaluation of congeners of ephedrine

W. L. Woolverton and G. Winger

William L. Woolverton discussed the stimulant/depressant program of the DEC, and its recent evaluation of ephedrine and its congeners. The Stimulant/Depressant program began in the mid-1980's with the goal of assessing the abuse potential of stimulants and depressants. The intention was to expand the drug testing of CPDD to include these important classes of abused drugs. The four laboratories and assays are: 1) Harris, locomotor activity in rodents; 2) Winger, i.v. self-administration by rhesus monkeys; 3) Woolverton, discriminative stimulus effects in rhesus monkeys; 4) France, physical dependence potential in rhesus monkeys. Most recently, the Stimulant/Depressant group has studied the congeners of ephedrine [(±) ephedrine, (-) ephedrine, (+) ephedrine, (+) pseudoephedrine, and (-) pseudoephedrine]. Interest in these compounds has come from the WHO, DEA and the FDA. The WHO is considering international controls on these compounds. The DEA is concerned that these compounds are being used as starting materials in the synthesis of methamphetamine. The FDA is concerned that they are added to various consumer products.

In the self-administration assay, monkeys were maintained on twice-a-day sessions of self-administration of cocaine or saline (FR 30 schedule, 10-minute time-out). When responding was stable, test doses of all compounds were made available in single sessions. All compounds except (-) pseudoephedrine functioned as positive reinforcers at doses between 0.1 and 1.0 mg/kg/inj. (-) Pseudoephedrine was tested up to a dose of 1.0 mg/kg/inj. Higher doses could not be tested because of solubility limitations. In the drug discrimination assay, monkeys were trained in a discrete-trials procedure (FR5, 30 trials/day, 30 seconds between trials, shock avoidance) to discriminate either 1.0 mg/kg *d*-amphetamine, or 10 mg/kg pentobarbital, from saline. All compounds partially substituted for the training dose of *d*-amphetamine at doses between 3.0 and 30 mg/kg, given intragastrically. The data were characterized by substantial variability. both across doses within a subject, and across subjects tested at the same dose. The most consistent amphetamine-like effects were seen with (±) ephedrine and (-) ephedrine. There was no drug-appropriate responding at any dose in any pentobarbital-trained monkey. Taken together, these data suggest

that the congeners of ephedrine may have some abuse potential in there own right, perhaps involving partial *d*-amphetamine-like subjective effects.

Changing methodologies for the study of physical dependence

C. P. France and L. R. Gerak

To the extent that discriminative stimulus effects in non-humans are predict subjective effects in humans, drug discrimination procedures can be used to examine and anticipate subjective states including those associated with chronic drug administration or with termination of drug administration. By the late 1970s it was clear that drug discrimination procedures were particularly efficient for studying psychoactive drugs and procedures were developed for studying antagonists in agonist-treated subjects (Gellert and Holtzman, 1979) under conditions that appeared to be relevant to the dependence potential of drugs.

The behavioral manifestations of opioid withdrawal in rhesus monkeys are very similar to those that emerge in humans, making the monkey a especially appropriate species for dependence studies. Beginning with the 1989 Annual Report from the University of Michigan drug evaluation program (Woods *et al.,* 1990), compounds submitted to the DEC have also been studied for their discriminative stimulus effects in morphine-treated rhesus monkeys that discriminate naltrexone. The discriminative stimulus effects of naltrexone in morphine-treated monkeys have the same properties as the withdrawal-precipitating effects of opioid antagonists under other conditions: dose- and time-dependent, pharmacologically selective, stereoselective, and correlated with other indices of withdrawal (France and Woods, 1989). There also is a time-related onset of discriminative effect that correlates with the onset of withdrawal and the discrimination is based on a centrally-mediated drug effect. Substitution studies evaluate whether an unknown compound substitutes for naltrexone and, therefore, whether it is likely to precipitate withdrawal under other conditions. Other studies, that are conceptually related to single-dose substitution studies, evaluate a test compounds in monkeys that are acutely deprived of morphine and, therefore, determine whether it is likely to reverse withdrawal under other conditions. Given the utility of discrimination procedures for studying opioid dependence and withdrawal, a parallel set of procedures was developed for studying dependence and withdrawal for benzodiazepines and related drugs. Like the naltrexone discriminative stimulus in morphine-treated monkeys, the flumazenil stimulus in diazepam-treated monkeys is qualitatively similar to the withdrawal-precipitating effects of flumazenil under other conditions. For the past 2 years compounds submitted to the DEC have been studied for their discriminative stimulus effects in separate groups of monkeys that are: treated with diazepam and discriminate flumazenil; or, not otherwise treated and discriminate between vehicle and midazolam or triazolam (France *et al.,* 1998). The development of antagonist discriminations in agonist treated monkeys has provided yet another approach for assessing compounds submitted to the DEC under conditions that appear to be predictive of subjective effects in humans.

The role of the Drug Evaluation Committee in national and international drug policy

L. S. Harris and M. D. Aceto

Louis S. Harris discussed the development of laws and regulations covering abused drugs, both domestically and internationally, and the College's (CPDD) interaction with the agencies enforcing the laws. It was noted that, until the enactment of the Comprehensive Drug Abuse Control Act of 1970, all domestic regulations were tax laws and governed by the Treasury Department. The 1970 act and the later 1984 Emergency Scheduling Act placed control in the Department of Justice. The international regulation of drugs of abuse began shortly after the first world war under the direction of the League of Nations. The program was reconstituted by the United Nations after the second world war. An Expert Committee on Drugs Liable to Produce Addiction (later the Expert Committee on Drug Dependence, ECDD) was created under the WHO and had its first meeting in 1949.

The CPDD and its DEC have been and continue to be heavily involved in these regulations both nationally and internationally. For instance, Dr. Nathan Eddy, CPDD's long time Executive Director, was either the Chair or Rapporteur of the WHO Expert Committee for its first 17 meetings. Since then the DEC has been continually

that the congeners of ephedrine may have some abuse potential in there own right, perhaps involving partial *d*-amphetamine-like subjectivc effects.

Changing methodologies for the study of physical dependence

C. P. France and L. R. Gerak

To the extent that discriminative stimulus effects in non-humans are predict subjective effects in humans. drug discrimination procedures can be used to examine and anticipate subjective states including those associated with chronic drug administration or with termination of drug administration. By the late 1970s, it was clear that drug discrimination procedures were particularly efficient for studying psychoactive drugs and procedures were developed for studying antagonists in agonist-treated subjects (Gellert and Holtzman, 1979) under conditions that appeared to be relevant to the dependence potential of drugs.

The behavioral manifestations of opioid withdrawal in rhesus monkeys are very similar to those that emerge in humans, making the monkey a especially appropriate species for dependence studies. Beginning with the 1989 Annual Report from the University of Michigan drug evaluation program (Woods *et al.,* 1990). compounds submitted to the DEC have also been studied for their discriminative stimulus effects in morphine-treated rhesus monkeys that discriminate naltrexone. The discriminative stimulus effects of naltrexone in morphine-treated monkeys have the same properties as the withdrawal-precipitating effects of opioid antagonists under other conditions: dose- and time-dependent, pharmacologically selective, stereoselectivc, and correlated with other indices of withdrawal (France and Woods, 1989). There also is a time-related onset of discriminative effect that correlates with the onset of withdrawal and the discrimination is based on a centrally-mediated drug effect. Substitution studies evaluate whether an unknown compound substitutes for naltrexone and. therefore, whether it is likely to precipitate withdrawal under other conditions. Other studies, that are conceptually related to single-dose substitution studies, evaluate a test compounds in monkeys that are acutely deprived of morphine and, therefore, determine whether it is likely to reverse withdrawal under other conditions. Given the utility of discrimination procedures for studying opioid dependence and withdrawal, a parallel set of procedures was developed for studying dependence and withdrawal for benzodiazepines and related drugs. Like the naltrexone discriminative stimulus in morphine-treated monkeys, the flumazenil stimulus in diazepam-treated monkeys is qualitatively similar to the withdrawal-precipitating effects of flumazenil under other conditions. For the past 2 years compounds submitted to the DEC have been studied for their discriminative stimulus effects in separate groups of monkeys that are: treated with diazepam and discriminate flumazenil; or, not otherwise treated and discriminate between vehicle and midazolam or triazolam (France *et al.,* 1998). The development of antagonist discriminations in agonist treated monkeys has provided yet another approach for assessing compounds submitted to the DEC under conditions that appear to be predictive of subjective effects in humans.

The role of the Drug Evaluation Committee in national and international drug policy

L. S. Harris and M. D. Aceto

Louis S. Harris discussed the development of laws and regulations covering abused drugs, both domestically and internationally, and the College's (CPDD) interaction with the agencies enforcing the laws. It was noted that, until the enactment of the Comprehensive Drug Abuse Control Act of 1970, all domestic regulations were tax laws and governed by the Treasury Department. The 1970 act and the later 1984 Emergency Scheduling Act placed control in the Department of Justice. The international regulation of drugs of abuse began shortly after the first world war under the direction of the League of Nations. The program was reconstituted by the United Nations after the second world war. An Expert Committee on Drugs Liable to Produce Addiction (later the Expert Committee on Drug Dependence, ECDD) was created under the WHO and had its first meeting in 1949.

The CPDD and its DEC have been and continue to be heavily involved in these regulations both nationally and internationally. For instance, Dr. Nathan Eddy, CPDD's long time Executive Director, was either the Chair or Rapporteur of the WHO Expert Committee for its first 17 meetings. Since then the DEC has been continually

represented at the ECDD and CPDD is currently a WHO Collaborating Center. With the enactment of the 1961, U.N. Convention on Narcotic Drugs, Drs. Eddy and Seevers recommended the use of a variety of animal and human test procedures, developed by CPDD, as the standard for the determining the abuse potential of drugs. This recommendation was adopted. CPDD also played an essential role in the design and enactment of the U.S. Comprehensive Drug Control Act and its counterpart, the International 1971 Convention on Psychotropic Substances, which have insured a role for scientific input into scheduling decisions. Since the late 1960s the DEC has provided abuse potential data on opioids, stimulants, depressants, and hallucinogens which have been vital in control decisions both nationally and internationally as exemplified by our ongoing collaboration with the DEA in connection with their emergency scheduling of drugs. The law allows the DEA to schedule drugs on an emergency basis but requires them to provide scientific data to substantiate the abuse potential of the scheduled agent. The DEC has provided this information in an expeditious and comprehensive manner and no scheduling decision that was based on DEC data has been overturned.

REFERENCES

Aceto MD, Bowman E, Butelman E, English JA, Harris L, Jacobson, AE, Mattson MV, Medzihradsky F, Patrick G, Rowlett, JK, Smith CB, Winger G, Woods, JH, and Woolverton, WL. Drug Alc Depend 42, 93- 104, 1996.

France CP, Winger G, Seggel MR, Rice KC, and Woods, J.H. Psychopharmacology 109, 291-291, 1992

France CP and Woods JH. J Pharmacol Exp Ther 250, 937-943, 1989.

France CP, Gerak LR, Rowlett JK, Woolverton WL, Winger G, and Woods JH. In LS Harris (Ed.), *Proceedings, Conmittee on Problems of Drug Dependence* (NIDA Monograph #178, pp. 429-439. Washington D.C.: U.S. Government Printing Office, 1998.

Gellert VF and Holtzman SG. J Pharmacol Exp Ther 211:596-605, 1979.

Woods JH, Medzihradsky F, Smith CB, Winger GD, and France CP. In LS Harris (Ed.), *Proceedings, Committee on Problems of Drug Dependence* (NIDA #105, pp. 682-724). Washington D.C.: U.S. Government Printing Office, 1990.

SYMPOSIUM XI

"AGONIST"-TYPE APPROACHES TO THE TREATMENT OF COCAINE DEPENDENCE

J. D. Roache*, M. J. Kuhar**, J. R. Glowa[§]', J. Grabowski[#], F. Levin, S. M. Evans, H. D. Kleber, and S. L. Walsh[•]

***Substance Abuse Research Center, University of Texas - Houston HSC; **Yerkes Regional Primate Center, Atlanta, GA; [§]Louisiana State University, Shreveport, LA; [#]Substance Abuse Medications Development Center, University of Texas - Houston HSC; Columbia University and NY State Psychiatric Institute and [•]Behavioral Pharmacology Research Unit, Johns Hopkins University**

Cocaine abuse and dependence have proven refractory to treatment and no single medication has been shown to be particularly effective. Because of the success of substitution therapy with other drug dependencies, stimulant drugs including dopamine agonists and uptake inhibitors must be examined as potential treatment agents. Pre-clinical animal models of cocaine reinforcement have suggested the efficacy of such agents to decrease drug intake in humans. However, the substitution approach for cocaine has been controversial. The concerns are multiple and involve a determination of the extent to which stimulant medication: 1) can safely or adequately "substitute" for cocaine; 2) will increase cocaine craving and drug use through "priming"; 3) will itself have too high of an abuse potential; and/or 4) will potentiate cocaine's abuse liability or cardiovascular toxicity. While several studies have taken specific neurochemical/neuropharmacoiogical approaches to the treatment of cocaine dependence, we accept a broader conceptualization of stimulant dependence which includes possible behavioral mechanisms for medication efficacy. This concept includes the idea that stimulants may substitute for cocaine sufficiently to reinforce treatment participation and facilitate cocaine abstinence. A compromise is sought between the risks, benefits, and effects of therapeutic regimen compared to the abused drug.

Phenyltropanes as Substitute Agonists for Cocaine Abuse

M. Kuhar

We and our collaborators have been examining phenyltropane analogs of cocaine. Many of them have properties thought important in substitute medications; these include high potency and selectivity, long duration of action. and slow entry into the brain. RTI-113, prototype of these compounds, reduces cocaine self administration when injected prior to the self administration session. These findings show that these compounds hold promise as medications for psychostimulant abusers. Our group is also studying a novel peptide neurotransmittcr, CART peptide, which is highly concentrated in the nucleus accumbens shell. This peptide may be a modulator of psychostimulants and these studies could lead to new strategies and new compounds as medications.

ACKNOWLEDGMENT: Supported by RR00165, OND6069, and DA10732.

Agonist Pretreatment Effects on Self-Administration

J. R. Glowa

A selective dopamine reuptake inhibitor, GBR 12909, has been shown to decrease cocaine-maintained fixed-ratio (FR) responding in rhesus monkeys at doses which do not decrease food-maintained behavior. These effects were sustained with repeated administration, and formulating GBR 12909 into a decanoate extended the effect for almost thirty days with a single injection. We obtained similar effects with phentermine, continuous infusions of cocaine and carbomethoxy-fluorophenyltropane (CFT). There are two issues relevant to these effects. The first has to do with the nature of the behavior affected by drug treatment. Studies in which the FR value, unit dose, or both have been manipulated prior to treatment with GBR 12909 tend to support the idea that behaviors maintained by more

efficacious reinforcers are more resistant to pretreatment effects. The second has to do with the nature of the drug effect. Recently we have been using progressive ratio (PR) schedules to identify food magnitudes and cocaine unit doses that maintain similar break points prior to assessing phentermine's effects on those baselines. Under a range of conditions, i.m. phentermine decreased responding maintained by either event to a comparable degree although slow infusions of phentermine were more effective in decreasing cocaine-maintained PR performance. Further work is needed to determine whether the route of administration (or rate of drug onset) is a critical variable in selectively decreasing cocaine reinforcement. Lastly, several reports indicate that dopamine agonists increase cocaine-maintained responding under PR schedules in rodents, but not monkeys. Although we replicated increased break points under PR schedules of food delivery in rodents, we have found that those increases diminish with repeated exposures. Thus, there may be species differences and/or experiential effects influencing the response to pretreatment.

ACKNOWLEDGMENT: Supported by DA09820.

Human Laboratory Safety Evaluations in Cocaine-Dependent Patients

J. D. Roache

We have conducted several human laboratory studies to address the safety and abuse potential of using stimulant agents to treat cocaine dependence. Three studies administered prescribed doses of methylphenidate or dextroamphetamine to cocaine dependent outpatients enrolled in a double-blind clinical trial. Compared to placebo, methylphenidate (20 mg sustained release, b.i.d.) increased heart rate and dysphoric subjective mood. A substudy administered up to 60 mg immediate release methylphenidate and showed a similar profile of effects. Methylphenidate did not increase cocaine craving or subjective euphoria and none of the cardiovascular effects were of clinical concern. Placebo, 15, and 30 mg of dextroamphetamine also have been tested in cocaine-dependent outpatients in the human laboratory. Still blinded interim analyses show evidence of increased blood pressure, heart rate, positive subjective mood, and cocaine craving. Two studies have combined doses of oral dextroamphetamine (0, 15, and 30 mg, p.o.) administered one-hour before cocaine (4, 48, and 96 mg, i.n.) in non-treatment seeking cocaine abusers. The results show dose-related effects of the two drugs given alone; however, the drug combination has not resulted in significant potentiation on cardiovascular measures or subjective ratings of cocaine craving or abuse potential. Our conclusions are that stimulant medications with mild positive mood or reinforcing effects can be safely administered to cocaine abusing or dependent populations. Whether or not this has therapeutic efficacy will probably depend upon the behavioral and psychotherapeutic environment of an outpatient treatment program.

ACKNOWLEDGMENT: Supported by DA09262 (JG).

Double-Blind Trials of "Agonist" Medication for Cocaine Dependence

J. Grabowski

An initial double-blind clinical trial with methylphenidate was equivocal, but there was no evidence of harm or increased cocaine use (priming) from medication administration. Two ongoing studies examine d-amphetamine sustained release. One study includes subjects with primary cocaine dependence and the other includes subjects who also are opiate dependent. For both studies, subjects are stabilized at 0, 15, or 30 mg for 1 month, then doses are doubled to 30 or 60 mg, with the opiate dependent patients also receiving 1.1 mg/kg of methadone. Distinct differences are emerging across the three dosing groups. A third study with a variant on the incremental design, stabilizes subjects on desoxyamphetamine for one month and then stringent contingencies for cocaine free urine screens are applied. Here the comparison is both of therapy condition and alternative amphetamine analogs. In a final placebo-controlled study, we are examining the combination of l-dopa/carbidopa for cocaine dependence. Recent analyses show clear beneficial effects of l-dopa/carbidopa.

Favorable profiles for replacement should include greater 'positive' effect compared to unpleasant side effects and slow onset and long duration of action. Combination with behavioral interventions may be important since the

dominant effect of simple replacement (as with methadone) may be treatment retention and reductions in stimulant use, but no change in other drug abuse. A combination, or sequence of medications, as initially proposed for opiate dependence by Goldstein, may be the most successful pharmacological strategy for stimulant dependence. The data support cautious, systematic and creative approaches for evaluating candidates in an efficient manner. The metric for effective replacement is enhanced retention and maintenance of 'treatment oriented behavior' as well as dose-dependent reductions in use of the previously abused stimulant. Concerns about abuse liability and "priming" with agonist pretreatment are not any more applicable to this analysis than they are for opiate or nicotine substitution.

ACKNOWLEDGMENT: Supported by DA09262.

Methylphenidate Treatment for Cocaine Abusers with Adult Attention-Defict/Hyperactivity Disorder

F. R. Levin, S. M. Evans, and H. D. Kleber

One factor that may contribute to poor outcome is the presence of comorbid disorders. To effectively treat cocaine abusers. clinicians may need to identify and tailor therapeutic interventions for subpopulations of patients, such as those with Attention-deficit/Hyperactivity Disorder (ADHD). Using a structured clinical interview, 281 cocaine abusers seeking treatment were assessed for childhood and adult ADHD. We found that the rate of adult ADHD (10%). or the combined rate of adult ADHD and subthreshold ADHD (15%), was higher amongst cocaine users than expected from population estimates. This suggests that psychostimulants used in the treatment of childhood ADHD, could be effective for a subpopulation of cocaine users with ADHD. We recently completed a laboratory study in which cocaine abusers with adult ADHD were maintained on placebo, or one of two doses of sustained-release MPH (40 and 60 mg/day). While maintained on placebo or methylphenidate, subjects were given repeated doses of placebo, and cocaine (16 or 48 mg/70 kg). Although cocaine produced larger increases in systolic and diastolic blood pressure when subjects were maintained on MPH, these increases were not clinically significant. In addition, we recently completed a single-blind treatment trial of sustained-release MPH in 10 cocaine abusers with adult ADHD. Our results showed that treatments of up to 80 mg/day were medically safe and there was no evidence of abuse or increased cocaine use. Instead, patients had a significant reduction in ADHD symptoms and cocaine use.

The choice of whether to use a stimulant as a treatment for dually-diagnosed populations is difficult and needs to be predicated on clinical judgment. If stimulant prescription is chosen, there are several ways to monitor medication use and limit the potential for abuse. These include: 1) limiting the number of pills dispensed; 2) keeping a log of the pills prescribed; 3) having frequent patient contact to review whether the medication is beneficial as well as to assess the possibility of misuse or abuse; 4) documenting improvement, preferably by using established instruments (e.g., the Adult Behavior Checklist); 5) periodically doing random urine toxicology tests; 6) stressing to the patient that the medication needs to be safeguarded; and 7) providing medication in the context of family support and monitoring. If there is no substantial change in cocaine use, then the clinician may need to discontinue medication and refer the patient for a more intensive, treatment. Although the foregoing emphasis has been on pharmacological interventions, simply providing medication without other treatment interventions is unlikely to change ingrained drug-taking behavior.

Discussion

S. L. Walsh

Three pharmacological mechanisms are believed to contribute to the efficacy of agonist substitution therapies in other drug dependence disorders. These include: 1) suppression of withdrawal; 2) substitution or satiation; and 3) the development of tolerance or cross-tolerance to the drug of abuse. Withdrawal from cocaine causes short-lived elevations in anxiety and depression which may be alleviated by an agonist substitution treatment; although no clinical data have yet shown the efficacy of this approach. Preclinical studies suggest that a variety of dopamine "agonists" can reduce cocaine self-administration, presumably by satiating or substituting for its reinforcing effects; and one exciting clinical trial suggests possible benefits in humans. Chronic treatment with psychostimulants could lead to either sensitization or tolerance, depending upon the specific dosing conditions employed. Since it is

SPECIAL SYMPOSIUM

BRAIN IMAGING IN DEVELOPMENT OF MEDICATIONS FOR DRUG ABUSE

Use of PET to Design Dosage Regimens

D. F. Wong

Department of Radiology, Johns Hopkins Medical Institutions, Johns Hopkins University, Baltimore, MD

Since the advent of neuroreceptor imaging using positron emission tomography (PET) and single photon emission tomography (SPECT) In the early 1980s, these techniques have been intimately intertwined with drugs developed by the pharmaceutical industry. Historically the first radioligands to be labeled for external imaging by PET or were predominantly drugs such as dopaminergic neuroleptics that already have been proven to be effective in vitro as a neuroscience tool as well as in vivo in some therapeutic sense. These specific molecules such as spiperone and raclopride and carfentanil, were considered suitable candidates for external imaging because of then well known properties. However, all of these compounds were developed primarily by the pharmaceutical industry with the intention of therapeutic use. In the following presentation the ways in which this technique can speed drug development as illustrated. There are at least four key areas where neuroreceptor PET/SPECT imaging can assist in drug development. These include measurement of drug biodistribution, rational drug dosing, mechanism of action, and therapeutic rationale.

Magnetic Resonance Spectroscopy Studies in Drug Development

P. F. Renshaw, M. J. Kaufman, J. D. Christensen, D. A. Yurgelun-Todd, S. E. Lukas*, and B. M. Cohen

Brain Imaging Center and Behavioral Psychopharmacology Research Laboratory, McLean Hospital, Belmont, MA, and Consolidated Department of Psychiatry, Harvard Medical School, Boston, MA

Magnetic resonance spectroscopy (MRS) employs standard magnetic resonance imaging devices to make measurements of chemical levels within the brain. MRS-visible compounds which can be measured non-invasively in human brain include psychotropic medications, such as lithium (Renshaw and Wicklund 1988) and some fluorinated polycyclic drugs (Komoroski *et al.* 1991; Renshaw *et al.* 1992), as well as endogenous cerebral metabolites. Two different MRS-visible nuclei are evaluated in most studies of brain biochemistry: phosphorus (31P) and hydrogen (1H).

Phosphorus MR spectra provide information on the concentration of high energy phosphate compounds (e.g., phosphocreatine adenosine triphosphate, etc.) and phospholipid metabolites (phosphomonoesters and phosphodiesters). The clinical utility of MRS has not yet been established, but the technical capability to perform studies is now available on most commercial scanners. In practice, the major limitation in the use of MRS is the low sensitivity of the technique, which in turn leads to poor spatial resolution (1- 10 cm3 for proton MRS and 25-150 cm3 for phosphorus MRS at 1.5 T) (Moore and Renshaw 1997).

Although the potential that MRS studies have for advancing our understanding of psychiatric and substance abuse disorders has recently been reviewed (Kaufman *et al.* 1996; Moore and Renshaw 1997; Soares *et al.* 1996; Yurgelun-Todd *et al.* 1996), in vivo MRS has not been used extensively for psychotropic drug development, despite the fact that clinical testing represents the single most expensive step in the process. In this paper, we highlight two early instances in which MRS was of value in the characterization of drug effects in the human central nervous system. In the first example, fluorine-19 (19F) MRS was used to quantitate brain levels of dexfenfluramine and norfenfluramine in primates and in humans (Christensen et al. 1998; Christensen *et al.* 1995). In the second instance, phosphorus-31 (31P) MRS was used to identify a characteristic pattern of altered brain biochemistry in heavy cocaine users (Christensen *et al.* 1996). In turn, this information was used to identify CDP-choline as a candidate treatment for stimulant dependence (Renshaw *et al.* this volume).

ACKNOWLEDGMENTS: This work was supported by NIDA grants 09448, 03996, and 00343.

Overview of Requirements for Development of Medications for Addictive Disorders

F. J. Vocci

Medications Development Division, National Institute on Drug Abuse, National Institutes of Health, Rockville, MD

Medications developed for addictive disorders must pass the rigorous safety and efficacy standards of the Food and Drug Administration to obtain marketing approval. In addition to the clinical requirements, medications must also be satisfactorily characterized for chemical synthesis quality, purity, stability, manufacturing controls, toxicology, and pharmacokinetics. The mission of the Medications Development Division (MDD), NIDA is to facilitate the development and marketing of medications to treat psychomotor stimulant dependence and opiate dependence.
Nuclear imaging techniques have not previously been used to assist the development of medications for these indications but could be helpful in several ways. These techniques have previously been used for hypothesis generation studies in rodents, primates, and human subjects- It is now conceivable to track changes in receptor and neuronal systems with positron emission tomography (PET) in animal species and to a lesser extent, in human subjects. Such work can lead to an increased understanding of dynamic changes in brain structures as a function of drug exposure and suggest new alternatives for therapeutic intervention. Nuclear imaging techniques can also be used to characterize the rate and extent of binding of: I) drugs of abuse; and 2) new ligands to central receptor sites. An example of the former situation would involve characterization of the rate and extent of binding of cocaine to the dopamine transporter and its possible alteration by peripheral blocking antagonist agents. In the latter situation, PET studies could document binding kinetics of putative dopamine transporter medications with the following profile: slow onset, long acting, produces less robust effects on dopamine levels than drugs of abuse. Such medications could be useful in the treatment of both cocaine and methamphetamine dependence although their long duration of action would necessitate careful characterization of dose-plasma level relationships. Further, the relationships between plasma pharmacokinetics and rate and extent of binding to a central site can be used to set dosing levels in human studies. Such a strategy could minimize toxicity and assist in setting dose and dosing regimen recommendations for clinical trials.

Imaging the Underlying Cerebral Pathology in Drug Abuse

E. D. London and S. Grant

Brain Imaging Center, National Institute on Drug Abuse, Baltimore, MD

The rational design of medications for the addictive disorders requires knowledge of the neurobiological pathology that contributes to compulsive drug seeking and self-administration. Contemporary noninvasive in vivo brain imaging techniques provide the opportunity to elucidate the relevant information in human subjects.

One current therapeutic approach involves the development of medications that interfere with the rewarding effects of abused drugs, as measured in animal models of addiction. It was hoped that elucidating the mechanisms by which the drugs produced reward/reinforcement in the human brain would aid in the development of new strategies for treatment of the addictive disorders. Another focuses on medications that mimic some of the effects of abused drugs but with lower abuse potential. Therefore. early studies that applied nuclear medicine imaging techniques to questions related to addiction focused on the cerebral responses to acute effects of abused drugs.

As addictions involve chronic disorders of brain function, and are characterized by relapse, a detailed understanding of the nature and distribution of metabolic. neurochemical and structural abnormalities in the brain of the drug abuser could be even more helpful in guiding the design of new therapeutic agents. For this reason. more recent research in this area has centered more on the fact that substance abusers suffer persistent persistent in brain function. and that these defects, whether or not they result from drug self-administration. could represent important therapeutic targets. This paper reviews some recent work relating to cerebral functional and structural abnormalities in drug abusers, with a view toward how elucidating such abnormalities might contribute to the pathology of addiction.

Micropet: A Dedicated PET Scanner for Small Animal Studies

S. R. Cherry, A. Chatziioannou, Y. Shao, T Farfuhar, R. W. Silverman, K. Meadors, and M. E. Phelps

Crump Institute for Biological Imaging, University of California Los Angeles, School of Medicine, Los Angeles, CA

MicroPET is a very high resolution positron emission tomography (PET) scanner developed at UCLA over the past four years and designed specifically for animal imaging The motivation for microPET was to permit repeat. non-invasive studies of biological parameters in viva particularly for experimental protocols which require a longitudinal design. Examples could include studies of metabolic brain development, measuring the long term biochemical effects of drugs of abuse or monitoring recovery following brain injury with and without therapeutic intervention. The overall goal of the project was to develop a PET scanner with significantly better performance for imaging small volumes and at a fraction of the cost of state-of-the-art clinical PET scanners such as the Siemens/CTI EXACT HR+ or the GE Advance.

MicroPET became fully operational in the summer of 1997 and has a wide range of capabilities including rapid dynamic studies and multi-bed studies, on-line randoms correction, corrections for attenuation, scatter, deadtime and detector efficiency, a computer controlled bed and laser alignment system. In terms of performance, microPET is able to resolve volumes as small as 6 μL (1.8 mm spatial resolution in all directions) and has an absolute sensitivity of up to 200 cps/,μCi. The volumetric resolution is fully one order of magnitude better than the best of the clinical PET scanners. The images from microPET have also been determined to be fully quantitative so that image counts can be related to the concentration of the radiolabeled tracer present in the tissues of interest.

MicroPET has been used in a range of animal models, including mice, rats, rabbits and small non-human primates. Over 150 studies have now been successfully completed on this prototype system using a variety of tracers such as [F18]fluorodeoxyglucose (FDG), 1F-181fluoroethylspiperone (FESP) and [C-11]WIN35,428 (WIN). Limitations of the current system include the small axial field of view and the limited sensitivity, both of which can be improved by adding more detectors to the system. A new research microPET is now belong developed at UCLA which addresses these limitations and attempts to push the resolution of PET imaging in small animals closer to the limits imposed by positron range and noncolinearity.

Development of New Imaging Agents for Positron Emission Tomography: Applications in Studies of Drug Abuse

Y. S. Ding, J. Fowler, and N. D. Volkow

Chemistry Departments, Brookhaven National Laboratory, Upton, New York

Positron emission tomography (PET) is a medical imaging method which uses radiotracers labeled with short-lived positron emitting isotopes, such as carbon-11 (half life is 20 min.), to track biochemical transformations, changes brought about by disease, as well as the movement of the drugs in the living human and animal body. PET has found increased application in the study of drugs affecting the brain, including drug pharmacokinetics (using a positron emitter labeled drug) and drug pharmacodynamics (using a labeled tracer). We have developed a new ligand for studying the dopamine system in human brain. Examples of the use of PET to study drug pharmacokinetics and pharmacodynamics with a special emphasis on its use to evaluate parameters that cannot be obtained any other way will be provided. These applications will be illustrated by two examples: 1) studies comparing the two enantiomers of methylphenidate (MP, Ritalin), a psychostimulant drug which is marketed as the racemic mixture; and 2) studies that measure the efficacy of cocaine and MP for blockade of the dopamine transporter. Comparative studies of enantiomerically pure [^{11}C]*d-threo*-MP and [^{11}C]*d-threo*-MP in both baboon and human brain demonstrate high specific to nonspecific binding, selectivity for dopamine transporters (DAT) and reversibility of [^{11}C]*d-threo*-MP MP as compared to mostly non-specific binding of [^{11}C]*d-threo*-MP. These PET studies along with microdialysis studies strongly indicate that pharmacological specificity of MP resides entirely in the *d-threo* isomer, supporting the further evaluation of using a single enantiomer *(d-threo-MP)* instead of racemic MP as the commercial drug form. These studies also demonstrate that PET imaging is an ideal way to examine the behavior of a chiral drug in the human brain, and is a valuable tool in drug development. Studies that measure the efficacy of cocaine for blockade of the DAT allow us to better understand the reinforcing ability of psychostimulant drugs. The comparative studies of oral MP and intravenous cocaine highlight the importance that route of administration and

hence rate of brain uptake have on the reinforcing effects. Application of multiple tracer strategy to investigate the relationship between brain glucose metabolism and the different elements of the dopaminc (DA) system in drug abuse, normal aging and in neurodegenerative diseases provides a powerful tool to probe various brain functions.

ACKNOWLEDGMENTS: Much of this work was carried out at Brookhaven National Laboratory under contract DE-AC02-98CH10886 with the U. S. Department of Energy and supported by its Office of Biological and Environmental Research. This work was also supported by NIH (NIDA and National Institute on Neurological Diseases and Stroke).

Cocaine Induced Brainstem and Subcortical Activity Observed Through FMRI

H. Breiter[1,2], R. Gollub[2], W. Edminster[1], T. Talavage[1], N. Makris[1], D. Kennedy[1], J. MelcherI, H. Kantor[1], I. Elman[2], D. Gatfriend[2], J. Riorden[2], T. Campbell, M. Foley[1], S. Hyman[3], R. Weiskoff[1], and B. Rosen[1]

[1]Massachusetts General Hospital (MGH)-Neuroradiology Magnetic Resonance Center, Charlestown, MA; [2]Department of Psychiatry, MGH, Boston, MA; and [3]Office of the Director, National Institutes of Mental Health, Bethesda, MD

Cocaine is one of the most reinforcing drugs know, both in humans and in animals (Johanson and Fischman 1989). Based on extensive investigations of rodent and primate modlels, the mesoaccumbens dopamine pathway. extending from the ventral tegmentum of the midbrain (VT) to the nucleus accumbens has been identified as a critical substrate of the reinforcing effects of cocaine (Koob 1996). Other regions such as the basal forebrain (Arvanitogiannis *et al.* 1996) and the amygdala (Everitt *et al.* 1991) have also been significantly implicated in reinforcement reward. We started two separate functional magnetic resonance imaging (fMRI) experiments to investigate a) subcortical circuitry mediating cocaine-induced euphoria and craving, and b) brainstem regions concurrently activated with subcortical reward circuitry. The first project sought to determine whether regions such as the VT. nucleus accumbens (NAc/SCC: nucleus accumbens plus subcallosal cortex given current fMRI spatial resolution). amygdala and basal forebrain would show short-term cocaine-induced signal changes, and thus correlate with ratings of euphoria. and whether or not any regions would show more long-term signal changes and potentially correlate with craving ratings. In the second study. we utilized cardiac gating with a clustered volume acquisition (CVA) (Edmister and Talvage submitted) to compensate for brainstem motion so we could evaluate brainstem monoaminergic nucleus function relative to reward circuitry function. We specifically sought to determine if repeated activation would be observed in the VT. and whether activation would occur in the vicinity of other brainstem monoaminerpic nucleus (for serotonin and norepinephrine) such as the raphe nuclei (dorsal raphe = RPd. median raphe = RPm) and the locus coeruleus (LC).

ACKNOWLEDGMENTS: This work was supported by NIDA DA09467-05, DA00265-04, DA00275-04 and NARSAD.

Love at First Sight: SPECT Imaging of Dopamine Release Following Amphetamine Challenge in Healthy Volunteers

M. Laruelle, L. Kegeles, and A. Abi-Dargham

Brain Imaging Division, New York State Psychiatric Institute, Department of Psychiatry, Columbia University, New York, NY

Cocaine-seeking behavior results principally from the positive reinforcing effects of cocaine (i.e., the desire to experience the pleasure provided by the drug), rather than from a desire to postpone the distress of a withdrawal symptom (negative reinforcement). Considerable preclinical literature support that, in rodents, positive reinforcing effects of cocaine are mediated by the mesolimbic dopamine systems, but the relevance of these preclinical data to humans remains to be firmly established. We present here a novel brain imaging technique to measure dopamine transmission in humans. The increase in dopaminc levels induced by psychostimulants like amphetamine or cocaine is associated with a decrease in the number of available D2 receptors. This change in D2 receptor

availability can be measured with SPECT and [123I]IBZM or PET and [11C]raclopride. We and others have demonstrated that the decrease in D2 receptors availability measured with SPECT or PET is linearly related to the magnitude of dopamine release elicited by the challenge. We used this new paradigm to study dopamine release following a single low dose amphetamine (0.3 mg/kg) in 13 healthy volunteers, never previously exposed to psychostimulants. These studies revealed 1) a remarkable heterogeneity in the subjective response and in DA release elicited by the challenge; 2) a significant correlation between the magnitude of DA release and the positive reinforcement effects perceived by the subjects. In a subset of the sample (n = 6), the experiment was repeated after two weeks. The repeated experiment demonstrated that both subjective and biochemical responses to amphetamine were very stable across subjects, suggesting that these responses constitute a trait of the individual, maybe under genetic control. To the extent that positive reinforcement experienced during the initial exposure plays a role in the development of addiction, these data suggest that the responsivitity of the DA system to the initial challenge mediates the pleasure provided by the drug and the desire to experience again the encounter. Everything else being equal, subjects with high dopamine release following psychostimulants might be at greater risk to develop addiction compared to subjects with low dopaminergic response.

Neuroimaging and Clinical Trials for Drug Development

R. Frank

Sanofi Pharmaceuticals, Malvern, PA

Neuroimaging is finding wide application in clinical trials for drug development. Given the competitive advantage these data represent, the results have been treated as proprietary by the sponsors. Over the next couple years, the breadth and scope of this work will become more widely known and the efficiency of drug development will increase as a result of wider application of these cutting-edge technologies and innovative protocol designs. Indeed, the potential yield from neuroimaging will increase as the validation data are published and the regulatory authorities recognize their value within a dossier. These clinical data make a logical bridge between the pre-clinical biomarkers used to select drug candidates for clinical development and the efficacy parameters used to define labeling for newly approved drugs.

The advent of mechanistic drug discovery, accompanied by the necessary technology for repeated, non-invasive assessment of drug effect, has catapulted humanity from the realm of superstition and serendipity into the green pastures of ethical and rational clinical investigation of mechanisms of action and efficacies of innovative compounds. Regarding drug abuse, the benefit of sooner and more rational drug development accrues not only to the individual patient, but also to society as a whole. This liberating effect of neuroimaging is evident in the expanded list of surrogates for efficacy, as well as increasing monitoring of potential toxic effects, the threat of which might otherwise have precluded ethical conduct of the proposed clinical study.

The National Institute on Drug Abuse (NIDA) will play an ever-expanding role in the development of therapies for treatment of drug abuse. It's parent, the National Institutes of Health, recently issued a request for proposals to develop tracers which could be used in studies of drug abuse, among other therapeutic applications. NIDA also has attracted top investigators, such as Dr. Edythe D. London, and have worked with ONDCP by making critical investments in such technology as an on-site cyclotron and PET scanner. Already they have contributed to the knowledge base for, and will continue in conceptual development of drug development strategies for treatment of illicit drug abuse. The leadership role being played by NIDA is further evident today in their hosting of this satellite symposium in conjunction with the College on Problems in Drug Dependence.

At the recent Medeval Symposium "Early Clinical CNS Drug Development: The Role of Neuroimaging" in Manchester, England, the other speakers and I were asked by Professor Guy Goodwin, University of Oxford, to endorse the one technology each of us considered most useful for clinical pharmacology in the new millennium. The answer to this question is, of course, very important as a guide to investment. The answer, however, is that the technology must be chosen according to the matter at hand, and no single neuroimaging technique will make us omniscient. The efficiency in investment will come from public-private partnerships and the merger of companies currently developing such diverse products as animal feeds and pharmaceuticals. Efficiencies will come not by

wagering on a single new machine. but by strategically aligning technologies for the biological and chemical processes common to a range of product lines. The technology presented today, along with the incredible energy and creativity of the presenters and their colleagues, will justify the necessary investment by facilitating logical drug development decision-making.

It is beyond the scope of this brief summary, and outside the boundaries of confidentiality, to discuss the drug candidates being studied by these techniques. However, the paradigms currently being validated for clinical studies of therapies for drug abuse will have certain and wide application in the pharmaceutical industry.

ORAL COMMUNICATIONS I

ENDOMORPHIN 1 AND ENDOMORPHIN 2 ARE IMMUNOSUPPRESSIVE

T. K. Eisenstein*, J. J. Meissler, Jr.*, E. B. Geller, T. J. Rogers*, and M. W. Adler

Departments of *Microbiology and Immunology, and Pharmacology, Temple University School of Medicine, Philadelphia, PA

Endomorphin 1 and endomorphin 2 are newly identified endogenous tetrapeptide ligands for the μ opioid receptor (Zadina *et al.,* 1997, Nature 386:499). We have previously shown that morphine added *in vitro* suppresses the capacity of murine spleen cell cultures to mount a secondary antibody response to sheep red blood cells. Titration of morphine showed maximal suppression (50% of control values) at doses of 10^{-6} to 10^{-9} M. Suppressive activity waned by 10^{-11} M. In the present experiments, endomorphin 1 and endomorphin 2 were tested for immunosuppressive activity. It was found that both tetrapeptides, when added to mouse spleen cells harvested from SRBC-primed mice, suppressed the secondary *in vitro* antibody response. However, the dose response curves were different from that of morphine. Endomorphin 1 and endomorphin 2 induced little or no suppression at doses of 10^{-7} to 10^{-9} M and maximal suppression (50%) was found at 10^{-13} to 10^{-15} M. Suppressive activity of the endomorphins waned by 10^{-17} M. Dose response curves of both tetrapeptides were nearly identical. Naloxone (10^{-6}M) and CTAP (10^{-6} M) were unable to inhibit immunosuppression induced by these peptides, whereas they both inhibited the effect of morphine on immune responses.

ACKNOWLEDGMENT: Supported by NIDA grant DA06650.

DIMINISHED CYTOKINE IL-6 RESPONSE IN MEN AND WOMEN AFTER I.V. COCAINE ADMINISTRATION

J. H. Halpern, J. H. Mendelson, J. Glowacki*, M. B. Sholar, A. Lesieur-Brooks*, A. J. Siegel, and A. L. Pesok

Alcohol and Drug Abuse Research Center, McLean Hospital–Harvard Medical School (HMS), Belmont, MA and *Brigham & Women's Hospital–HMS, Boston, MA

Increased rate of infections, including HIV, has been associated with cocaine use. Preclinical and cellular models have found immunomodulatory effects from cocaine exposure, thus promoting the hypothesis that cocaine induces abnormalities of immunity. In particular, cytokines are involved in the communication process among immunocompetent cells to strike a complex balance of cellular and humoral immune responses to antigen challenges. Eighteen healthy adult men and women who met DSM-IV criteria for cocaine abuse (matched for age, weight, and body mass index) provided informed consent for participation in studies of neuroendoctine and immunologic responses to intravenous cocaine or saline placebo. After saline or 0.4 mg/kg of cocaine was i.v. injected over 1 minute to semi supine subjects, blood samples were collected from the opposite arm at 2, 4, 12, 16, 20, 30, 40, 60, 80, 120, 180, and 240 min. Peak cocaine, ACTH, and cortisol levels occurred at 8, 8, and 40 min. respectively, and no significant gender differences were found except for women having a higher cocaine level at 2 min. Catheter-induced intravascular inflammation caused an increase in the level of cytokine interleukin-6 (IL-6) over time, but this response was significantly blunted when comparing the mean change from pre-cocaine values to 240 min for those given cocaine versus placebo [3.87 ± 0.50 vs 12.94 ± 5.62 pg/ml (p= 0.02)]. There were no gender differences in this IL-6 suppression or in monitored cardiovascular response. Since cocaine produces a significant stimulation of the hypothalamic-pituitary-adrenal axis, suppression of IL-6 process for risk of infectious disease will be discussed.

ACKNOWLEDGMENTS: Supported in part by NIDA grants P50-DA04059, K05-DA00064, KO5-DA00101, and T32-DA-7252.

EXPOSURE TO THE ABUSED INHALANT, ISOBUTYL NITRITE, ENHANCES TUMOR GROWTH *IN VIVO*

L. S. F. Soderberg

Department of Microbiology and Immunology, University of Arkansas for Medical Sciences, Little Rock, AR

Kaposi's sarcoma is more prevalent among male homosexuals than other AIDS demographic groups and has been correlated with a history of nitrite inhalant abuse. To evaluate the effects of inhalant exposure on tumor growth, we used a mouse tumor model. C57BL/6 mice were injected in the right flank with syngeneic PYB6 tumor cells, 2.5 x 10^3 cells/mouse. Starting 6 days after tumor injection, groups of 14 mice were exposed to 0 or 900 ppm isobutyl nitrite for 45 min/day in an inhalation chamber. Tumor incidence was significantly increased from 21 % in control mice to 75% ($p<0.05$) in the nitrite exposed mice. In addition, the mean tumor weight increased 4-fold faster ($p<0.005$) in nitrite treated mice. When the initiation of nitrite dosing was delayed until the day of first tumor appearance (day 13), the tumor burden still increased faster than it did in control mice ($p<0.02$). Exposure of tumor cells to isobutyl nitrite *in vitro* did not enhance cell growth, suggesting that suppression of immunity was responsible for the increased tumor growth. Inhalation exposure to isobutyl nitrite inhibited the induction of cytotoxic T cells and peritoneal exudate macrophage tumoricidal activity.

ACKNOWLEDGMENT: Supported by NIDA grant DA-06662.

OPIOID MODULATION OF HIV-1 REPLICATION AND CHEMOKINE EXPRESSION

M. A. Wetzel*, T. K. Eisenstein*, M. W. Adler, E. E. Henderson*, and T. J. Rogers*

Departments of *Microbiology and Immunology, and Pharmacology, Temple University School of Medicine, Philadelphia, PA

A correlation between HIV-l infection and intravenous opioid abuse has been established, but the drugs' role in HIV-l-induced disease progression is still uncertain. The current practice of administering opioids as analgesics for treatment of pain in HIV-l infected individuals and the high risk of HIV infection associated with intravenous drug use suggest the importance of investigating the potential interaction between opioids and HIV-f-infected cells. Currently, our laboratory is working on identifying the mechanism by which opioids modulate HIV-1 replication, and whether opioids act by modulating the expression of chemokines and their receptors. The use of selective opioid antagonists permits the identification of specific opioid receptors involved in the modulation of HIV replication, measured by reverse transcriptase assay, P24 ELISA, and syncytia counts. Secondly, our laboratory is examining the effects of opioids on the expression of the critical chemokines and chemokine receptors during HIV-1 infection, measured by RNase protection assay. Preliminary data suggest that opioid administration and HIV-1 infection modulate chemokine and chemokine receptor mRNA levels. The overall objective of this research is to determine how opioids exert their effect on HIV-l replication and whether the chemokines and chemokine receptors are modulated during infection following opioid administration.

ACKNOWLEDGMENTS: Supported by NIDA grants DA06650 and DA11130, as well as NCI grant R55CA/OD75909-01.

OPIATE-INDUCED EFFECTS ON VIRAL REPLICATION, IMMUNE STATUS AND PHYSIOPATHOLOGY: OBSERVATIONS IN THE FELINE MODEL OF AIDS

S. J. Henriksen, S. Huitrón-Reséndiz, M. C. Barr, J. N. Billaud, V. Hampton, F. E. Bloom, J. H. Elder†, and T. R. Phillips

Departments of Neuropharmacol./Mol. Biol.†, The Scripps Research Institute, La Jolla, CA

The precise interaction of opiates with the human immunodeficiency virus (HIV), is not known. However, it has been proposed that intravenously administered opiates may accelerate or otherwise alter the disease course elicited by the virus by suppressing immune responses and/or by enhancing virus replication. We have previously reported that an infectious molecular clone of the feline immunodeficiency virus (FIV-PPR) causes sensory and motor neurological pathology and sleep alterations in the infected cats. These changes are comparable to the early neurological deficits observed in HIV-1 positive patients. Our recent findings in the animal model also demonstrate that morphine enhances FIV replication nearly 10-fold, in vitro. These data further validate the FIV/cat system as a valuable new model to study opiate effects on functional pathogenesis. In a new cohort of 16 cats we have investigated, *in vivo,* whether chronic, intermittent morphine treatment (given intermittently on two successive days/week) will alter the immune status and/or neurological measures in four experimental groups: 1. FIV-alone (N=4); 2. Morphine 2 mg/kg, alone (N=4); 3. Morphine and FIV-inoculation, (N=4), and; 4. Saline i.m.(N=4). Monthly assessment of T cell CD4/CD8 numbers, mitogen stimulated proliferative responses and sensory evoked responses were made. Data presented will focus on the time-course of changes of these parameters with respect to the opiate injection paradigm.

ACKNOWLEDGMENTS: Supported by grants DA-10198 (TRP) and MH-47680 (FEB).

SUBSTANCE ABUSE AND INFECTIOUS DISEASES IN A SOUP KITCHEN POPULATION

S. Magma, P. Nwakeze, A. Rosenblum, H. Joseph*, H. Saadat**, and R. Morales

National Development and Research Institutes, New York, NY; *NYS Office of Alcoholism and Substance Abuse Services; and **St. John's Bread and Life Program

Objective: To study substance abuse and infectious diseases among guests in an inner-city meal program ("soup kitchen"). Methods: Separate random samples of 100 adult males and 119 adult females were interviewed concerning past and current drug use; received serum tests for HIV antibody, hepatitis B and syphilis exposures; and provided scalp hair for radioimmunoassay tests for cocaine and opiates. Results: Sample was 72% black, 23% Hispanic, 5% white/other; mean age=39 yrs, homeless/unstable residence in past year (59%). Infectious disease rates were: HIV+ (16%); syphilis (14%), hepatitis B (21%). Of those HIV+, 71% were unaware of their serostatus. Self-reported drug use in the past 30 days - cocaine/crack (49%), heroin/opiates (13%) - was lower than results of hair testing - cocaine (87%), opiates (24%). Only 26% of guests reported current enrollment in any drug abuse treatment program. Among guests testing positive for drugs, hair concentrations were: mean cocaine - 407ng/10mg of hair; mean opiates 22ng/10mg. In multivariate analysis, unstable living arrangements were associated with being HIV+ and Hep-B+. Conclusion: Almost all guests at the soup kitchen were using cocaine/crack. Although drug use was very high, current enrollment in drug abuse treatment was relatively low. Most HIV+ guests were unaware of their serostatus. There is a need for an effective outreach effort that would help soup kitchen guests utilize drug abuse treatment, HIV counseling/testing and housing assistance.

ACKNOWLEDGMENT: Supported by NIDA grant R01 DA10188.

SUBSTANCE ABUSE AND INFECTIOUS DISEASE AMONG HOMELESS CLIENTS OF A MEDICAL VAN

A. Rosenblum, L. Nuttbrock, H. McQuistion, J. DelValle*, S. Magura, H. Joseph**, and M. Marthol*

National Development and Research Institutes, Inc., New York, NY; *Project Renewal, NY, NY; and **New York State Office of Addiction and Substance Abuse Services, NY, NY

Introduction: Preliminary data are reported on biological data for substance abuse and infectious diseases among 128 clients of a mobile medical van for the homeless in New York City. **Method & Results:** Majority of respondents were male (68%) and non-white (black 63%; Hispanic 16%), averaging 40 years of age; 20% reported ever having injected. 80% reported one or more days homeless in the past month. Based on radioimmunoassay of hair, 75% and 17% of the clients used cocaine and opiates, respectively, during the last 90 days. Saliva (for HIV) and blood (for all other diseases) test results were: HIV antibodies 16%; hepatitis C (HCV) antibodies 30%: any hepatitis B marker 53%; syphilis exposure 14% (by the rapid plasma reagin test). Abnormal liver function was routinely observed (23%). Among 87 subjects who followed with a PPD protocol, 39% were PPD positive. All subjects were provided pre- and post-test HIV counseling. Lifetime injection history was associated with hepatitis B (83%) and C (78%). After controlling for injection, hepatitis C was shown to be positively associated ($p < .05$) with cocaine concentrations in hair (collapsed into quartiles) and age. **Conclusion:** These findings strongly implicate injection history and to a lessor extent, cocaine use in the etiology of hepatitis-C among the homeless and highlight the need for effective outreach and intervention strategies.

ACKNOWLEDGMENT: Supported by NIDA grant RO1 DA10431.

TUBERCULOSIS SCREENING AT ENTRY TO DRUG DETOXIFICATION

N. Salomon, D. C. Perlman, P. Friedmann, and C. Eber

Beth Israel Medical Center, New York, NY

Objective: Describe outcomes of tuberculosis (TB) screening for new entrants to a drug detoxification (detox) program. **Methods:** A random sample of detox patients received PPD and anergy skin testing, a chest radiograph (CXR), and a questionnaire including a query of TB related symptoms. CXRs were reviewed by a single radiologist blinded to PPD & clinical status and classified according to the presence of specified TB-related features and to an overall radiographic impression of the likelihood of latent or active TB. **Results:** Between 9/95-9/97, of 735 persons with CXR, PPD and questionnaire data, 73% were mate, 44% black, 40% Hispanic, 14% white, 2% other; mean age 38 years (range 20-73). 70% injected drugs, 81% inhaled drugs. 21% were HIV+, 63% HIV-, 16% HIV unknown. PPD reactions: 15% $\geq$ 10mm, 78% PPD-, 7% HIV+/anergic. 12% reported cough, 1% hemoptysis for $\geq$ 3 weeks; 8% ,10%, 37% reported fever, nights sweats and weight loss respectively. 46% reported $\geq$1 symptom and 5% (3 symptoms. Specific CXR findings were: 1% granuloma, 0.3% apical pleural thickening, 4% fibrosis. 1% consolidation, 0.6% reticulonodular patterns, 0.7% adenopathy, 0.8% other. 21 (3%) were graded as having a CXR impression of possible TB. TB-related CXR abnormalities were more frequent in those with $\geq$3 weeks of cough (35% vs 10%) or fever/chills (19% vs 7%), both $p < .001$. Only 4/394 (1%) of those with no symptoms had CXR impression of possible TB vs. 15/339 (4%) with $\geq$1 symptoms ($p < .004$). 3/54 (6%) HIV+ anergic persons, 2/42 (5%) HIV- anergic persons, 2/109 (2%) PPD+ persons, and 7/530 (1%) of PPD- persons had a CXR impression of TB. HIV+ anergic persons had CXR impression of possible more frequently than PPD- persons ($p = 0.056$). **Conclusions:** In an area with a high prevalence of HIV and TB, the frequency of potentially TB-related CXR abnormalities identified at admission to detox is low, particularly among those with no TB-related symptoms. This suggests that if symptom status can be assessed at entrance, for TB purposes routine CXRs could be restricted to those with symptoms, reactive PPDs, or HIV-related anergy.

ORAL COMMUNICATIONS II

ANTISOCIAL PERSONALITY DISORDER AND TREATMENT OUTCOME IN OPIOID DEPENDENT OUTPATIENTS

M. Kidorf, R. K. Brooner, V. L. King, and K. Stoller

Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD

The present study examined the impact of antisocial personality disorder (APD) on the drug use and treatment retention of 259 male opioid dependent outpatients receiving methadone maintenance. Patients completed the Structured Interview for the DSM III-R (SCID) at month 1 and the Addiction Severity Index at months 1 and 12, and were followed for one year of treatment. Patients received daily methadone dosing, and individual and group counseling. Urine specimens were tested randomly 1 - 4 times per month. APD patients (n = 87) reported a more substantial history of drug use and psychosocial problems prior to treatment, and were more likely to be diagnosed with a current Axis I psychiatric disorder, than non-APD patients (n = 172). They also exhibited higher rates of cocaine (0.43 vs. 0.33; $\underline{p} < .01$) and "any" positive urine specimens (0.55 vs. 0.47; $\underline{p} < .05$) and reported more legal problems during treatment than patients without APD. Treatment retention was similar between groups. Patients were then classified into one of four study groups: 1) APD only ("pure APD"; n = 60), 2) APD plus psychiatric disorder ("mixed APD"; n = 27), 3) other psychiatric disorder (n = 41), 4) no psychiatric disorder (n = 131). "Pure APD" patients exhibited the highest rate of opioid and cocaine positive urine specimens during treatment, while "mixed APD" patients exhibited the highest rate of sedative positive urine specimens. Rates of retention remained similar across these subgroups. The results show that APD is associated with higher rates of drug use. The presence or absence of comorbid psychiatric disorder with APD appears to affect the class of illicit drug used during treatment.

ACKNOWLEDGMENT: Supported by NIDA grant 1 P50 DA 05273.

CO-MORBIDITY IN DRUG RELATED ADMISSIONS TO A PSYCHIATRIC EMERGENCY ROOM

C. K. Chung, S. L. Simon, J. N. Kennan, R. Rawson, and W. Ling

Harbor UCLA Medical Center, Los Angeles, CA and *VA Medical Center, Los Angeles, CA

There were 1,422 admissions to the Psychiatric Emergency Room of the Harbor UCLA Medical Center during the first three months of 1995. Of these, 842 received urine toxicology screening upon admission. Among these admissions, 320 were positive for drugs, (Methamphetamine (MA), Cocaine, opiates, marijuana, or PCP). Forty five percent of the MA users were Caucasian males, while 36% of the cocaine admissions were male African Americans. Co-morbidity found in admissions with urine positive for drugs is psychosis (40%). substance abuse or use disorder (18%), adjustment and anxiety disorders (16%) and mood disorder (13%). Admissions with negative urines were diagnosed with psychosis (45%) adjustment disorder plus anxiety disorder (12 %), and mood disorder (22%). The average length of stay was highest in the cocaine positive (18.38 hrs.), followed by MA positive (17.30 hrs.), other drug (14.98 hrs.), and clean urine cases (12.46 hrs). Upon discharge, 56% with negative urine results were admitted as inpatients, 34% were sent home with referrals, and 4% were given medical referrals. Of those with positive urines, 61% were sent home, 28% had inpatient hospitalization and 5% were referred to medical service. In summary, admissions positive for drugs have a high co-morbidity with psychiatric disorders (12%). Patterns of disposition on discharge were influenced by two factors: 1. Acute drug psychosis is resolved in about 24 hours with neuroleptic treatment; 2. Psychiatric staff don't treat drug abuse patients.

ACKNOWLEDGMENT: Supported by the NIDA/DVA inter-agency agreement no. 1Y01 DA 50038-00.

DRUG DEPENDENCE AND SUICIDE ATTEMPT IN A NATIONALLY REPRESENTATIVE SAMPLE

G. Borges[¶], R. Kessler*, and E. Walters*

[¶]Institute Mexicano de Psiquiatria, Mexico City, Mexico and *Department of Health Care Policy, Harvard Medical School, Boston, MA

The aim of this study was to estimate the effect of drug use, abuse and dependence on suicidal behavior among participants of the National Comorbidity Survey (NCS). The NCS is based on a stratified, multi-stage area probability sample of persons aged 15-54 in the noninstitutionalized civilian population in the 48 coterminous States. Suicide attempt and DSM-III-R psychiatric disorders were assessed with data collected by lay interviewers using a revised version of the Composite International Diagnostic Interview. Discrete-time survival models in which person-time (person-year) is the unit of analysis were used. After holding sociodemographic factors and other psychiatric disorders constant, lifetime alcohol users and lifetime drug users had increased risk of suicide attempt. Respondents with alcohol abuse were significantly more likely to report a suicide attempt (odds ratio [OR]=1.64) than those with no alcohol abuse. Respondents with alcohol dependence were also more likely to report a suicide attempt (OR=2.24). Drug abuse and drug dependence were also significantly associated with suicide attempt (OR=2.3 and 1.99, respectively). Persons who had substance abuse/dependence alone with no comorbid psychiatric disorder showed an increased risk for suicide attempt (OR=4.71). Finally, persons with comorbid mood, anxiety, antisocial and substance disorders had a greater likelihood of suicide attempt than respondents with only the first three disorders (OR=9.96). We also found an association between suicide attempt and a subset of substances that included sedatives, inhalants. alcohol, stimulants, heroin, tranquilizers and marijuana. For the group of participants that were current users of 6 or 7 of these drugs, the risk of suicide attempt was about 27 times higher compared to non-current users. Further researches that focus on the effect of specific drugs in multinational contexts are needed.

ACKNOWLEDGMENTS: Supported by NIDA grant R01 DA10570 and a NIDA-INVEST fellowship.

GAMBLING AND PSYCHIATRIC DISORDERS AMONG ST. LOUIS DRUG USERS: RECRUITED FROM DRUG TREATMENT SETTINGS AND FROM THE COMMUNITY

R. M. Cunningham-Williams, L. B. Cottler, S. Woodson, and W. M. Compton

Department of Psychiatry, Washington University School of Medicine, St. Louis, MO

The St. Louis Epidemiologic Catchment Area (ECA) study has illustrated that problem gamblers with at least one gambling problem are at higher risk for other psychiatric and substance use disorders compared to recreational gamblers with no gambling problems and non-gamblers (Cunningham-Williams *et al.,* 1998). Other studies have shown that drug users in treatment have higher rates of problem gambling than other population groups. However, we know little about gambling rates of drug users recruited from drug treatment compared to those recruited from the community. We use the Diagnostic Interview Schedule (DIS) to provide lifetime prevalence estimates of DSM-III-R problem gambling and pathological gambling (i.e., at least four gambling problems) and describe the association between gambling and psychiatric disorders for drug users recruited from drug treatment settings and from the community who were first interviewed in 1989-90 as a part of two NIDA-funded St. Louis studies (Cottler PI of both): 1) Substance Abuse and the Risk of AIDS (SARA)--a random sample of drug users recruited from drug treatment settings (n=512); and 2) Efforts to Reduce the Spread of AIDS (ERSA)--a study of drug users recruited through street outreach (n=478). Results indicate the prevalence of problem gambling to be 22% (pathological gambling=11%). Drug users who are problem gamblers are more likely to be: male (OR=3.4), African-American (OR=3.1), recruited from drug treatment (OR=1.5), have antisocial personality disorder (OR=1.9), and have any illicit drug abuse/dependence (OR=2.2), compared to drug users who are recreational and non-gamblers. We discuss the clinical and research implications of our findings. **REFERENCES:** Available from the senior author.

ACKNOWLEDGMENTS: Supported by NIDA grants DA 06163 and DA 05619 of the NIH.

SCREENING FOR ATTENTION DEFICIT HYPERACTIVITY DISORDER IN SUBSTANCE USING PATIENTS WITH THE WENDER UTAH RATING SCALE

A. J. Saxon, K. L. Sloan, D. A. Calsyn, and J. P. Reoux

Center of Excellence in Substance Abuse Treatment and Education, VA Puget Sound Health Care System and Department of Psychiatry and Behavioral Sciences, University of Washington, Seattle, WA

The Wender Utah Rating Scale (WURS), a self-report measure that solicits retrospective ratings of childhood behaviors relevant to Attention Deficit Hyperactivity Disorder (ADHD), was completed by polysubstance using, alcohol dependent men starting disulfiram (n=52). WURS scores of 46 or above on 25 selected items, a cut point previously shown to distinguish subjects with adult ADHD (WURS+), were obtained by 14 patients (26.9%). WURS+ patients did not differ significantly from other subjects in demographics, number of sexual partners, or years of lifetime substance use reported on the Addiction Severity Index (ASI). Rates of clinical drug dependence diagnoses were comparable between WURS+ and other subjects and were respectively: Amphetamine 0% vs. 5.3%, cocaine 42.9% vs. 39.5%, cannabis 14.3% vs. 23.7%. opioid 14.3% vs. 5.3%. Similarly rates of other Axis I clinical psychiatric diagnoses did not differ significantly between WURS+ and other subjects and were respectively: Bipolar 14.3 vs. 18.4, depression 21.4% vs. 42.1%, PTSD 14.3% vs. 39.5%, schizophrenia 21.4% vs. 15.8%. WURS+ patients more frequently endorsed anxiety problems in the past 30 days (78.6% vs. 39.5%; x^2=4.8, p<.03) but were not significantly more likely to endorse serious depression, violent or suicidal behavior, trouble understanding concentrating or remembering, or to have received medications for psychiatric problems in the past 30 days or in their lifetimes. Nor did they differ on ASI medical or alcohol composite scores, but they did have higher drug (mean=0.085, sd=0.063 vs.0.045, 0.060; t=2.1, p<.05) and psychiatric composite scores (mean=0.45, sd=0.19 vs.0.25, 0.21; t=3.2, p<.004) and reported higher frequency of psychiatric hospitalization (78.6% vs. 39.5%; x^2=4.8, p<.03). Thus WURS+ patients had more global psychiatric distress that could not be explained by common categorical clinical diagnoses, though none received a clinical diagnosis of ADHD. These findings support the notion that adult ADHD is common but very difficult to distinguish clinically in substance using patients.

RISK FOR SUBSTANCE USE DISORDERS IN YOUTH WITH CHILD- AND ADOLESCENT-ONSET BIPOLAR DISORDER

T. E. Wilens, J. Biederman, R. Millstein, J. Wozniak, and T. Spencer

Pediatric Psychopharmacology Unit, Massachusetts General Hospital, Harvard Medical School, Boston, MA

Objective: Previous work in adults has suggested that early onset bipolar disorder (BPD) is associated with an elevated risk for substance use disorders (SUD). To this end, we studied the risk for SUD in child- vs adolescent-onset bipolar disorder with attention to comorbid psychopathology. **Methods:** We systematically studied all youth (aged 6-17 years) on whom structured psychiatric interviews were available. From clinic subjects (N=969) we identified 220 subjects with DSM-III-R BPD. To evaluate the risk for SUD and BPD attending to developmental issues, we stratified the BPD sample into child-onset BPD ($\leq$ 12 years of age, N=182) and adolescent-onset BPD (13-18 years of age, N=38). **Results:** Adolescent-onset BPD cases were 5.5 times more likely to manifest a SUD compared to child-onset BPD (p<0.003). The presence of conduct disorder within BPD did not account for the risk of SUD. Two-thirds of the BPD+SUD youth had the onset of their BPD prior to or within one year of the onset of SUD. **Conclusions:** Adolescent-onset BPD is associated with a much higher risk of SUD than child-onset BPD which was not accounted for by comorbid psychopathology.

SUICIDAL IDEATION VARIES BY COCAINE AND OPIATE USE PATTERNS

L. B. Cottler, W. M. Compton, R. M. Cunningham-Williams, and A. B. Abdallah

Department of Psychiatry, Washington University School of Medicine, St. Louis, MO

An association is clearly established between female gender and depression: in fact, depression is thought to play a role in bringing female drug abusers to treatment. An association between more severe symptoms of depression-suicidal ideation--and drug abuse would warrant specific interventions for depression among persons in substance abuse treatment. This association was tested among 990 drug users in and out of treatment interviewed from 1990 to 1994 from two NIDA-funded studies: I) The Substance Abuse and Risk for AIDS Study (SARA)--substance users in treatment, and 2) Efforts to Reduce the Spread of AIDS (ERSA)--substance users recruited through street outreach. In both studies, the Diagnostic Interview Schedule (DIS) was used to assess the presence of DSM-III-R Major Depression. To determine the association of the four suicidal criterion items with drug use patterns, the sample was stratified into: cocaine use only, opiate use only, neither, or both. Polydrug use was hypothesized to discriminate those with suicidal idcation. Additionally, cocaine was thought to increase that risk. Our results indicate that 52% of drug users reported thoughts of death, a period of wanting to die, thoughts of committing suicide or attempting suicide. In general, the highest rates of thoughts of death, wishing to die and attempting suicide were found for polydrug users, followed by opiate only users, followed by cocaine only users. followed by neither cocaine nor opiate users. When the sample was stratified by gender, however, cocaine was more likely to be associated with suicidal ideation in men, but in women, opiates were more likely to be associated with suicidal ideation. Injection drug use, regardless of drug used, was also found to increase the risk for suicidal ideation. These original findings point out the need for considering both specific drug use patterns and suicidality among drug users.

ACKNOWLEDGMENTS: Supported by the NIH NIDA grants DA 06163 and DA 05619.

PSYCHIATRIC COMORBIDITIES IN PATIENTS WITH SUBSTANCE USE DISORDERS: DATA FROM A NATIONAL PRACTICE RESEARCH NETWORK

D. Zarin[1], D. Svikis[2], H. Pincus[1], and T. Tanielian[1]

[1]American Psychiatric Association, Washington, DC and [2]Johns Hopkins University School of Medicine, Baltimore, MD

Prevalence of DSM-IV substance use disorders (SUD) was examined in a sample of 1,245 psychiatric patients sampled through a national psychiatric practice research network (N=415 respondents). Nearly one-fourth (21%) of patients in routine psychiatric practice settings had diagnoses of one or more SUD (17% with 1 diagnosis; 3% with 2 diagnoses; 1% with 3 diagnoses, and 0.2% with 4 diagnoses). The most prevalent disorders were alcohol dependence (7%), alcohol abuse (5%), polysubstance dependence (2.7%) and nicotine dependence (2.6%)Patients with one or more SUD did not differ demographically from patients with no SUD. With nicotine dependence excluded, patients without SUD (N=1,007) were compared to patients with alcohol only (N=119), drug only (N=87), and alcohol and drug diagnoses (N=32). Rates of anxiety disorders were highest in patients with no SUD (23.4%), followed by patients with drug only (18.4%), alcohol only (16.0%), and alcohol and drug (6.3%) disorders ($p<.029$). The four groups did not differ in prevalence of major depression, bipolar, psychotic, somatoform, eating, sleep, and impulse control disorders. For Axis II disorders, prevalence of one or more personality disorders was highest in the drug only group (47.1%), followed by the alcohol and drug (37.5%), alcohol only (29.4%) and no SUD (24.2%) groups ($p<.001$). Similar patterns were observed for the more prevalent personality disorders. For example, antisocial personality disorder was most prevalent in the drug only group (10.3%), followed by the alcohol and drug (6.3%), alcohol only (0.8%) and no SUD (0.8%) groups ($p<.001$).These data suggest that the type and prevalence of psychiatric comorbidities vary in patients with different forms of SUD. Additional analyses will examine variations in treatment patterns, payment mechanisms, and other clinical factors. The findings also highlight the utility of practice-based research for collecting national data to examine such interactions.

DRUG ABUSE COMORBIDITY AND PROBLEM SEVERITY AMONG PROJECT MATCH OUTPATIENTS

N. A. Haug, C. C. DiClemente, and L. E. Bellino

Department of Psychology, University of Maryland Baltimore County

The treatment of alcohol use disorders is often complicated by comorbid abuse of illicit substances. Clients who present for alcohol treatment with concurrent drug abuse may exhibit different characteristics, such as more severe drinking patterns and psychopathology. This study examined baseline characteristics in 3 subgroups of Project MATCH outpatient clients. Groups were created to reflect levels of drug abuse involvement since drug dependent individuals were excluded from the study. The first group (n = 75) consisted of a matched subgroup of alcohol abusers without any comorbid drug abuse (Alcohol Only; AO). The second group (n = 62) comprised alcohol and marijuana abusers who did not display other illicit DSM-III-R drug abuse diagnoses (Alcohol + Marijuana; AMJ). The third group (n=56) consisted of alcohol abusers who met SCID DSM-IIIR criteria for opiate, cocaine, stimulant or sedative abuse at baseline (Alcohol + Other Drugs; AOD). Results indicated no demographic differences, however; the number of drinks per drinking day ($F = 3.04$, $p < .05$) differed significantly, as did the AUDIT total scale score ($F = 4.22$ $p < .02$) with the AOD group displaying more drinks per drinking day and a higher AUDIT total score than the AO group. The Alcohol Use Inventory (AUI) subscale of guilt and worry associated with drinking was also significant ($F = 3.16$, $p = < .05$) with AOD > AMJ. The AMJ group emerged as less ready for treatment than both AO and AOD on the SOCRATES ($F = 3.95$, $p < .03$). No differences were found among the three groups on measures of temptation or self-efficacy, except for confidence in negative affect situations which appeared to be higher in AO than AMJ and AOD ($F = 6.78$, $p < 01$). No differences were found among the groups on Major Depression, GAD, or ASPD diagnoses, however; differences emerged on the ASI Psychiatric Composite score ($F = 3.85$, $p < .03$) with AOD > AO, AMJ; Beck Depression Inventory total score ($F = 4.53$, $p < .02$) with AOD > AO, and the CPI Sociopathy core ($F = 4.06$, $p < .02$) with AOD > AO. It is suggested that alcohol dependent individuals who *abuse* other drugs may present for treatment as more problematic both in intensity of drinking behavior and in level of complicating problems. These findings have implications for the assessment and intervention of primary alcohol clients with comorbid drug abuse.

ORAL COMMUNICATIONS III

GENDER DIFFERENCES IN PHARMACOLOGIC TREATMENT FOR COCAINE DEPENDENCE

J. Campbell, E. J. Nickel, E. C. Penlick, B. Liskow, and B. J. Powell

Departments of Psychiatry, VA Medical Center, Kansas City, Mo. and University of Kansas Medical Center, Kansas City, KS

Reports of gender differences in response to treatment for cocaine dependence prompted us to examine response by gender to pharmacotherapy for cocaine craving and dependence. Subjects were randomly assigned to an 8-week trial of desipramine, carbamazepine, or placebo while attending psychosocial treatment activities in a community mental health center. Outcome measures were retention in treatment, percent positive urine toxicology, and change in variables associated with cocaine craving measured with the Halikas Drug Impairment Rating Scale. Blood levels of desipramine and carbamazepine were obtained at two-week intervals and medications were adjusted by a physician blind to medication status, according to blood level and side effects. Desipramine was more effective in retaining subjects in treatment when blood level was at least 50 ng/ml than was carbamazepine when blood level was at least 4 mcg/ml, or than placebo. Males receiving desipramine were retained in treatment longer than females receiving desipramine or all subjects receiving carbamazepine or placebo. These results suggest a differential response by gender and by blood level.

ACKNOWLEDGMENT: Supported by NIDA R18 DA-06954.

AMANTADINE HYDROCHLORIDE IS EFFECTIVE TREATMENT FOR COCAINE DEPENDENCE

S. Shoptaw[1,2], P. C. Kintaudi[1], V. C. Charuvastra[1], R. A. Rawson[1,2,3], and W. Ling[1,2,3]

[1]L.A. Addiction Treatment Research Center, [2]Long Beach VA MDRU, and [3]UCLA School of Medicine, Department of Psychiatry and Biobehavioral Sciences, Los Angeles, CA

Amantadine hydrochloride, a dopamine agonist, seems conceptually suitable as a candidate for cocaine depndence treatment. We report on a 16-week double-blind, randomized, placebo-controlled rapid evaluation of amantadine (100 mg bid) with 69 cocaine dependent subjects (34 amantadine; 35 placebo) in a community-based clinic in LA. Matrix Model counseling served as the psychosocial base for the trial. Subjects attended clinic 3 times per week (M, W, F) to provide data (urine samples, questionnaires) and to receive counseling (90 minute groups). Five efficacy parameters were used: cocaine use, cocaine craving, adverse events, retention, and global change. Urine toxicology was assessed using Treatment Effectiveness Score (i.e., the number of "clean" urines for each subject) and Joint Probability at 8 and 16 weeks (i.e., number of subjects providing "clean" urines divided by number of subjects in that condition at that point). Though TES analyses fall just short of significance for amantadine (M_A=16.12 "cleans"; M_P=11.00 "cleans"), we found significantly fewer amantadine subjects used cocaine at weeks 8 (A=13/34 subjects (0.38); P=5/35 subjects (0.14); z=2.27, p=.01) and 16 (A=9/34 subjects (0.27); P=3/35 subjects (0.09); z=2.27, p=.01) using JP. Percentage of urine samples negative for cocaine metabolite showed the conditions to be similar (A=51.4%, P=48.2%), though longest period of continuous cocaine abstinence for amantadine subjects was twice as long as for placebo subjects (17.15 days vs 8.63 days). Visual analogue scales of cocaine craving in the past 24-hours were similar for the two conditions. Adverse event incidents were low for the trial and distributed comparably across conditions. No severe adverse events occurred for amantadine subjects. Amantadine subjects retained longer in the trial (16 weeks=35.3%) than placebo subjects (14.3%; Mantel-Cox=2.79, df=1, p=.09) and were seen as having better global improvement than placebo (F=3.04, df=1.66, p<.09). Findings indicate that amantadine is well tolerated by cocaine dependent patients and is sufficiently promising in efficacy to warrant further evaluation with large scale clinical trials.

DOSE RESPONSE EFFECTS OF PERGOLIDE IN THE TREATMENT OF 'COCAINE DEPENDENCE

R. Malcolm, K. Brady, J. Moore, and S. Sutherland

Center for Drug and Alcohol Programs, Medical University of South Carolina, Charleston, SC

Because of its long half life, mixed dopamine receptor affinity and early encouraging opened label results. a double blinded dose response trial of Pergolide was undertaken. This was a comparison of placebo (N=153), low dose pergolide (LDP, N=155) and high dose pergolide (HDP, N=156) treatment for twelve weeks in cocaine-only (N=255) and in cocaine plus alcohol dependent (N=191) subjects. There were no significant differences in the proportion of negative urine drug screens (UDSs) for the overall sample during treatment. Cocaine-only HDP subjects had poorer treatment retention (x^2=14.177, p=0.001) and a trend toward a higher percentage of positive UDSs (F=2.76, df=204, p=0.067), findings not observed in the cocaine-alcohol group. Mean treatment effectiveness scores (TES) for the cocaine-only group indicated the best outcome scores for the placebo group: 31.7, intermediate scores for LDP: 25.2, and the lowest score for the HDP: 14.1; (F=6.2, df=254, p=0.0023). At follow-up, off medication, the LDP had significantly more negative UDSs than either placebo or HDP at two months (x^2=9.172. p=0.010) and at four months (x^2=8.075, p=0.018). The LDP group reported fewer number of days of cocaine use (x^2=9.5961, df=2, p=0.0082). **Conclusions:** Both doses of pergolide were ineffective for the treatment of cocaine dependence. HDP for the cocaine-only group appeared to worsen treatment outcome in terms of TES scores, Lower retention, and a trend of more positive UDS. At follow-up, subjects in the LDP group had improved treatment outcome by self-report and UDS, over both placebo and HDP. This latter finding may represent a latent D_1 receptor rebound effect.

A CONTROLLED TRIAL OF ISRADIPINE IN COCAINE DEPENDENCE: PRELIMINARY ANALYSIS

S. L. Batki, M. Bradley, J. Moon, K. Delucchi, D. Sexe, S. Bennett, M. Schissel, C. Rocha, P. Jacob III, and R. T. Jones

University of California, San Francisco, Department of Psychiatry, San Francisco General Hospital, Division of Substance Abuse and Addiction Medicine, San Francisco, CA

Objective: A controlled pilot trial of isradipine, a dihydropyridine calcium channel blocker, was conducted to determine its efficacy in treating cocaine dependence. In animal studies, isradipine attenuates cocaine-related behaviors. **Method:** Eight week randomized, placebo-controlled parallel group design with a 1 week single-blind placebo lead-in followed by ISR or PLA 2.5 mg BID in Wk 2. Medication was increased to 5 mg BID in Wks 3 through 7, then tapered to 2.5 mg BID in Wk 8, and discontinued. This analysis includes self-report and urine measures for the first 31 Ss (17 ISR, 14 PLA). All were DSM-IV primary cocaine dependent, with a mean of 7.8 yrs of cocaine use. Mean age was 37.9. 26 (84%) were male, 19 (62%) African American, 7 (23%) white, 2 (6%) Asian, 1 (3%) Hispanic, and 2(6%) Other. **Results:** ISR was associated with significantly worse retention than PLA. Mean retention was 4.9 wks for ISR, and 6.5 wks for PLA (log rank chi square, p=.03). There were no significant differences between the 2 groups in any of the outcome measures: days of cocaine use/wk, dollars worth of cocaine use/wk, number of times of cocaine use/week, or in quantitative urine benzoylecgonine (BE) concentrations. There were no differences between groups in cocaine craving or quality of high. There were no differences in self-reported adverse effects between the ISR and PLA groups. Self-report of medication compliance was not significantly different between the 2 groups. **Conclusion:** Isradipine did not appear to be associated with reductions in cocaine use. It was, however, associated with significantly greater attrition than placebo. Further work may be required to confirm these findings.

ACKNOWLEDGMENTS: Supported by NIDA grants P50 DA01696 and P50 DA09253.

ASSESSMENT OF COCAINE AND ALCOHOL DEPENDENT METHADONE PATIENTS

G. A. Rowan-Szal, L. R. Chatham, G. W. Joe, and D. D. Simpson

Institute of Behavioral Research, Texas Christian University, Fort Worth, TX

Several studies have focused on the problem of polydrug-using methadone patients, especially those addicted to cocaine and/or alcohol. Patients who enter treatment with multiple drug problems are difficult to engage and retain in treatment. This study focused on 167 methadone maintained patients diagnosed at admission to have cocaine, alcohol, or both cocaine and alcohol dependence (DSM-IV). Statistical comparisons were made between the dependent and non-dependent subgroups, identifying differences in treatment engagement during the first 6 months of treatment and for outcomes in the year after discharge. Results show several differences between the drug dependence subgroups. At admission, patients dependent on both cocaine and alcohol had more legal problems, lower motivation for treatment, and higher hostility scores; and after 6 months of treatment they were less engaged, as evidenced by lower session attendance and poorer counselor ratings. These patients also were less likely to complete a year of treatment, compared to all other groups. The conceptual importance of this study is that it begins addressing therapeutic and engagement factors involved in the poorer outcomes of cocaine dependent methadone patients.

ACKNOWLEDGEMENT: Supported by NIDA grant R01 DA06162.

PROPRANOLOL FOR THE TREATMENT OF COCAINE DEPENDENCE: A DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL

K. M. Kamptnan, J. R. Volpicelli, A. I. Alterman, H. Pettinati, E. Muller, T. Acosta, D. Leidertnan*, P. Bridge*, P. Gariti, J. Cornish, C. Boardman, and C. P. O'Brien

University of Pennsylvania School of Medicine, Philadelphia, PA and *National Institute on Drug Abuse, Rockville, MD

Background: Propranolol is a beta adrenergic blocker useful for the treatment of anxiety. Anxiety is often associated with cocaine craving and frequently encountered during early cocaine abstinence. In an open pilot trial, propranolol improved treatment outcomes in cocaine dependent patients. Presented here are preliminary results from a controlled trial of propranolol for cocaine dependence. **Methods:** This was an 8 week, double-blind, placebo-controlled, trial involving 108 cocaine dependent outpatients. Patients received either propranolol 100 mg daily, or identical placebo capsules. Psychosocial treatment consisted of twice weekly, individual, cognitive behavioral therapy. Urine toxicology screens were obtained at thrice weekly evaluation visits. **Results:** There were no significant differences between the groups in any baseline variable. Fifty-seven patients (53%) completed the trial. There was no difference between groups in treatment retention. Weekly mean quantitative urinary benzoylecgonine levels did not differ significantly between the two groups. There was no significant difference between the two groups in the percent benzoylecgonine-negative urine samples submitted by treatment completers. ASI composite drug scores declined in both groups with no significant difference between groups. Cocaine withdrawal scores declined in both groups. There was a trend for greater reduction in the propranolol group (repeated measures ANOVA, $F(2,38) = 2.39$, $p < .10$). Baseline ASI psychiatric composite scores predicted lower mean benzoylecgonine levels in the propranolol group ($\beta = -.28$, $p = .05$). **Conclusions:** In the overall sample, propranolol was not more efficacious than placebo in promoting abstinence or improving treatment retention. Propranolol may be more effective in cocaine dependent patients with more severe psychiatric symptoms. Further analysis needs to done to identify which psychiatric symptoms predict better response to propranolol.

ACKNOWLEDGMENTS: Supported by NIDA grants K20 DA00238 and Y01 DA30012.

BACKGROUND AND PROXIMAL FACTORS IN COCAINE RELAPSE AND NEAR MISS EPISODES

J. R. McKay, A. I. Alterman, F. D. Mulvaney, and J. Koppenhaver

Department of Psychiatry, University of Pennsylvania, Philadelphia, PA

Current models of relapse to addictive behaviors assert that relapse is a function both of background factors that increase vulnerability and proximal factors that immediately precede and trigger the onset of episodes of use. Little is known, however, about the extent to which these models apply to the cocaine relapse process. This study tested several predictions from these models with data on cocaine relapse and "near miss" episodes from 100 cocaine-dependent patients who were followed up for one year following entrance into aftercare. Results indicated that the situations in which patients tended to use cocaine prior to treatment were generally not good predictors of similar proximal factors in relapse or near miss episodes. Psychiatric and family/social problem severity background factors predicted similar proximal factors in near misses, but were generally not related to proximal factors in relapses. On the other hand, proximal measures of coping, sensation seeking, positive experiences, and unpleasant affect differentiated relapses from near misses in a within-subjects analyses. These findings are generally supportive of current relapse models, in that they suggest that while background factors predict the circumstances that will create a "high risk" situation for the recovering cocaine abuser, whether the situation remains a near miss or escalates into a relapse is more a function of proximal factors such as coping, strength of craving or sensation seeking, and affect. However, the findings raise some questions about the efficacy of "individualizing" relapse prevention interventions on the basis of data collected at intake to treatment.

ACKNOWLEDGMENTS: Supported by NIDA grants K02 DA00361, R29 DA08399, and P50 DA05186.

FOLLOW-UP EVALUATION OF SUBJECTS WHO DROP FROM TREATMENT

K. L. Drenner, J. M. Schmitz, A. L. Stotts, H. M. Rhoades, and J. Grabowski

Substance Abuse Research Center, University of Texas - Houston

The high rate of treatment dropout has long been recognized as a clinical and a methodological dilemma for addiction researchers. Traditionally, subjects who drop from treatment have been difficult to follow and are generally classified as "treatment failures". An equally plausible, but less popular, opinion is that some dropouts may modify or cease using drugs on their own, and thus be classified as "successes" at follow up. To address this issue empirically, we have been collecting follow up data on subjects who drop out of two large randomized clinical trials of psychotherapy and pharmacotherapy for cocaine abusers. Of the 126 subject in the studies, 85 have dropped out of treatment prematurely (67.5%). The median survival time in treatment was 5.89 weeks. While completers clearly had more cocaine negative urines at follow-up, 38.4% of the dropouts had cocaine negative urines at the 3 month follow-up, 50% at 6-months, and 40% at the 9-month follow-up. Comparison of intake and follow-up ASI scores of subjects who dropped out of treatment revealed significant improvement over time in the number of days using cocaine in the past 30 and in areas of drug, alcohol, family/social, and psychiatric problem severity. When the dropouts who attended follow-up were compared to those dropouts who did not attend, there was a significant difference in weeks in treatment (6.43 vs 3.31). In sum, despite intensive efforts, we have obtained follow-up information on relatively few subjects who drop from treatment prematurely (<18%). Many of these subjects, however, would not be classified as "failures".

ACKNOWLEDGMENTS: Supported by NIDA grants DA-09262-02 and DA-08654.

TREATMENT AND TREATMENT RESEARCH MEASURES OF ABSTINENCE: DO THEY TELL THE SAME STORY?

J. B. Milby, J. E. Schumacher, C. McNamara, S. Usdan, D. Wallace, D. Stange, and M. Michael*

University of Alabama at Birmingham and *University of Kansas Medical Center

From a 2 group randomized controlled study of abstinence contingencies for housing and work as an adjunct to behavioral day treatment (DT+) vs. day treatment alone (DT) with homeless cocaine abusers (n=141), this study explored relationships among commonly used abstinence outcomes. ASI and urine toxicology measures were compared. Various graphed indexes of the variable "percent abstinent at assessment point" compared measures derived from "reported days used in the last 30 days" (ASI) and urine toxicologies, both measured at scheduled assessment points at 0, 2, 6 and 12 months. These indices were compared with 1-2 per week random (unscheduled) toxicologies for weeks 1-24 at 0, 2, and 6 months respectively, which showed DT+=50% vs DT=48% abstinent; DT+ 72% vs. DT 33% (Chi Sq.= 18.71, df=1, p=0.001); DT+=39% vs. DT 16% (Chi Sq.=7.4, df= 1, p=0.007). In the context of robust significant differences in abstinence measured by random urine toxicologies, abstinence outcomes at scheduled follow-ups show much smaller differences with great disparities among measures for DT but not DT+. Investigators suggest difference in disparity between groups may be due to non-abstinent subjects in each group who reschedule and/or temporarily cease drug use to give negative urine and ASI. Apparent inconsistency with literature showing verbal report, compared to toxicology standard, is reasonably accurate in the absence of abstinence contingencies, may be explained by notion of perceived contingency.

ACKNOWLEDGMENT: Supported by NIDA grant RO1 DA08475.

SOCIAL NETWORK STRATEGIES FOR OUTPATIENT COCAINE TREATMENT

L. R. Goehl, A. R. Childress, A. V. Hole, R. Ehrman, A. Buckzkowski, and C. P. O'Brien

University of Pennsylvania and Philadelphia VA Medical Center

Problematic social relationships have been linked to poor treatment outcome for substance abusers. Persistent deficiencies in drug patients' social networks (a lack of positive support: poor and/or drug using relationships) often undermine their efforts at abstinence. In order to address these issues, we have developed a series of manual-guided social network exercises to help patients bolster positive interpersonal relationships and manage relationships which threaten recovery. The exercises are taught in individual sessions. and include *Communication; Trust; Enjoyment/Satisfaction: Daily Hassles; Handling Problems and Conflicts;* and *Intimacy.* The social network exercises are combined with our previously tested active coping strategies (deep relaxation, delay/behavioral *alternatives, negative/positive consequences, aversive/positive imagery, mastery imagery, cognitive interventions).* We are now evaluating the treatment outcome of cocaine patients (n=75 thus far) randomized either to a combination of anti-craving tools *and* social network exercises or to an equivalent amount of professional attention in an ongoing 12 week protocol. Interim analyses show that after 4 weeks of treatment and a maximum of 8 therapy sessions. the experimental group shows significant improvement in social support compared to the control group ($U(N1, N2) = 168.0$, $p<.034$). Additionally, subjects with high levels of social support had significantly less drug use over the 12 week study than subjects with low levels of social support. Although there is no significant difference between the control and experimental group in terms of drug use outcome, those subjects whose social support was low at baseline and improved significantly at the one month follow-up had significantly less drug use than subjects with no improvement ($p < 0.02$).

ACKNOWLEDGMENTS: Supported by NIDA Merit Award DA 3008 and Va Center Grant (CPO))

ORAL COMMUNICATIONS IV

MORPHINE'S EFFECTS ON SPEECH SOUND PERCEPTION BY BABOONS AS A FUNCTION OF TASK DIFFICULTY

R. D. Hienz and J. V. Brady

Johns Hopkins University School of Medicine, Baltimore, MD

Perceptual functions in baboons were examined to determine how the effects of rnorphine varied with the complexity of a speech sound discrimination task. Three baboons were trained to discriminate differences between a "standard" human vowel sound and four "comparison" vowel sounds. Baboons pressed a lever to produce a repeating vowel sound (e.g.,"aw"), and released the lever only when that sound changed from the standard vowel to one of the four comparison vowels (e.g., "eh"). Continuous broadband masking noise was introduced during testing sessions. and discrimination difficulty was manipulated by adjusting the level of the background masker to produce 3 different performance accuracy levels. Response accuracy as well as response latencies, or "reaction times", were compared following i.m. administration of saline and morphine. The results showed that in the absence of noise. morphine reduced discrimination accuracy for the comparison vowel most similar to the standard vowel. but had little effect on the discriminability of the remaining 3 comparison vowels. In the presence of noise, morphine produced greater decrements in discrimination accuracy, with the size of the decrement being a direct function of the noise intensity. Further, those vowel discriminations previously unaffected in a quiet background were also impaired in the presence of the background noise. These results suggest that the differential sensitivity of these two performances to morphine is related to the baseline level of stimulus control and its effect upon the "complexity" of the task.

ACKNOWLEDGMENTS: Supported by NIDA grants DA 02490, DA 04731, and DA 00018.

EFFECTS OF TRAINING DOSE ON THE GENERALIZATION OF MORPHINE TO THE PARTIAL OPIOID AGONIST NALORPHINE

S. D. Grabus and A. L. Riley

Psychopharmacology Laboratory, American University, Washington, DC

Rats trained to discriminate the mu agonists fentanyl or morphine from their respective vehicles generalize to the partial *mu* agonist nalorphine incompletely and inconsistently. Any number of factors may influence the generalization patterns obtained, one of which being the specific dose of the full opioid agonist used during training, a factor reported to influence generalization with other partial opioid agonists. To assess if training dose influences stimulus generalization to nalorphine and to support its role in the aforementioned variability across studies, rats were trained to discriminate one of two doses of morphine (i.e., either 5.6 or 10 mg/kg) from distilled water within the taste aversion baseline of drug discrimination learning. Subjects were then given a range of doses of morphine, nalorphine, methadone or naloxone to assess the degree of generalization (if any) of the training dose of morphine to these compounds. For all subjects, morphine fully generalized to itself and failed to generalize to the opioid antagonist naloxone. Morphine generalized to nalorphine in subjects trained at the lower dose but not in subjects trained at the higher dose. Methadone, a full *mu* agonist, substituted for the morphine training stimulus in the group tested (i.e., the high dose group), and naloxone blocked morphine stimulus control in all subjects, suggesting that morphine control was based on opioid activity at the *mu* receptor. These results further suggest that the substitution patterns of nalorphine in morphine-trained subjects are a function in part of the dose of morphine used in training and support the position that nalorphine is a partial *mu* opioid agonist with intermediate efficacy at the *mu* opioid subtype.

ACKNOWLEDGMENT: Supported by a grant from the Mellon Foundation (ALR).

DOPAMINE/OPIATE-ACTIVE N-BUTYROPHENONE PRODINE-LIKE COMPOUNDS PRODUCE HEROIN'S STIMULUS EFFECTS

P. M. Beardsley and L. S. Harris

Department of Pharmacology, Medical College of Virginia of Virginia Commonwealth University, Richmond, VA

A series of N-butyrophenone prodine-like compounds were reported to simultaneously bind to dihydromorphine-labeled opiate and spiroper-idol-labeled dopaminergic receptors and to produce opiate-agonist and neuroleptic-like effects (M. A. Iorio, *et al.,* 1991). A compound which emerged from this series, NIH 10873 [(+)-N-3(p-fluorobenzoyl)propyl-3-methyl-4-phenyl-4-propionyloxypiperidine], was reported to block cocaine-induced hyperarousal and to attenuate morphine withdrawal effects in rhesus monkeys (E. R. Bowman, *et al.,* 1995; M. D. Aceto, *et al.,* 1996). Compounds with the simultaneous ability to attenuate cocaine-like affects while relieving opiate withdrawal effects might have a role as medications in treating drug dependency disorders, especially in individuals with histories of co-abusing cocaine and heroin. In order to further elucidate the pharmacology of NIH 10873, it, as well as 3R,4S-(+)- and 3S,4R-(-)-N-3-(p-fluorobenzoyl) propyl-3-methyl-4-phenyl-4-propionyloxypiperidine fumarate (NIH 10639 and NIH 10640, respectively), were evaluated in rats trained to discriminate 0.3 mg/kg S.C. heroin from vehicle in a FR10, food-reinforced operant task during daily (M-F) 30-min sessions. NIH 10639 and NIH 10873 dose-dependently, and completely, generalized from the heroin stimulus at 0.3 and 1.0 mg/kg, respectively. NIH 10640 (0.01-18 mg/kg) produced low (<13%) levels of heroin-lever responding. These results suggest that some N-butyrophenone prodine-like compounds, which may attenuate cocaine's effects as well as opiate withdrawal effects, may also produce heroin-like subjective effects and, hence, may have acceptance as treatments by heroin addicts.

ACKNOWLEDGMENT: Supported by NIDA grant DA 5-8060.

EFFECTS OF DOPAMINE AND OPIOID ANTAGONISTS ON "SPEEDBALL" SELF-ADMINISTRATION BY RHESUS MONKEYS

N. K. Mello and S. S. Negus

Alcohol and Drug Abuse Research Center, Behavioral Science Lab, McLean Hospital—Harvard Medical School, Belmont, MA

The simultaneous i.v. administration of heroin and cocaine, called a "speedball," is often reported clinically, and we have modeled this type of polydrug abuse in the rhesus monkey (Mello *et al.,* 1995). The development of effective pharmacotherapies for "speedball" and other forms of polydrug abuse is a continuing challenge. In this study, we explored the possibility that treatment with *combinations* of dopamine and opioid antagonists might reduce speedball self-administration more effectively than either antagonist alone. Speedballs (0.01 mg/kg/inj cocaine and 0.0032 mg/kg/inj heroin) and food (1 gm banana pellets) were available in four daily sessions on a second-order schedule of reinforcement [FR4 (VR16:S)]. Monkeys were treated for 10 days with saline or the dopamine antagonist flupenthixol and/or the opioid antagonist quadazocine alone and in combination. Each antagonist alone had no significant effect on speedball or food-maintained responding. However, flupenthixol and quadazocine in combination significantly reduced speedball self-administration in comparison to the saline treatment baseline ($P < 0.05$) and to flupenthixol ($P < 0.03$) or quadazocine alone ($P < 0.01$) with no significant changes in food-maintained responding. A speedball dose-effect curve was determined using 3:1 cocaine-heroin combinations. During saline treatment the speedball dose effect curve had an inverted U shape. Treatment with the same flupenthixol plus quadazocine combination produced an approximately 10-fold rightward shift in the speedball self-administration dose-effect curve. Our findings suggest that mixtures of two or more medications, designed to target each component of the abused drug combination, may be an effective approach to polydrug abuse treatment.

ACKNOWLEDGMENTS: Supported in part by NIDA, NIH P50-DA04059, RO1-DA02519, and KO5-DA00101.

EFFECTS OF BUPRENORPHINE AND DRUG ABSTINENCE ON HYDROMORPHONE REINFORCEMENT

C. R. Schuster, M. K. Greenwald, and C. E. Johanson

Department of Psychiatry and Behavioral Neurosciences, Wayne State University, Detroit, MI

This study examined effects of buprenorphine (BUP; maintenance on 2, 4, 8, 4 and 2 mg s.l. in two-week phases) on the reinforcing effects of hydromorphone (HYD; 0, 4, 8, 16 mg/70 kg i.m.) in heroin-dependent volunteers. Following the first week of maintenance at each BUP dose (stabilization), volunteers received single injections of the four HYD doses 3 hrs post-BUP on different days in random order under double-blind conditions. Semiquantitative urinalyses verified that 8 volunteers (Abstainers) were heroin-free during HYD test weeks, whereas 6 volunteers remained heroin-positive (Nonabstainers). On each injection day volunteers completed the Multiple Choice Procedure, choosing between receiving today's HYD dose again versus 30 money amounts ranging from $20.00 to $0.25. On the fifth day, one of the 120 choices was randomly selected and the volunteer received the chosen reinforcer. Among volunteers for whom BUP was effective (Abstainers), HYD had minimal reinforcing value (mean money amount at which volunteers choose money over drug) whereas in Nonabstainers, for whom BUP was ineffective, there were marked dose-related increases in HYD reinforcing value (Group*HYD dose and HYD dose effects, $p< .05$). A similar pattern was found for HYD subjective agonist effects. Heroin craving among Nonabstainers was significantly higher during BUP treatment, and was reduced in a dose-related manner when HYD was administered. In contrast, abstinence status had no effect on pupil diameter (although BUP and HYD produced dose-related miosis). In summary, BUP doses from 2 to 8 mg were differentially effective for Abstainers (compared with Nonabstainers), and BUP effects on opioid reinforcement were consistent from outpatient setting (heroin abstinence) to laboratory setting (decreased HYD reinforcement). These findings support the external validity of this laboratory model.

SAFETY OF BUPRENORPHINE: CEILING EFFECT FOR SUBJECTIVE MEASURES AT HIGH INTRAVENOUS DOSES

M. A. Huestis, A. Umbricht, K. L. Preston, and E. J. Cone

Intramural Research Program, NIDA, NIH, Baltimore, MD

Buprenorphine (BUP), a partial agonist under development for treatment of opioid dependence, produces prototypic opioid-like pharmacodynamic effects. The present study was conducted to test the safety and abuse potential of intravenous (IV) BUP in the range of doses used for maintenance treatment. Subjective effects of BUP SL (12 mg) and IV/SL placebo (in random order) and BUP IV (2, 4, 8, 12, and 16 mg in increasing dose order) were evaluated in separate sessions in this single-blind, double-dummy study. Data were collected from 6 non-dependent male opioid abusers. Subjective measures included visual analog scales of global drug effects, ARCI subscales, and adjective rating scales. All active BUP conditions produced increases in positive subjective measures compared to placebo, including high, drug effect, good effects, drug liking, opioid agonist adjective rating scale, and MBG scale of the ARCI. Peak effects occurred 1 to 1.5 hr after IV doses and 3 to 6 hr after SL BUP. Duration of action was 24 hours or longer (28 to 72 hr on some measures). Effects did not increase in an orderly dose-related manner. On many measures, the magnitude of effect was not different among all active doses. The effects of 16 mg IV tended to be less than those of 12 mg IV and varied in comparison to other active doses. The effects of 12 mg SL were similar in magnitude to 4, 8, and 12 mg IV. The results are consistent with a ceiling effect and partial agonist activity. The abuse potential of IV BUP does not appear to increase with dose, nor does there appear to be a substantial difference in abuse potential between IV and SL BUP at the doses tested.

PHARMACODYNAMIC PROFILE OF ENADOLINE, A SELECTIVE KAPPA (κ) AGONIST, IN HUMANS

S. L. Walsh, E. C. Strain, M. E. Abreu, and G. E. Bigelow

Johns Hopkins University School of Medicine, Baltimore, MD

Characterization of κ-agonist opioid actions in humans has been based largely on studies of drugs with mixed pharmacological activities. This study examined the physiological and subjective effects of enadoline (CI-977), a selective κ-opioid agonist, in comparison to the mixed-opioid butorphanol and the p-agonist hydromorphone. During twice-weekly inpatient test sessions, opioid-abusing volunteers (n=9) received an acute i.m. dose of enadoline (10-160µg/70kg), butorphanol (1.5-12mg/70kg), hydromorphone (1.5-6mg/70kg) or placebo. Randomized and double-blind conditions were used, except enadoline was given in ascending-dose order for safety. Before and for 5 hr after drug administration, subjective, physiological, and urinary data were collected. Each drug produced dose-related increases on ratings of "any drug effect;" however, enadoline increased ratings of "bad effects," while hydromorphone and butorphanol increased ratings of "liking." Both enadoline and butorphanol produced dose-related increases on a subjective scale of depersonalization. Hydromorphone and butorphanol, but not enadoline, decreased respiratory rate and pupil diameter. Enadoline did not produce significant sensory disturbances or other side effects at doses up to 80 µg; however, two subjects receiving the 160 µg dose, prior to its exclusion, had either frank visual hallucinations or visual distortions and other adverse behavioral effects. These data indicate that enadoline produces dysphoria but is well-tolerated at doses under 80 µg, while higher doses can produce psychotomimetic effects.

ACKNOWLEDGMENTS: Supported by NIDA R01 DA 10753, R01 DA04089, and T32 DA07209.

BEHAVIORAL AND PHYSIOLOGICAL EFFECTS OF OPIOID MU AGONISTS IN HEALTHY VOLUNTEERS: CUMULATIVE DOSING

D. J. Walker, J. L. Hill, P. Sadeghi, J. M. Klafta, P. A. Klock, and J. P. Zacny

Department of Anesthesia and Critical Care, The University of Chicago, Chicago, IL

Subjective, psychomotor, and physiological effects of three opioid mu agonists were studied using a cumulative-dosing procedure. Sixteen healthy volunteers with no history of drug abuse received i.v. injections of saline (S). morphine (MOR), hydromorphone (HM), or meperidine (MEP) in a randomized, double-blind, crossover design. Subjects received one injection per hour for the first four hours, and a 3-hr recovery period followed. S was injected first during each session; then S or increasing doses of drug were administered every hour for the next three hours. These doses were MOR 2.5, 5, and 10 mg/70 kg; HM 0.33, 0.65, and 1.3 mg/70 kg; and MEP 17.5, 35, and 70 mg/70 kg. Subjects completed mood forms and psychomotor tests, and vital signs were recorded at selected times following each injection and during recovery. Dose-related increases in subjective effects were observed, including increased scores on the PCAG and LSD scales of the ARCI and increased ratings of drug-effect strength, high, floating, and sedated. Ratings of drug liking were variable within and across subjects. All drugs impaired psychomotor performance in a dose-related manner, with MOR having the mildest effects. Dose-related miosis was observed for all drugs, with MEP showing the smallest effect. Although the doses tested were putatively equianalgesic, MOR appeared to affect mood and psychomotor performance to a lesser extent than the other mu agonists, and MEP increased ratings of mood effects typically associated with drug-induced "high" (e.g., high, floating, coasting, lightheaded, dizzy) to a greater extent than the other drugs.

ACKNOWLEDGMENT: Supported by NIDA grant DA-08573.

BEHAVIORAL EFFECTS OF PENTAZOCINE AND MORPHINE IN NON-DRUG ABUSING VOLUNTEERS

J. P. Zacny, J. L. Hill, M. L. Black, and P. Sadeghi

Department of Anesthesia & Critical Care, The University of Chicago, Chicago, IL

The purposes of this study were to characterize the subjective, psychomotor, and physiological effects of pentazocine in non-drug abusing volunteers, to compare and contrast the effects of pentazocine to those of morphine, and to determine if gender modulated the non-analgesic effects of pentazocine. Sixteen subjects (eight females and eight males) without histories of opiate dependence were injected in an upper extremity vein with 0, 7.5, 15, 30 mg/70 kg pentazocine, or 10 mg/70 kg morphine, using a randomized, double-blind, crossover design. Pentazocine increased scores on the PCAG and LSD scales and decreased scores on the BG scale of the Addiction Research Center Inventory, increased adjective checklist ratings of "nodding, " "sweating," and "turning of stomach," and increased visual analog scale ratings of "difficulty concentrating," "drunk," and "having unpleasant bodily sensations." Pentazocine (30 mg) had a greater propensity to increase ratings associated with dysphoria than did 10 mg morphine. Pentazocine produced impairment on several measures of psychomotor performance, but 10 mg morphine produced minimal psychomotor impairment. Both pentazocine and morphine induced miosis, but 10 mg morphine had a greater magnitude of effect than did 30 mg pentazocine. No gender differences on any of pentazocine's effects were noted. The results of the present study demonstrate that 7.5-30 mg pentazocine had orderly, dose-related effects on subjective, psychomotor, and physiological variables. Further, a clinically relevant dose of pentazocine, 30 mg, produced a greater magnitude of dysphoric subjective effects than did 10 mg of morphine, which is consistent with the literature of pentazocine having a greater likelihood of inducing psychotomimesis than other opioids.

ACKNOWLEDGMENT: Supported by NIDA grant DA-08573.

ORAL COMMUNICATIONS V

HIV RISK IN WOMEN WHO TRADE SEX FOR DRUGS, MONEY OR BOTH

C. F. Kwiatkowski and R E. Booth

University of Colorado School of Medicine, Denver, CO

Historically, studies have treated 'women who exchange sex for money or drugs' as a homogenous group. This assumption precludes an understanding of potentially important differences between women who exchange sex for drugs only, those who exchange for money only and those who exchange sex for both money and drugs. In this study, we analyzed responses from 2,042 women in 23 U.S. cities in the NIDA Cooperative Agreement on drug use and HIV risks. All reported exchanging sex in the 30 days prior to their interview for either drugs only (n=117), money only (n=960) or drugs and money (n=965). Results comparing the three groups indicated that women who exchanged sex for drugs only, and for money and drugs, were more likely to use alcohol and smoke crack than those who exchanged for money only. They were also more likely to have unprotected sex, the proportion of times they had unprotected sex was higher, and they were more likely to have had sex with a drug injector. Those who exchanged sex only for drugs reported having sex half as often as the other two groups and had one-fourth the number of partners, but they used condoms the least. Conclusions point to the importance of promoting condom use and increasing availability of condoms with this high risk population. Research into the relationship between crack use and sex-related HIV risk behaviors is also needed. Women who exchanged sex for money only were the most likely to inject drugs, particularly heroin, and were the least likely to have had unprotected sex. The importance of interventions, possibly drug treatment, to reduce the risk of infection through needle sharing is discussed. Future research is called on to determine if these three groups represent distinct types of women, or whether women move from one group to another, and if so, whether there is a predictable pattern. This would improve our efforts to prevent HIV infection in this population.

ACKNOWLEDGMENT: Supported by NIDA DA09832-03 and DA06912.

CLIENT AND COMMUNITY DIFFERENCES IN HIV RISK REDUCTION IN A NATIONAL TREATMENT SAMPLE (DATOS)

K. M. Broome, G. W. Joe, and D. D. Simpson

Institute of Behavioral Research, Texas Christian University, Fort Worth, TX

In the NIDA-funded Drug Abuse Treatment Outcome Study (DATOS), many clients in outpatient methadone treatment (OMT, N=956) and outpatient drug-free (ODF, N=1836) modalities were admitted with multiple sex- and needle-risk behaviors, and these risks were reduced significantly during treatment. Using hierarchical linear model (HLM) regression analysis, we examined client and treatment program characteristics as predictors of initial risk and improvement. Clients who used cocaine frequently or who had antisocial personality disorder entered both modalities with elevated risks. Cocaine users showed significant risk reduction in both modalities, but antisocial clients did so only in OMT. It was interesting that program-level comparisons showed treatment agencies in cities with higher prevalence of HIV/AIDS had clients with lower baseline levels of risk behavior than agencies in other cities. OMT programs in lower-prevalence cities had better rates of risk reduction than in higher-prevalence cities. Reduction of sex and needle risks during OMT and ODF indicates the importance of outpatient drug abuse treatment to national HIV-prevention policy.

ACKNOWLEDGMENT: Supported by NIDA grant U01-DA10374.

THE EFFECTS OF PSYCHIATRIC COMORBIDITY ON RESPONSE TO AN HIV PREVENTION INTERVENTION

W. M. Compton, L. B. Cottler, R. Cunningham-Williams, and A. B. Abdallah

Department of Psychiatry, Washington University School of Medicine, St. Louis, MO

Drug abusers, with psychiatric comorbidty are at high risk for becoming exposed to HIV. To address this compelling public health issue, our randomized HIV prevention study compares the effectiveness of the NIDA standard HIV testing and counseling protocol to a four session, peer-delivered, educational intervention. Among the 927 out-of-treatment injection drug (IDU) or crack cocaine using subjects who have completed the three month follow-up so far, we found significant improvement for both intervention groups in: crack cocaine use and number of drug injections, number of IDU sex partners and overall sex partners, but not condom use. In addition, subjects in the peer-delivered intervention improved more than the standard on crack cocaine use (83% vs. 78%, $p < .05$). We are now focusing on the effects of antisocial personality disorder (ASPD) and major depression on the prevention interventions because these disorders have been associated with higher than expected rates of HIV risk behaviors. Overall, for subjects with ASPD and/or depression, significant improvement was seen in all behaviors except condom use. For subjects with ASPD, there was a trend for less improvement in crack cocaine use, multiple sex partners and IDU sex partners. For subjects with depression, there was a trend for greater improvement in crack cocaine use. We conclude that drug users with ASPD and depression respond well to HIV prevention interventions.

ACKNOWLEDGMENT: Supported by the NIH NIDA grant DA 08324.

HIV RISK BEHAVIORS AMONG WOMEN MANDATED TO DRUG TREATMENT: DIFFERENCES BETWEEN NEW YORK AND PORTLAND

S. M. Strauss and G. P. Falkin

National Development and Research Institutes, Inc., New York, NY

The prevalence of HIV/AIDS is quite high among substance-abusing women offenders in New York City, but virtually nonexistent in Portland, Oregon. Yet, in both cities women offenders comprise a high risk population for HIV infection. Condom use with male partner is inconsistent, at best. A large number inject drugs and exchange sex for money or drugs. This paper compares the extent to which women who have been mandated to drug treatment in New York City (N~550) and Portland (N~400) engage in various HIV risk behaviors. The women are interviewed at intake to drug treatment in eight community-based and corrections-based programs participating in project WORTH (Women's Option for Recovery, Treatment and Health), a NIDA-funded evaluation of treatment programs for women offenders. Although self- reported HIV seropositivity is about 15% in New York City, the rare is close to zero in Portland. In contrast, the rate of injection drug use is significantly lower in New York City than in Portland (where about one third of the sample inject drugs). The paper compares the various risk behaviors of the two samples, focusing on indicators of the frequency of risky sexual behaviors (e.g., lack of condom use with steady partners, casual partners, and clients; unprotected sex with injection drug users and with men who are HIV seropositive) as well as risky drug using behaviors (e.g., sharing needles).

HIV RISK REDUCTION AMONG CRACK SMOKERS AFTER BEHAVIORAL DAY TREATMENT: 6 AND 12-MONTH FOLLOW-UP

J. E. Schumacher, D. Ross, J. B. Milby, P. Sekar, S. Usdan, C. McNamara, and R. DiClemente

University of Alabama at Birmingham Schools of Medicine and Public Health

HIV risk has been associated with a crack smoking lifestyle. Little research has demonstrated the reduction of HIV risk as a function of drug treatment. This study measured the reduction in HIV risk among crack smokers at 6 and 12 months after participating in a 2 month Behavioral Day Treatment (BDT) program for drug dependency. Subjects (N=111) were 78% male, 86% African-American, 41 (SD=15.5) years of age, crack cocaine dependent, homeless persons. They were administered the AIDS Risk Assessment for Crack (ARA-C) at baseline, 6 and 12 months follow-up after completing 2 months of BDT. Results (Chi Square and Paired t-tests) revealed significant ($p < .05$) reductions at 6 and 12 months, respectively, in any crack (-51.8%, -48.3%) and alcohol (-40.7%, -31.6%) use and reduced HIV risk in 4 out of 5 ARA-C constructs: Condom Use, Sex and Crack, Partners, IV Use and AIDS Awareness, with no change in Sexual Negotiation. At 6 and 12 months, subjects reported fewer unique sex partners, fewer sex partners shared crack with, fewer times traded sex for crack, and fewer times traded crack for sex. (p's $< .05$). Condom use with spouse/mate or date/trick did not increase at significant levels. These findings demonstrate the impact of drug treatment on HIV risk reduction.

ACKNOWLEDGMENT: Supported by NIDA grant R01 DA08475.

USING NEEDLE EXCHANGE PROGRAMS TO REDUCE DRUG USE

*R. K. Brooner, M. Kidorf, V. L. King, D. Vlahov, and P. Beilenson**

Johns Hopkins University School of Medicine, Baltimore, MD and Baltimore City Health Department, Baltimore, MD*

Although lowering incidence rates of human immunodeficiency virus (HIV) transmission is the primary goal of needle exchange programs, other desirable outcomes are possible. Referring exchange participants to more comprehensive drug abuse treatment programs has the potential to reduce or eliminate the use of drugs. In the present study, new admissions (1994-1997) to a drug abuse treatment program were first grouped by referral source (needle exchange, NEP; n = 82) vs. standard referral, SRS; n = 243) and then compared on admission demographic and clinical variables, and response to treatment during the first three months. Patients in both referral groups received daily methadone dosing, and individual and group counseling. All patients completed the Structured Clinical Interview for the DSM III-R (SCID) and the Addiction Severity Index (ASI) at baseline. Urine specimens were collected and tested one time per week. The results showed that NEP patients were more likely to be older, African American, and unemployed, and less likely to have a treatment history. At intake, NEP patients reported more heroin use (29 vs. 17 days) and cocaine use (15 vs. 5 days) during 30 days per-treatment; they were also more likely to be diagnosed as cocaine dependent (71% vs. 41%). NEP patients also reported more days involved in illegal activity (12 vs. 3 days), and more days injecting drugs (26 vs. 14 days) and sharing needles (5 vs. 2 days) during 30 days pre-treatment. Despite these baseline differences, both groups achieved comparably good short-term treatment outcomes (including reduced drug use and criminal activity for profit); treatment retention was also good, although slightly better in the SRS group (88% vs. 76%). These data demonstrate the feasibility and merits of creating strong linkages between needle exchange programs and more comprehensive drug abuse treatment clinics.

ACKNOWLEDGMENTS: Supported by NIDA grants R01 DA 09237, P50DA 05273, and RO1 DA 05569.

ORAL TESTING FOR HIV WITH DRUG USERS: OBSERVATIONS

J. Hoffman[1], H. Klein[1], D. Clark[1], L. Baskerville[1], and E. Moolchan[2]

[1]Friends Research Institute, Baltimore, MD and - [2]National Institute on Drug Abuse - Intramural Research Program, Baltimore, MD

As part of NIDA's Cooperative Agreement for AIDS Community-Based Outreach/Intervention Research Program. the Washington, D.C. site, Project NIA, has conducted HIV risk reduction interventions with over 1,600 drug users since 1993. In February of 1997, Project NIA replaced blood testing for HIV with oral testing. using the OraSure HIV-1 Oral Specimen Collection Device with nearly 400 drug users. The OraSure collection pad (in the shape of a small toothbrush) is placed in the back of the mouth for 2 minutes to collect the sample. The pad contains salts and proteins that draw antibody-rich oral mucosal transudate from the lining of the gum and cheek and onto the pad. The pad is placed in a specimen vial and sent to the lab for EIA testing and Western Blot confirmation. Studies have shown oral test results to be 99.9% consistent with blood test results. Prior to using oral testing. we were only able to obtain blood samples for approximately 85% of recruited subjects. For many subjects we could not obtain samples because their veins were inaccessible due to their extensive injection history. Outreach workers (trained in phlebotomy techniques) were unable to draw the blood. even after numerous attempts. With oral testing we have been able to obtain oral samples from 100% of new subjects and both subjects and outreach staff reported a preference for the oral test. In addition, oral testing greatly reduces the risk to outreach workers of HIV exposure through accidental needle sticks. Based on our experience, we would recommend the consideration of oral testing for HIV in research studies with drug-using populations.

DRUG TREATMENT AND HIV: IT'S NOT JUST ABOUT NEEDLES ANYMORE

T. Freese[1], S. Shoptaw[1,2], A. Huber[1,2,3], R. Rawson, and W. Ling[1,2,3]

LA Addiction Treatment Research Center, West LA VA Medical Center, UCLA Department of Psychiatry and Biohehavioral Science

Studies of HIV-risk among substance users have typically focused on needle use as a the primary factor for HIV transmission and infection. More recent studies have shown that in addition to needle sharing, users frequently engage in high-risk sexual behavior while on drug. Baseline and follow-up data (minimum 12-weeks post baseline) were collected on three cohorts of substance users in pharmacological or behavior treatment in Los Angeles: Primary cocaine users in pharmacological or behavioral treatment (n=126), primary opiate users in pharmacological treatment (n=198), and dually addicted users (opiates and cocaine) in combined pharmacological and behavioral treatment (n=105). Cocaine users reported seldom sharing needles (M=0.21 times in 30 days) compared to opiated users (M=25 times in 30 days) and dually addicted people (M=13 times in 30 days; $p<.001$). By contrast. cocaine users were more than 6 times more likely than opiate users to report trading sex for money drugs or gifts (6.6% vs. 0.9%; ($x^2=10.12$, df=2, $p<.01$). Findings indicated that needle risks were low for primary cocaine abusers. but sexual risks were high. For primary opiate abusers, needles risks were prevalent, but sexual risks were low. For dually addicted people, both sexual and needle risks were reported. Treatment corresponded to significant reductions in injection and needles sharing behaviors but little reduction in sexual risk behaviors or increase in perception of risk for contract HIV. Results indicate that treatment must include recognition of sexual risk behaviors that do not directly correspond to drug use in order to maximally reduce HIV risk.

ORAL COMMUNICATIONS VI

INTERACTIONS OF LOBELINE AND NICOTINE WITH AMPHETAMINE: *IN VITRO* DA RELEASE AND DRUG DISCRIMINATION IN RATS

L. P. Dwoskin, J. B. Acri*, P. A. Crooks, L. H. Teng, and J. M. Witkin*

College of Pharmacy, University of Kentucky, Lexington, KY and *Drug Development Group, NIDA Addiction Research Center, Baltimore, MD

Lobeline (LOB) is used as a smoking cessation agent and binds to nicotinic receptors. LOB does not act as a nicotinic agonist to release dopamine (DA) from rat striatal slices, but alters presynaptic DA storage by potently (IC_{50}= 0.88 μM) inhibiting DA uptake into synaptic vesicles (Teng *et al.,* 1997). Amphetamine (AMP) also inhibits (IC_{50}=4 μM) vesicular DA uptake (Ary and Komiskey, 1980), whereas nicotine (NIC) does not (Teng *et al.,* 1997). Current work shows that LOB and AMP inhibit (IC_{50}=0.9 and 40 μM, respectively) [^{3}H]dihydrotetrabenazine (TBZ) binding to vesicular membranes. Thus, in contrast to AMP, LOB interacts with the TBZ site on the vesicular monoamine transporter to inhibit DA uptake. Both LOB and AMP evoked DA release from vesicles (EC_{50}=25 and 2.2 μM, respectively). Thus, in contrast to AMP which equipotently inhibits DA uptake and promotes DA release from vesicles, LOB more potently (28-fold) inhibits DA uptake than it evokes release to redistribute presynaptic DA storage. LOB (0.1-1.0 μM) inhibited AMP (0.1-1.0 μM)-evoked DA release from striatal slices, suggesting that LOB-induced redistributed the DA pool accessed by AMP. To determine whether LOB would alter AMP's effect *in* vivo, rats were trained to discriminate 1 mg/kg methamphetamine (MAMP) from saline using a two-lever operant procedure. NIC (0.1-1.0 mg/kg) and LOB (1.0-10.0 mg/kg) did not result in MAMP-lever responding. Both drugs produced significant decreases in response rates, indicating that the doses were behaviorally active. Despite lack of substitution for MAMP, coadministration of NIC (0.1 or 0.3 mg/kg), dose-dependently and significantly potentiated the discriminative stimulus effects of MAMP. In contrast, coadministration of LOB (1.0 or 3.0 mg/kg), neither potentiated nor blocked the discriminative stimulus effects of MAMP. The results suggest that while neither NIC nor LOB are AMP-like in vivo or in vitro, NIC interacts with AMP via a mechanism different from that of LOB.

ACKNOWLEDGMENTS: Supported by NIDA grant DA05312 and the Tobacco and Health Research Institute, Lexington, KY.

ACUTE TOLERANCE TO NICOTINE DISCRIMINATION

K. Perkins, C. Fonte, W. White, and A. Wilson

Departments of Psychiatry and Anesthesia, University of Pittsburgh, Pittsburgh PA

We examined whether nicotine pre-treatment would attenuate the discriminative stimulus effects of acute nicotine intake by nasal spray, suggesting acute tolerance to nicotine discrimination. Male and female smokers (n=8) were trained to discriminate 20 ug/kg nicotine nasal spray from placebo (0) and tested for reliability of this discrimination (≥80% correct) on Day 1. On Days 2-4, subjects were first tested for retention of this discrimination and then pre-treated (in random order across days) with placebo, moderate, or high dose transdermal nicotine. The moderate dose was 14 mg or 21 mg for subjects weighing <70 kg or ≥70 kg, respectively, while the high dose was 28 mg or 42 mg, resp. After 4 hr, subjects were tested on generalization of discrimination across 0, 3, 6, 12, and 20 ug/kg nicotine by nasal spray (in random order) using a quantitative behavioral discrimination task. Afterwards, they engaged in nicotine self-administration trials. On all days, subjects abstained overnight from smoking. Results showed somewhat reduced accuracy of discrimination across generalization doses following moderate (e.g., 11% and 65% nicotine-appropriate responding for 0 and 20 ug/kg, resp.) and high (29% and 84%, resp.) transdermal nicotine pre-treatment conditions, compared with the placebo (10% and 86%, resp.) condition. Subjective stimulation and subsequent nicotine self-administration were simlilarly attenuated as a function of nicotine pre-treatment. Acute tolerance to nicotine's discriminative stimulus effects may develop in humans, helping to explain smoking patterns over the course of a day.

ACKNOWLEDGMENT: Supported by NIDA grant DA08578.

MECAMYLAMINE BLOCKS TOLERANCE TO NICOTINE IN RATS: IMPLICATIONS FOR THE MECHANISMS OF TOLERANCE

S. E. McCallum[1], A. R. Caggiula[1,3], L. H. Epstein[4], S. Saylor[1], T. Ploskina[1], and A. F. Sved[2]

Departments of Psychology[1] and Neuroscience[2], University of Pittsburgh, University of Pittsburgh Cancer Institute[3], and Department of Psychology, and University of Buffalo[4]

Mecamylamine, a non-competitive antagonist which prevents activation of nicotinic cholinergic receptors, does not prevent receptor upregulation produced by intermittent nicotine injections. Since upregulation, as a reflection of chronic receptor desensitization, has been proposed as the mechanism of chronic tolerance, the present experiments determined whether mecamylaminc also fails to prevent the development of tolerance. In all experiments. male. Sprague-Dawley rats were used as subjects and data were analyzed using ANOVAs and linear contrasts. In one experiment, 6, daily injections of mecamylamine (1 mg/kg s.c.) when given alone, did not alter the effects of a subsequent. acute injection of nicotine bitartrate (0.35 mg/kg, free base) in inducing antinociception in rats ($p>.05$; $n=27$). In other experiments. 6 daily pairings of mecamylamine with nicotine did block the development of tolerance to nicotine-induced antinociception (0.35 mg/kg)($p<0.001$; $n=36$) and to the ability of nicotine to suppress milk intake (0.66mg/kg)($p<0.001$; $n=36$). There was no evidence that after 6 pairings of mecamylamine with nicotine, the cues associated with mecamylamine delivery took on conditioned antagonistic properties. These findings suggest that unlike the receptor upregulation that results from either continuous or repeated nicotine administration, the tolerance following a short series of intermittent nicotine injections is dependent on receptor activation.

ACKNOWLEDGMENT: Supported by NIDA grant DA07546.

A BEHAVIORAL-ECONOMIC ANALYSIS OF NICOTINE REPLACEMENT PRODUCTS: DOSE, TYPE, PRICE, AND INCOME MANIPULATIONS

G. J. Madden, W. K. Bickel, and J. R. Hughes

Departments of Psychiatry and Psychology, University of Vermont, Burlington, VT

In a laboratory setting, human cigarette smokers could repeatedly self-administer two cigarette-puffs by completing a response requirement. Smokers abstained from smoking for 5 hours before each 3-hour session. Across sessions, the response requirement (price) varied from 2 to 4,000 pulls on a plunger. At each price, smokers administered placebo, 2, or 4 mg/hr nicotine nasal spray (NNS). Per session smoking was a decreasing function of cigarette price. Active NNS doses decreased smoking at the lowest price investigated, but no significant effects of NNS were observed at higher prices. In a second experiment, abstinent smokers were given incomes ranging from $0.25 to $8.00. In one condition, smokers could spend this money on cigarette puffs ($0.25 each) or 4 mg pieces of nicotine gum ($0.02 for 5 mins of chewing). In another condition, money could be spent on puffs ($0.25 each) or one 0.5-mg administration of nicotine nasal spray ($0.02 each). Money remaining at the end of a session was forfeited. Fewer smokers spent their income on NNS than on nicotine gum. Of those who did purchase these replacements, using the replacement decreased smoking below baseline levets and income had no consistent effect on the rate at which replacements were used. Together, the results of these experiments suggest that if cigarette price increases result in an income constraint, then smoking will decline, but nicotine replacements will not further reduce smoking. If a cigarette-price increase does not constrain income, however, concurrent use of nicotine replacements and cigarettes may decrease smoking, thereby benefiting public health. In order for any of these effects to be realized, however, nicotine replacements must have a substantial price advantage over cigarettes.

ACKNOWLEDGMENTS: Supported by NJDA grants DA06526 and DA07242.

COMPARISON OF INTRAVENOUS COCAINE AND NICOTINE IN CIGARETTE SMOKING COCAINE ABUSERS

I. A. Liebson[1], H. E. Jones[1], B. E. Garrett[1], and R. R. Griffith[1]

[1]Johns Hopkins University School of Medicine, Baltimore, MD and [2]Yerkes Regional Primate Research Center, Emory University, Atlanta, GA

The subjective and physiological effects of intravenously administered cocaine and nicotine were compared in 10 cigarette smoking cocaine abusers. Subjects resided on a behavioral pharmacology research unit. Subjects abstained from smoking for a minimum of 8 hours before each session. Under double-blind conditions, subjects received intravenous injections of placebo, cocaine (10, 20, 40 mg/70 mg) or nicotine (0,75, 1.5 and 3.0 mg/70 mg) in mixed order. Physiological and subjective data were collected before and repeatedly after each intravenous drug administration. At the end of each session, subjects completed a drug vs. money multiple choice procedure in which they chose between that day's drug and 44 monetary values. Overall, although both cocaine and nicotine increased subjective ratings of drug effect, rush, good effects, liking, high and stimulated, only nicotine increased ratings of bad effects and jittery. At doses that produced comparable ratings of drug effect (e.g., 40 mg/70 kg cocaine vs. 1.5 mg/70 kg nicotine), cocaine produced significantly greater good effects while nicotine produced greater bad effects. Cocaine also tended to increase reports of euphoria (MBG) whereas nicotine decreased MBG scores and increased somatic effects (LSD) and sedation (PCAG). The drug vs. money measure showed that the highest cocaine dose was worth twice as much as the highest nicotine dose. Thus, at comparable doses, cocaine and nicotine can be differentiated by their subjective and behavioral effects.

ACKNOWLEDGMENT: Supported by NIDA grant DA-03890.

NICOTINE AND ALCOHOL DEPENDENCE: OPIOID COMPONENT?

S. Krishnan-Sarin, M. Rosen, C. Farren, and S. S. O'Malley

Department of Psychiatry, Yale University School of Medicine, New Haven, CT

Nicotine and alcohol abstinence syndromes consist of signs and symptoms similar to those seen during abstinence from opiates. We used the naloxone challenge test, which is commonly used to precipitate opiate withdrawal and document dependence on opiates, to establish a role for the endogenous opioids in nicotine and alcohol withdrawal. Smokers (≥1 pack per day), alcoholic smokers (≥1 pack per day, 25-40 drinks/week) and controls (nonsmokers, nonalcohol-dependent) participated in four laboratory sessions which were separated by at least 48 hours. Subjects were required to abstain from drinking alcohol, smoking and eating for at least 10 hours prior to each session which ran from 8-10 am. The study medication (saline, 0.8 mg/70kg, 1.6 mg/70kg or 3.2 mg/70kg of naloxone) was administered intravenously at 9 am, following which the severity of withdrawal (Clinical Institute Narcotic Assessment; CINA), changes in craving for cigarettes (Tiffany), changes in craving for alcohol (Alcohol Urge questionnaire) and corresponding physiological changes (skin temperature, blood pressure) were assessed for 1 hour. Naloxone produced dose-related increases in total CINA scores in smokers ($p<0.05$) and in "feeling tired" ($p<0.05$) when compared with nonsmokers; skin temperature was also altered in a naloxone dose-dependent manner ($p<0.05$) with increases seen in nonsmokers compared with smokers. Smokers also exhibited increased "urges to smoke" following challenge with the two lower doses of naloxone ($p<0.05$) but not following the highest dose (3.2 mg/70 kg). Preliminary results from a small sample of alcoholic smokers (n=3) indicate that these subjects also experienced increases in CINA scores when compared with control nonsmokers, which were not significantly different from those experienced by smokers. These results suggest a role for the endogenous opioids in acute nicotine withdrawal; the role of opioids in alcohol withdrawal and dependence remains to be determined.

ACKNOWLEDGMENTS: Supported by R01-AA11139, K02-AA00171, and M01-RR00125.

SELEGILINE EFFECTS ON SMOKING AND ABSTINENCE

E. J. Houtsmuller and M. L. Stitzer

Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD

Nicotine administration increases dopamine (DA) levels in mesolimbic brain areas, and this effect appears to be involved in its reinforcing effects. Furthermore, brain levels of the enzyme monoamine oxidase-B (MAO-B), which metabolizes DA, are reduced in smokers as compared to nonsmokers. Thus, in smokers, lowered MAO-B levels may enhance nicotine-induced DA transmission in the brain. MAO-B inhibition by cigarette smoke appears to be reversible, suggesting levels rise during abstinence. In smokers attempting to quit, these increasing MAO-B levels in the absence of nicotine-induced DA release may produce a significant decrease in DA activity. Since DA release in the mesolimbic system in the brain is associated with reward and reinforcement, this reduction in brain DA activity may underlie some of the discomfort and craving associated with smoking abstinence. Pharmacological inhibition of MAO-B levels during abstinence may reduce some of these withdrawal symptoms. Fifteen adult smokers completed this randomized, double-blind, placebo controlled, within-subjects design study. Subjects reported to the lab daily during each of two 5-day experimental phases. They received the MAO-B inhibitor selegiline (10 mg., p.o.) or placebo on days 1-4 of each phase (in counterbalanced order), with a 17 day wash-out period between the two phases. Subjects were required to abstain for 48 hrs after their third lab visit of each phase, and withdrawal symptoms and difficulty abstaining were assessed daily. During the third and fifth visit of each phase, 60 min. ad lib smoking was analyzed using smoking topography measures, and physiological and subjective responses to smoking were recorded. Results suggest that selegiline did not affect subjective ratings of withdrawal. or smoking behavior in the lab assessed under controlled conditions. Smoking behavior in the natural environment was not affected either. These findings do not provide support for the use of selegiline as a smoking cessation aid.

ACKNOWLEDGMENT: Supported by NIDA grant DA03893.

ORAL COMMUNICATIONS VII

PHARMACOKINETIC DETERMINANTS OF WITHDRAWAL SEVERITY IN METHADONE MAINTENANCE PATIENTS

J. M. White, K. R. Dyer, D. J. R. Foster, J. S. Hanna, A. Menelaou, F. Bochner, and A. A. Somogyi

Department of Clinical & Experimental Pharmacology, University of Adelaide, Australia

Approximately one third of methadone maintenance patients frequently experience withdrawal symptoms before each dose and are at risk of returning to illicit opioid use. We studied 18 patients, 9 who did not experience such withdrawal ('holders') and 9 who did ('non-holders') to determine if the two groups had different racemic methadone pharmacokinetics and/or pharmacodynamics. Each patient underwent a 24 hour interdosing interval study, during which (i) 13 venous blood samples were collected to measure plasma racemic methadone concentrations, and (ii) various opioid effects were quantified on 11 occasions. For the whole group, MBG score and analgesia were directly related to methadone concentration, while withdrawal, respiratory rate and pupil diameter were inversely related. Withdrawal severity was significantly higher for the non-holder group. Comparison between the two groups on several pharmacokinetic parameters showed no difference in trough concentration or area under the curve, an index of clearance, but a significant difference in peak rate of decline in plasma concentration. Over the whole subject group, withdrawal severity was significantly correlated with the peak rate of decline in plasma concentration. In a follow-up study of 5 subjects, all non-holders, the pharmacokinetic profile for each subject was shown to be consistent over 3 inter-dosing intervals. For area under the plasma concentration-titne curve, the ratio of inter- to intra-individual variability was 15:1. The results suggest that withdrawal late in the inter-dosing interval is a result of more rapid metabolism or distribution of methadone that is characteristic of a significant sub-group of methadone maintenance patients.

ABSTINENCE REINFORCEMENT AND METHADONE DOSE INCREASES FOR TREATMENT OF OPIOID DEPENDENCE

K. L. Preston, A. Umbricht, and A. DeJesus

NIDA Intramural Research Program, Baltimore, MD

Methadone maintenance is an effective therapy for heroin dependence, though some patients continue use while in treatment. This study evaluated whether abstinence reinforcement, methadone dose increases, and their combination would be more effective than standard treatment without a dose increase in reducing heroin use in methadone maintenance patients. Patients who used heroin during the first 5 weeks of maintenance treatment (methadone 50 mg/day plus weekly counseling) were randomly assigned to 4 groups (N = 29-31/group): contingent vouchers for opiate-negative urine specimens plus methadone dose increase to 70 mg/day; contingent vouchers with no dose increase; dose increase plus noncontingent vouchers; and a control group that received noncontingent vouchers with no dose increase. Study interventions were in effect for 8 weeks; observed urine specimens were collected MWF. Vouchers were exchangeable for goods and services and given for each opiate-negative specimen (Contingent) or independent of urine results (Noncontingent). Preliminary analyses showed that opiate use decreased during the intervention period by about 10% in the control group and by about 30% in the three experimental groups. Thus, abstinence reinforcement and methadone dose increase were equally effective in decreasing opioid use, and both were more effective than noncontingent vouchers with no dose increase. However, their combined effects were not greater than either treatment alone.

ACKNOWLEDGMENT: Supported by the NIDA Intramural Research Program.

DAY TREATMENT VERSUS ENHANCED STANDARD METHADONE SERVICES IN A VETERAN POPULATION

S. M. Stine, S. K. Avants, A. Margolin, M. H. Usubiaga, K. T. Thompson, and T. R. Kosten

Yale University and VA Connecticut Healthcare System, CT

The optimal intensity of psychosocial services for methadone patients has been investigated in several published studies. A simultaneous replication study was conducted at the APT Foundation in New Haven and at the West Haven campus of VA Connecticut Healthcare. Patients were randomized to day or weekly treatment for 12 weeks and retention and drug use were primary outcome measures. Secondary outcome measures included employment, ASI and RAB scores. Results from the APT site (CPDD 1997) did not show a difference in outcome between the two interventions. At the VA site, 54 unemployed veterans, age 44 ± 0.9 (SEM), 24% African-American, with 17 ± 1.4 (SEM) years of opiate dependence were randomized to day or manual-guided weekly treatment (with similar components to the day program). Groups were balanced with respect to most baseline variables. A group imbalance occurred with respect to ASI subscales: years of opiate use, drug severity and psychiatric severity were higher in the day group. Urine toxicology for opiates showed significant improvement with time and a trend toward greater improvement for day treatment patients (RMANOVA: df 1,52, F=2.876, p= .096 for treatment effect and df 13,52, F=11.26, p=.000 for time effect) in spite of greater baseline severity but there was no time by treatment interaction. There was no significant effect on cocaine toxicology or retention. Several ASI subscores improved significantly with time as did total RAB score and drug risk subscore. There was a trend toward greater improvement in ASI psychiatric severity (time by treatment interaction) in the day group. Post-hoc analyses in subjects with and without psychiatric diagnosis revealed different patterns of improvement in these subjects. Although day treatment did not prove more effective than weekly treatment, there may be a differential benefit from intensive treatment to patients with co-occurring psychiatric disorders.

ACKNOWLEDGMENT: Supported by NIDA grant DA08754.

LAAM AND METHADONE MAINTENANCE TREATMENT: DEMOGRAPHICS, RETENTION AND DRUG USE

J. Annon, D. Longshore, and M. D. Anglin

UCLA Drug Abuse Research Center, Los Angeles, CA

This is a preliminary report on the first year of a four year study of heroin addicts comparing the differential effects of methadone and levo-alpha-acetyl methadol (LAAM) on retention in treatment and drug use. It is hypothesized that the "window of vulnerability," the period during which blood levels of the maintenance drug are lowest and craving for heroin highest, is smaller for LAAM subjects than for those on methadone and thus there will be greater retention and less drug use for LAAM maintenance clients. This study is recruiting 320 heroin addicts in the Los Angeles area and randomly assigning them to either a methadone or LAAM maintenance treatment condition. The first 160 clients in the study are 70% male, 13% white, 46% African American and 36% Latino. Of the 79 clients who have reached their one year anniversary date, 45% of the methadone maintenance subjects completed treatment, compared to 67% of the LAAM maintenance subjects. Incarceration continues to be the primary reason for discharge while methadone clients had more "no-shows" and "leaving for medical reasons" than LAAM clients. There were no differences in opiate use during treatment, while cocaine use seemed more prevalent among LAAM clients than methadone clients in treatment. Plans for future analysis included contrasting drug use patterns within groups, as well as comparing MM and LAAM HIV risk behavior at six month follow-up.

ACKNOWLEDGMENT: Supported by NIDA grant RO1-DA10422.

THE FIRST 100: LAAM TREATMENT WITH AND WITHOUT TAKE-HOME PRIVILEGES

A. Huber[1,2], R. Rawson, C. L. Cantu[1], S. Sirusuk[1], P. Kintaudi[1], and W. Ling[1,2]

[1]LA Addiction Treatment Research Center, Long Beach and [2]VA MDRU, Los Angeles, CA

Clinicians continue to have questions about using LAAM for opiate pharmacotherapy that involve standard LAAM use issues and about allowing for take home doses. We report on the first 100 patients randomized to receive standard LAAM treatment (SLT) or to receive an experimental paradigm in which take home (THL) doses could be earned. There was no difficulty generating patient interest in trying LAAM and nearly all patients tolerated a standard induction schedule. Attendance at the clinic was very good for both groups (95%); illicit opiate use was reduced by encouraging patients to increase their dose; other substance use continued unless addressed by counselors. Most patients completed the 48 week protocol; reasons for early discontinuation are similar to those seen at methadone clinics (jail, moving, transportation problems). Patients who were employed at baseline were more likely to earn take home LAAM (Earned TakeHome = 15.3 days worked vs. No TakeHomes = 6.5 days worked, $p<.01$) as were patients without concurrent cocaine dependence (Earned TakeHome = 1.2 days used vs. No TakeHomes = 5.8 days used, $p<.01$). Overall, THL patients showed better clinical outcome as measured by retention and urine toxicology, but not at statistically significant levels. THL patients also had no more adverse reactions than SLT patients and there has been no evidence of diversion over the three years. There were few adverse events over 3400 patient-weeks of LAAM treatment and none were LAAM specific. Findings indicate that take-home dosing for LAAM is feasible and there is no empirical evidence for restricting take home dosing. Additionally, offering take-home doses may encourage heroin users not currently in treatment to start treatment.

BUPRENORPHINE AND METHADONE - A RANDOMIZED COMPARISON STUDY

H. Eder, G. Fischer, W. G. Gombas, R. Jagsch, C. Nagy, C. Lennkh, and S. Kasper

Department of General Psychiatry, University of Psychiatry, Vienna, Austria

The efficacy of buprenorphine in opioid dependent patients was compared to methadone maintained subjects in a randomized comparison trial. Primary outcome measures were abstinence from other drugs and retention in treatment. During a 24 week study period, no significant difference in the retention rate of 20 patients on a mean dosage of 7,3 mg buprenorphine (sublingual tablets) and the retention rate of 20 patients on a mean dosage of 63 mg oral applicable methadone (racemat of L- and D-Methadone) could be found. There was also no significant difference within the two groups during the treatment time in regard to additional consumption of opiates, benzodiazepines and cocaine. The drop-out rate in the buprenorphine group was 55% in comparison to 25% in the methadone group. A significant longer treatment period could be calculated for methadone-maintained subjects ($p = 0.04$). These patients remaining in the buprenorphine treatment program showed a lower additional consumption rate during the last weeks of the study. The results of this trial demonstrate the efficacy of using an alternative opioid with respect to oral maintenance therapy in opioid dependency. The upper dosage limit of the daily 8 mg sublingual tablets as used in this trial was probably set too low.

CONTROLLED CLINICAL TRIAL COMPARING MAINTENANCE TREATMENT EFFICACY OF BUPRENORPHINE (BUP), LEVOMETHADYL ACETATE (LAAM) AND METHADONE (M)

M. Chutuape, R. E. Johnson, E. C. Strain, S. L. Walsh, M. L. Stitzer, D. A. Bloch, and G. E. Bigelow

Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD

M and LAAM are approved and BUP is currently under review by the FDA for the treatment of opioid dependence. Randomized controlled trials have compared the efficacy of M to LAAM and M to BUP; however, none have compared all 3 medications. Opioid dependent subjects (N=220; 55/group) enrolled in this randomized, stratified, parallel group, double-blind, triple-dummy study comparing the 3 medications. Subjects (enrolled Jan 17, 1996 - May 31, 1998) were stratified on age, race, sex, cocaine use, ASP, and marital status. BUP and LAAM were dosed M-W-F (placebo M on Tu, Th, Sa, Su); the two M groups (high and low dose) were dosed daily. Flexible maintenance doses were used for BUP [16-32 mg (M-W; 50% increase on F)], LAAM [75-115 mg (M-W; 40% increase on F)], and high dose M (60-100 mg/day); a fixed 20 mg/day dose was used for low dose M. Treatment included 2 weeks of dose induction and 15 weeks of maintenance. Urine samples were collected M-W-F. Subjects not responding to treatment were rescued from the protocol, with low dose M subjects rescued as early as 6 weeks. Preliminary results on mean maximum dose, study retention and opioid and cocaine urinalyses are presented. Mean maximum doses for BUP, LAAM and high dose M were 28, 100, and 90 mg, respectively. Study retention for BUP, LAAM, and high dose M was 58%, 53%, and 73%, respectively, and significantly differed from low dose M (20%; $p<.003$). Retention also differed between high dose M and LAAM ($p<.02$), but not BUP ($p=.10$). Mean % of opioid-negative urine samples for BUP, LAAM, and high dose M was 34%, 39%, and 40%, respectively, and significantly differed from low dose M (16%; $p<.05$). Mean % of cocaine-negative urine samples among the groups did not differ (range = 37-45%). These results demonstrate that all 3 medications are effective treatments for opioid dependence. However, more detailed analyses are needed to determine whether differences exist among the 3 medications. Further analyses may also provide information regarding patient-treatment matching.

ACKNOWLEDGMENTS: Supported by NIDA grants P50 DA05273, K05 DA00050, K20 DA00166 and T32 DA07209.

ORAL COMMUNICATIONS VIII

ANANDAMIDE AND *MURINE* CANNABINOID RECEPTOR GENETICS

E. S. Onaivi, L. Stubbs, A. Chakrabarti, L. Chitterndern, D. P. Hurst, B. E. Akinshola, D. Shire, and P. H. Reggio

Dept. of Pharmacology and Psychiatry, Vanderbilt Univ., and NRI, Nashville, TN; Lawrence Livermore Nat. Lab. Livermore, CA; Kennesaw State College, Marietta, GA; Howard Univ. Coll. Med., Washington, DC; and Sanofi Recherche, Labege Cedex, France

The abundant expression of the cannabinoid receptors, *Cnrs,* and the discovery of endocannabinoids suggests that the cannabinoid system represents a previously unrecognized elaborate neurochemical net-work in the CNS and PNS whose biological role is incompletely understood. We have identified a number of sequence tags activated in the brains of mice treated with methanandamide. Differentially expressed cDNAs were re-amplilied and cloned in pCR-TRAP vector. The inserts were amplified from the plasmids isolated from these clones and sequenced. In addition, we have cloned, sequenced, constructed the 3D helical structures and localized the *murine* CB, and CB_2 *Cnr* genes to chromosome 4. Using interspecific backcross methods, the genetic map of *murine* CB_1 and CB_2 genes were localized to different spots on chromosome 4. Interestingly, CB, and CB_2, GABARR1, and GABARR2 and CGA are linked together both in the mouse and on human chromosome 6q. The chromosomal location of the mouse and human CB_1, and CB_2 genes adds a new marker to the region of the human 6q genes of mouse-human homology. 3D models of the transmembrane helix bundles of the mouse CB_1 were compared to CB_2 receptors using the chem-X modeling program. There were striking similarities and significant differences that may explain the differential Gprotein coupling properties and the binding and docking profile of cannahinoid ligands to CB_1 and CB_2 *Cnrs.* It is not obvious if there are links between the chromosomal map established for the *Cnr* genes and existing mouse mutations.

ACKNOWLEDGMENT: Supported by NIH/NHLBI- K01-HL03319 to ESO and NIDA grant 03934 (PHR).

(R)-METHANANDAMIDE AS A DISCRIMINATIVE STIMULUS IN RATS: TESTS WITH ANANDAMIDE AND Δ^9-THC

T. U. C. Jarbe, R. J. Lamb, A. Makriyannis*, S. Lin*, and A. Goutopolos*

Allegheny Univ. Hlth Sci., Dept. Psychiat, Philadelphia PA, and *Univ. Connecticut, Dept. Molec. Cell Biol., Storrs, CT

Eight male Sprague-Dawley rats (Taconic Farms, NY) were trained to discriminate between 10 mg/kg (R)-methanandamide (RM), a biologically more stable chiral analog of the endogenous ligand anandamide, and vehicle (3 ml/kg, i.p., 15 min. prior to session onset). A two lever operant methodology (FR-10) was used (session length = 20 min.). Once trained. the animals were tested on separate occasions (session length = 6 reinforced trials with both levers operable) with various doses of RM (range: 1 to 18 mg/kg) and Δ^9-THC (THC; range: 0.1 to 3 mg/kg) at 15 and 30 min. post injection. Both RM and THC dose-dependently occasioned RM appropriate responding. THC was more potent than RM at both test intervals (ED50, linear regression: THC, 0.45 mg/kg and 0.54 mg/kg; and RM, 6.07 mg/kg and 6.63 mg/kg. for the 15 and 30 min. post administration tests, respectively). Additional time course tests with two fixed doses of RM revealed that the effects were reduced to half at ≈ 63 min. and 124 min. for 10 and 18 mg/kg RM, respectively. Tests with anandamide (10 and 18 mg/kg, i.p., 15 min. after administration) yielded a maximum of (15% RM appropriate responding. However, in tests commencing 3 min. after i.p. administration of 10 and 18 mg/kg anandarnide, ≈ 41% and ≈ 85% RM appropriate responding occurred with the two doses. respectively. A corresponding test with vehicle (i.e., 3-min. post) resulted in only ≈ 7% RM appropriate responding. Work is in progress to further characterize the RM ligand as a cannahimimetic discriminative stimulus.

ACKNOWLEDGMENTS: Supported by NIDA grants DA 09064 and DA 00253 (Philadelphia): and DA 03801, DA 9158, DA 7215, and DA 00152 (Storrs).

EFFECTS OF Δ^9-THC ON MEMORY IN MONKEYS

J. M. Moerschbaecher, P. Lambert, and P. J. Winsauer

Department of Pharmacology, LSU Medical Center, New Orleans, LA

We have previously reported that Δ^9-THC (0.056 - 0.32 mg/kg) increases the percentage of errors in a learning task while having little or no effect on accuracy of responding in a comparable performance task. A similar differential effect does not, however, obtain between the tasks in terms of the effects of Δ^9-THC on overall response rate. The present study was designed to characterize the effects of Δ^9-THC in terms of it's actions on memory processes utilizing a repeated-acquisition and delayed-performance procedure. In this procedure each session was divided into three phases: an acquisition phase, a delay phase and a delayed-performance phase. Retention was quantified through the use of a percent savings measure. When administered immediately after acquisition and 60 min prior to the delayed-performance testing, Δ^9-THC (0.01-0-1 mg/kg) decreased percent savings in a dose-related manner, but had little or no effect on rate of responding. The maximal effects on percent savings were obtained at doses approximately 1/2-log unit lower than those required to disrupt learning or performance in our previous study. Together these data would suggest that Δ^9-THC disrupts short-term memory at doses lower than those required to effect both "working" (learning) and long-term (performance) memory.

ACKNOWLEDGMENT: Supported by DA04775.

RESPONSES TO ORAL Δ^9-TETRAHYDROCANNABINOL IN MARIJUANA USERS AND NONUSERS

J. M. Kirk and H. de Wit

Department of Psychiatry, The University of Chicago, Chicago, IL

An individual's drug use history affects the quality of subjective effects they experience following administration of clinically used psychoactive drugs such as barbiturates, diazepam and morphine. However, it is not known whether drug use history affects responses to therapeutic cannabinoids such as Δ^9-THC. The current experiment compared the subjective and behavioral effects of oral Δ^9-THC in two groups of volunteers. Users (n = 11), who reported using marijuana at least 100 times and Nonusers (n = 10) who reported using marijuana 10 or fewer times, participated in 3 sessions during which they received Δ^9-THC (7.5 and 15 mg) and placebo. They completed subjective effects questionnaires (e.g., visual analog scales, ARCI) for 5 hours following administration. In Users, but not Nonusers, the lower dose (7.5 mg) markedly increased ratings of "feel" drug and "high" as well as ratings on the ARCI Marijuana scale, suggestive of expectancy effects or sensitization. In contrast, at the higher dose (15 mg), the Users' ratings were lower than the Nonusers, suggestive of tolerance. Additionally, Nonusers reported greater sedation than Users following both doses of Δ^9-THC, again possibly suggesting tolerance to the sedative effects of this drug. These findings demonstrate that marijuana use history may affect the subjective effects of oral Δ^9-THC in complex ways. These findings may have important implications for the clinical use of this drug.

ACKNOWLEDGMENT: Supported by NIDA grant DA03517.

EFFECTS OF MARIJUANA ON HUMAN SENSITIVITY TO CHANGES IN REWARD FREQUENCY

S. D. Lane, D. R. Cherek, D. M. Dougherty, and F. G. Moeller

Human Psychopharmacology Laboratory, Department. of Psychiatry and Behavioral Sciences, University of Texas Health Science Center - Houston, Houston, TX

Light to moderate marijuana users (1-8x in the past 60 days) were recruited into the study and screened during personal interviews. Subjects were excluded for any history of medical or Axis I psychiatric illness, or current drug use detected by urine drug screens. Subjects worked on a computer based laboratory task in which they had 2 response options. Monetary rewards were obtained for each response made after a variable time period, averaging every 5 seconds, had elapsed (Random Interval). On baseline days. options were not available concurrently, but switched every 6 minutes (multiple RI 5s - RI 5s). This created equal response patterns between the 2 options. On experimental days, immediately following either placebo or active marijuana administration (1/2 1.77%, 1.77%, 3.58% Δ^9-THC), the task provided both alternatives concurrently (concurrent RI 5s - RI 5s) - subjects were free to choose either option at any time. In the first 10 minutes of a 50 minute session, each response option provided rewards with the same frequency. Every subsequent 10 minutes, the initially preferred option systematically decreased in reward frequency. Under placebo subjects' response distributions reflected the changes in reward frequency, but higher doses of marijuana blunted subjects' tracking of changes in reward frequency, resulting in significantly less monetary gain. The data suggest that THC acutely affects rewards systems, and these effects can be measured behaviorally via responding in choice paradigms.

ACKNOWLEDGMENTS: Supported by NIDA grants F32-DA05774 (SDL) and DA10592 (DRC).

EFFECTS OF MARIJUANA ON MOOD, EQUILIBRIUM, AND SIMULATED DRIVING

A. Liguori, C. P. Gatto, and J. H. Robinson

Department of Physiology and Pharmacology, Wake Forest University School of Medicine, Winston-Salem, NC

Delta-9 tetrahydrocannabinol (THC) is frequently found in the blood of drivers involved in automobile accidents, and marijuana use has been associated with impaired performance on field sobriety tests. The present study used a within-subject design to compare the effects of marijuana (0, 1.77, or 3.95% THC) on equilibrium and simulated driving. Ten marijuana users (7 men, 3 women) smoked a marijuana cigarette at the beginning of each session. Two minutes later, they began a 60-minute test battery that included 1) subjective effects scales, 2) a computerized test of body sway, 3) brake latency measurement in a driving simulator, 4) a rapid judgment task in the simulator (JUDGE), 5) critical flicker fusion (CFF), and 6) a choice reaction time task (CRT). Self-report ratings of "high" and "drug potency" increased comparably following both active doses. The high but not the low dose significantly increased body sway. The high dose also increased brake latency by 55 msec, which is comparable to an increase in stopping distance of nearly 5 feet at 60 MPH ($p < 0.10$). JUDGE, CFF, and CRT scores did not differ with THC dose. The equilibrium and brake latency data with 3.95% THC are similar to prior results in our laboratory in participants with breath alcohol concentrations near 0.05%.

ACKNOWLEDGMENT: Supported by NIDA grant 10997.

ABSTINENCE SYMPTOMS FOLLOWING DISCONTINUATION FROM LONG-TERM HEAVY MARIJUANA USE IN HUMANS

E. M. Kouri[1,2], H. G. Pope, Jr.[2], and S. E. Lukas[1]

[1]Behavioral Psychopharmacology Research Laboratory and [2]Biological Psychiatry Laboratory, McLean Hospital/Harvard Medical School, Belmont, MA

Even though marijuana is the most commonly used illicit drug in the United States, it is still undetermined whether withdrawal from chronic use results in an abstinence syndrome in humans. We have previously reported significant increases in aggressive responding during the first week following abrupt discontinuation from long-term heavy marijuana use. The present study was conducted to further characterize and identify, with a 13-item diary, symptoms that may be associated with marijuana withdrawal following chronic use. The diary contains items assessing changes in mood, ability to concentrate, sleep, appetite, anxiety, irritability, physical tension, physical symptoms, and desire to use marijuana. To participate in the study, subjects had to have smoked marijuana on at least 5,000 separate occasions (the equivalent of smoking daily for approximately 14 years) and had to be smoking regularly when recruited. Subjects came to the laboratory every day during a supervised 28-day abstinence period to provide urine samples that were analyzed quantitatively for Δ^9 THC and to fill out the diaries. Our findings indicate that subjects experienced the greatest symptom severity during the initial 7 days of abstinence. Specifically, subjects reported increases in anxiety, irritability and physical tension, and decreases in appetite and sleep. All of these symptoms returned to pre-withdrawal levels within 28 days of abstinence. In addition, symptom severity during the first week of abstinence did not correlate with subjects' self-report of frequency of use. Instead, there was a significant correlation between urinary THC levels at baseline and the severity of symptoms experienced during the first week. The findings from this study provide important information regarding the nature, severity, and time course of symptoms associated with marijuana abstinence following chronic use and suggest that THC levels are a better predictor of symptom severity during abstinence than lifetime history of use.

ACKNOWLEDGMENTS: Supported by grants DA10346, DA03994, and DA00343.

RESIDUAL EFFECTS OF MARIJUANA USE: AN fMRI STUDY

D. A. Yurgelun-Todd, S. A. Gruber, R. A. Hanson, A. A. Baird, P. F. Renshaw, and H. G. Pope, Jr.

Brain Imaging Center, McLean Hospital, Belmont, MA

High speed echo planar magnetic resonance (EPMR) techniques provide a powerful non-invasive methodology for investigating brain dysfunction related to chronic drug use. Studies of cerebral activation in normal controls suggest that the dorsolateral prefrontal cortex (DLPFC) demonstrates a significant increase in metabolism during working memory tasks. Recent studies of marijuana users have reported deficits in cognitive functioning, particularly in the executive/attentional systems. In an effort to clarify the residual effects of marijuana for moderating the cerebral hemodynamic response to cognitive processing, we applied fMRI to eight chronic smokers at two time points of washout: after twenty-four hours, and after twenty-eight days; and eight healthy control subjects. Chronic use was defined as having smoked more than 5000 times in a lifetime, and including current daily use. All subjects were screened for a history of psychiatric and neurologic illness. Scanning was performed on a 1.5 GE Signa, using a quadrature head coil. Images were acquired in the coronal plane in succession using a modified echo planar imaging technique for each activation phase. All images were motion corrected. The challenge paradigm was a visual working memory task with known sensitivity to the DLPFC. Cortical activation was measured using neuroanatomically defined regions of interest based on conventional MR and EPMR images. Control subjects produced significant activation in the DLPFC during the challenge paradigm. In contrast, smokers who completed twenty-four hours of washout showed diminished activation in this region. This effect remained diminished after twenty-eight days of washout, although some increase in the DLPFC activation was noted relative to the twenty-four hour time point. In contrast, smokers produced increased activation in the cingulate during both washout conditions, whereas controls did not. These results indicate that even after an extended washout period, specific differential patterns of cortical activation exist in subjects with a history of heavy marijuana use.

CANNABIS DEPENDENCE: A ONE YEAR FOLLOW-UP OF LONG-TERM CANNABIS USERS

W. Swift, W. Hall, and J. Copeland

National Drug and Alcohol Research Centre, University of New South Wales, Sydney, Australia

While there is an established body of research on cannabis dependence among general population samples, there are few detailed examinations of use and dependence among long-term cannabis users. This paper reports on the one year follow-up of a cohort of 200 long-term cannabis users in Sydney, Australia, who had been smoking at least weekly for an average of 11 years. Half (56%) were daily smokers, and a majority (92%) met lifetime DSM-III-R dependence criteria, although only a third (33%) believed they had a cannabis problem. Eighty one percent of the sample (n= 162) were re-interviewed at one year. Half (51%) were daily smokers, while one in live were smoking less than weekly or not at all. The majority (81%) received a dependence diagnosis for the last year on at least one of three dependence measures: the short University of Michigan CIDI (UM-CIDI), a measure of ICD-10 dependence and the Severity of Dependence Scale. Again, one third believed they had a cannabis problem. Pearson correlations and Cohen's kappa indicated variable levels of agreement among these measures. Frequency and quantity of use, the likelihood of receiving a dependence diagnosis and the belief that cannabis was a problem were stable between interviews. Multivariate longitudinal analyses revealed that quantity of use, dependence and problematic use at initial interview were the primary predictors of those same variables at follow-up. These data complement existing literature on cannabis use patterns and dependence, and support the notion that they are fairly stable among long-term users.

ACKNOWLEDGMENT: Supported by a National Drug Strategy Research Scholarship, Commonwealth Department of Health and Family Services, Australia.

BRIEF COGNITIVE BEHAVIOURAL INTERVENTIONS FOR CANNABIS DEPENDENCE

V. Rees[1], J. Copeland[1], W. Swift[1], R. Roffman[2], and R. Stephens[3]

[1]National Drug and Alcohol Research Centre, Sydney, Australia; [2]University of Washington, WA; and [3]Virginia Polytechnic Institute, VA

The rapidly increasing demand for treatment for cannabis dependence in Australia and internationally has lead to the identification of significant gaps in knowledge of effective interventions. A randomized, controlled trial of brief cognitive behavioral (CBT) interventions for cannabis dependence was undertaken to address this issue. A total of 240 subjects were assessed and allocated to either a six-session CBT program, a single-session brief intervention, or a waiting list control group. Subjects were assisted in acquiring skills to promote cannabis smoking cessation and maintenance of abstinence. These include behavioural self monitoring, coping with urges, managing triggers and high risk situations, cognitive restructuring and relapse prevention strategies. Subjects were followed up six months after treatment or allocation to waiting list. The characteristics of the sample of cannabis users seeking treatment and psychological and social problems associated with this group will be presented. Preliminary outcome data of the treatment interventions indicate that CBT interventions provide an effective method for treating cannabis dependence.

ACKNOWLEDGMENT: Supported by a grant from the Research into Drug Abuse grants Scheme of the Commonwealth Department of Health and Family Services.

ORAL COMMUNICATIONS IX

ALCOHOL MISUSE IN KOREAN AMERICAN ADOLESCENTS

J. Nakashima[1] and M. M. Wong[2]

[1]UCLA Policy Center and [2]WestEd

There is scant research on alcohol and other drug use among Asians and Pacific Islanders (API) living in the United States. Prior research has often grouped together Asians and Pacific Islanders of all subgroups (e.g., Koreans, Guamanian), overlooking subgroup differences in drug use prevalence. Indeed, little information is available on alcohol and other drug use for individual API groups in the U.S. Our previous research indicates that there are differences in alcohol and other drug use among API groups. This project examines alcohol misuse in ninth and twelfth grade Korean American adolescents from Los Angeles and Orange County schools. Data for the entire database (N=13,374) were collected from California schools with a student population of at least 25% API. Our sample consisted of 578 Korean Americans and a comparison group of 1,728 whites. Using logistic regression models, we found the following significant ($p<.05$) independent variables for Korean Americans: (1) grade (9th grade use <12th grade use), (2) born in the U.S. (non-U.S.<U.S.), (3) friends ask youth to get drunk a lot (0=no, 1=yes), and (4) school adjustment (inverse relationship). For whites, significant variables were: (1) grade (9th<12th), (2) born in the U.S. (non-U.S.<U.S.), (3) family would stop youth from getting drunk (0=no, 1=yes, inverse), (4) friends ask youth to get drunk a lot, (5) friends ask youth to get drunk a lot (0=no, 1=yes), (6) school adjustment, (7) depression, (8) self-esteem, (9) perceived prejudice (inverse), and (10) safe where you live (0=no, 1=yes). Tailoring prevention programs with sensitivity to ethnic group-specific correlates (risk/protective factors) may help curtail drug involvement in our nation's youth.

ACKNOWLEDGMENT: Supported by NIDA grant R01 DA08269 to WestEd (MMW).

TRANSITIONS IN CIGARETTE USE FROM ADOLESCENCE TO ADULTHOOD

H. R. White, R. J. Pandina, and P. H. Chen

Center of Alcohol Studies, Rutgers University, Piscataway, NJ

There are progressive stages in the development of smoking behavior from initiation to dependence. Although the initiation/experimentation stage has been characterized extensively, much less is known about the nature of transitions between stages. Despite the addictive potential of cigarettes, some individuals seem to be able to maintain regular long-term cigarette smoking without meeting dependence criteria. Yet, what factors protect these occasional smokers from progressing to dependence are unknown. The purpose of this study was to delineate the progression from cigarette use initiation to regular use and dependence during the transition from early adolescence into young adulthood and to examine sex differences in this progression. Four waves of prospective data (N=1201) from the Rutgers Health and Human Development Project spanning the ages of 12 to 31 were used. More than three fourth of the subjects had tried cigarettes, and about one third became dependent (smoked one half pack or more daily). Four in ten of those who tried became dependent. Females were significantly more likely to ever try and ever become dependent, but once exposure was controlled, the sex difference for becoming dependent was not statistically significant. The average age of first use (shortly before age 13) did not differ significantly for males and females. Females were significantly more likely than males to become dependent at a younger age (age 16 vs. 17, respectively) and to take fewer years to become dependent (4 vs. 5, respectively). Also, the younger subjects began smoking, the longer they took on an average to become dependent. In sum, the data suggest that there are a number of transition points in the development of cigarette smoking. Also there are complex patterns in terms of starting, stopping, continuation and timing.

ACKNOWLEDGMENT: Supported by NIDA 03395 and The Robert Wood Johnson Foundation.

DISCRIMINANT VALIDITY OF SELF-REPORT: SUBSTANCE-INVOLVED DELINQUENTS VERSUS CONTROLS

T. J. Crowley, S. K. Mikulich, M. J. Macdonald, and K. M. Ehlers

Dept. of Psychiatry, Addn. Rsch. and Trmt. Service, Univ. of CO Sch. Med., Denver, CO

Adolescents in substance treatment often have conduct disorder, one symptom of which is lying. However, clinicians and researchers rely heavily on patients' self-reports. Since patients might minimize problem reports, we tested the **Hypothesis:** that substance-involved, delinquent adolescent patients would report more problems than community controls. **Method:** Male and female adolescent subjects included 40 patients in substance treatment programs and 36 similar-neighborhood controls. After assent/consent procedures subjects were paid for providing a drug-free urine sample and for completing structured interviews and questionnaires. **Results:** Patients and controls did not differ significantly in age, gender, or racial-ethnic distribution. All of the following differed ($p < 0.03$): Despite neighborhood similarities, patients' SES was lower. Among patients 85 percent qualified for conduct disorder diagnoses; 2.8 percent of controls did. Criteria for diagnoses of substance dependence were met by 85 percent of patients and 5.6 percent (all nicotine) of controls. Patients, compared to controls, reported more days of alcohol/drug use (65 vs 3 of the past 180 days) and days on probation (83 vs 0/180). They reported fewer days residing in their parents' homes (69 vs 180/180). More patients reported inpatient treatments (55 vs 0 %), conception of children (17.5 vs 0 %), and not attending school (44 vs 0 %). Patients reported more total times of drug dealing (93 vs. 0 times) and drug stealing (71 vs 0 times). More patients reported having parents who received substance treatments (45 vs 14 %) or criminal convictions (50 vs 14 %). Patients had higher scores on scales for aggression (4.9 vs 1.2) and depression (11.6 vs 4.7) and reported experiencing more types of abuse or neglect (4.5 vs 0.7). **Conclusion:** Self-reports significantly discriminate (in expected directions) adolescent, substance-involved patients from neighborhood controls, supporting the validity of patients' self-reports.

ACKNOWLEDGMENTS: Supported by NIDA grants DA09842 and DA11015.

THE EFFECT OF SOCIAL RELATIONSHIPS UPON SUBSTANCE USE AND DISTRESS

E. L. Lombardi, V. Cargill[#], R. Stephens[+], and R. Gigliotti[+]

***Drug Abuse Research Center UCLA, [#]Case Western Reserve University, and [+]University of Akron**

The purpose of this study is to examine the relationship between teens' social relationships, substance use, and distress. We hypothesize that parents would be associated with lower levels of substance use, while peers and siblings who use drugs or alcohol would be associated with higher levels of substance use. However, the presence of parents, peers, and siblings would be associated with lower levels of distress, while substance use would be associated with higher levels of distress. Finally, having no one to talk to about important matters would be associated with greater levels of substance use and distress. The study sample consisted of 398 teens with data gathered at three points in time (baseline, six-month, and twelve-month). The social network variables at baseline were measured using an egocentric social network generator. Distress was measured at the twelve-month point using the CES-D depression scale. Alcohol and marijuana use once a week or greater were both measured for the previous six weeks at all three time points. Multiple logistic and linear regressions were used to assess the effects social relationships have upon substance use, and how it influences distress. This study found that parents and substance using peers were associated with marijuana use, while marijuana use and social isolation had the greatest impact upon distress. Future studies need to examine in greater detail the relationship between social support networks, substance use, and distress.

ACKNOWLEDGMENTS: Support for this research was provided by grants from the National Institute of Nursing Research, and NIDA training grant 513DA07272.

YOUNGER AND FEMALE ADOLESCENTS AT HIGHEST RISK AMONG NEW INTAKES AT A PUBLIC SUBSTANCE ABUSE SERVICES CLINIC AND JUVENILE JUSTICE SYSTEM

P. R. Marques, E. R. Rahdert, and E. R. Danseco*

Public Services Research Ctr, Pacific Institute for Research and Evaluation, Landover, MD and *National Institute on Drug Abuse, Rockville, MD

Several studies have identified a higher relative risk among girls evaluated upon intake at adolescent services centers. Female risk is often highest in the mental health-related problem cluster. Can the use of quick screening tools by adolescent substance abuse counselors facilitate risk identification? This study identified variables associated with risk in two samples: primarily white, middle class, adolescents referred for intake at a public substance abuse services clinic in Charles County Maryland (N=463, age=16.5 ± 1.3 yrs), and primarily white juvenile offenders in the state of Kansas (N=1917, age=15.3 ± 1.4 yrs). Data sources included: demographics, prior treatment information, and the Problem-Oriented Screening Instrument for Teenagers (POSIT), a validated ten life domain risk screening instrument. To identify predictors, the POSIT domains were set as dependent in a MANOVA in the first sample. In the clinic sample, at the multivariate level there was no gender by age interaction, but both younger age and female gender accounted for 10% of the POSIT risk variance independently. Along with female and younger, covariates of lower family income, prior psychiatric history, previous substance treatment were also significant predictors of POSIT risk both on the multivariate vector and on specific domains. On the mental health scale young females had the highest mean relative risk. These gender and age results were replicated in a second larger sample of juvenile offenders on both the multivariate analyses and on specific domains. At the end of a service episode among the clinic sample, neither gender nor age predicted unsatisfactory discharge codes, but the POSIT domain indicating family relations problems was a potent predictor of unsatisfactory discharge. Among juvenile offenders, the domain indicating family relations problems was the second strongest predictor of felony convictions and more violent offenses. These findings suggest that both the youngest and female referrals--especially those with family troubles--need special attention. The use of screening tools along with referrals to speciality professionals, when appropriate, may improve care.

ACKNOWLEDGMENT: Supported by NIDA Contract 263-MJ-637909.

ASSOCIATION OF DRUG USE TO CARD PRESERVATION TASK PERFORMANCE AND POST TASK SELF REPORT

C. A. Martin, M. K. Rayens, T. H. Kelly, and C. Leukefeld

University of Kentucky College of Medicine, Lexington, KY

The potential utility of performance on the Card Perservation Task (Card Task) and a Post-Task Self Report Scale (Self Report) measuring feeling states following task completion, as predictors of drug use, were examined. Ninety adolescents with psychiatric or behavioral problems (60 males, age 16.3 ± 21.1 30 females age 17.2±2.1) were assessed. Drug use histories were obtained using structured questionnaires. The Card Task and the Self Report were administered. Subscales (Distress, Happy) on the Self Report were identified using factor analysis. Correlational analysis demonstrated that cards played on the Card Task were associated with cigarette use, marijuana ($p \leq 0.01$), cocaine and hallucinogen ($p \leq 0.05$) dependence symptoms. Money Won was negatively associated with nicotine and marijuana dependence symptoms ($p \leq 0.05$). Distress on the Self Report correlated with nicotine, alcohol, marijuana, sedative, narcotic, hallucinogen, PCP and solvent ($p \leq 0.01$). These findings provide evidence that performance on the Card Task and post-task feeling states are related to drug use. This may be a model for clinically evaluating frustrating experiences and associated feeling states that may be related to individual differences in current and future drug use.

PSYCHOMETRIC PROPERTIES OF THE COMPREHENSIVE ADOLESCENT SEVERITY INVENTORY (CASI)

K. Meyers, A. Webb, M. Randall, P. McDermott, F. Mulvaney, W. Tucker, and A. T. McLellan

Center for Studies of Addiction, University of Pennsylvania, Philadelphia, PA and Treatment Research Institute, Philadelphia, PA

The Comprehensive Adolescent Severity Inventory (CASI) obtains demographic and administrative information as well as age of onset and past year functioning in ten life areas: health, education, stressful life events. drug/alcohol use, use of free time, peers, sexual behavior, family/household, legal, mental health. Treatment planning, chronicity, and outcomes scores are generated. Age of onset and item reliability were examined for four CASI modules (drug/alcohol, legal, family/household, mental health) among 103 adolescents receiving treatment. With the exception of lack of household rules (ICC=.43), hostility/physical violence (ICC=.41) and animal cruelty (ICC=.48), youth reliably reported age of symptom onset across diverse assessment domains [other ICC values ranged from .58 (impulsivity) to .99 (spent time in detention)]. Similarly, with the exception of barbiturates (ICC=.56), the number of days various substances were used in the month preceding the assessment were reliably reported. ICC values ranged from .74 for cocaine to .94 for tobacco. Past year pattern of drug use (e.g., weekly) was also reliably reported [with the exception of amphetamines (weighted kappa=.55; exact agreement=57%)]. Weighted kappa values ranged from .75 for inhalants (exact agreement=71%) to .85 for marijuana (exact agreement=84%). Reliability of past year functioning was fair to excellent with kappa values ranging from .47 (anxious/tense; exact agreement=78%) to .92 (on probation: exact agreement=97%). Highest agreement was found on items that were concrete, severe, and unambiguous. Lowest agreement was found on items that required judgment, inference, or opinion. A review of discrepancy data suggested that reliability was influenced by how a youth was feeling at the time of the interview, whether s/he had experienced a "crisis" which colored his/her perceptions. and whether s/he had the ability to make judgments about his/her behaviors/feelings. Being cognizant of these issues appears important during adolescent assessment.

ACKNOWLEDGMENT: Supported by NIDA grant DA07705-06.

P300 DECREMENTS IN CONDUCT-DISORDERED TEENAGERS: IMPLICATIONS FOR BRAIN DEVELOPMENT AND DRUG ABUSE RISK

L. O. Barter and V. M. Hesselbrock

Department of Psychiatry, University of Connecticut School of Medicine, Farmington, CT

P300 electroencephalographic potentials were evaluated in 257 subjects, aged 15 to 20 years. Subjects were assigned to 1 of 12 groups defined by the crossing of 3 between-subjects factors: (1) gender; (2) ranking below vs. above the median number of conduct disorder behaviors for their gender; and (3) no family history of alcohol/drug dependence vs. familial alcohol dependence vs. familial heroin or cocaine dependence. P300s were elicited in the context of a visuospatial "oddball" task, involving easy and difficult judgments about task relevant stimuli. P300 amplitude was smaller among subjects reporting a greater number of conduct disorder behaviors versus those reporting fewer behaviors, but only on difficult judgment trials and in the posterior region of the scalp. No main or interactive effects of family history were detected. To confirm the null family history finding, subjects were reassigned to groups based upon the prevalence of either alcohol or drug dependence within the family. Again, no family history effects were found. A third set of analyses examined the effects of age on conduct disorder-related decrements in P300. Smaller P300 amplitudes within the posterior scalp region were associated with a greater number of conduct disorder behaviors among subjects younger than 16.5 years. Among subjects greater than this median age, the effects of conduct disorder were only apparent over the frontal scalp. It is concluded that a family history of alcohol/drug dependence is neither a necessary nor sufficient cause of P300 amplitude reductions. Rather, P300 decrements previously attributed to family history might be the result of coincident conduct disorder. The analysis of age interactions suggests that P300 amplitude decrements observed at posterior scalp sites among subjects with more conduct disorder behaviors disappear at approximately 16-17 years of age. After that age, decrements in frontal brain function may begin to emerge in the subset of conduct-disordered subjects who develop adult ASPD.

ORAL COMMUNICATIONS X

THE D1 RECEPTOR AGONIST SKF-82958 ENHANCES BRAIN STIMULATION REWARD

E. L. Gardner, M. Lepore, X. Liu, and C. R. Ashby Jr.

Departments of Psychiatry and Neuroscience, Albert Einstein College of Medicine, New York, NY and Department of Pharmaceutical Health Sciences, Saint John's University, New York, NY

Cocaine's abuse potential has been linked to its actions on dopamine (DA) synaptic mechanisms in brain reward loci. The use of selective DA receptor agonists for cocaine addiction therapy has been proposed. Indeed, Self *et al. (Science* 271: 1586-1589, 1996) have reported that the D1 selective agonist SKF-82958 suppresses the priming effect of cocaine in the reinstatement model of intravenous cocaine self-administration without inducing priming effects by itself, and suggested that SKF-82958 and other D1 agonists could be used to treat cocaine craving and relapse. We examined the effect of SKF-82958 on electrical brain stimulation reward (BSR) in the rat medial forebrain bundle, using a rate-frequency curve-shift quantitative electrophysiological BSR paradigm. Animals were tested on cocaine, SKF-82958, or cocaine plus SKF-82958 combinations. Cocaine lowered BSR thresholds in a dose-dependent fashion. SKF-82958 (1.0 mg/kg) also significantly lowered BSR thresholds to a similar extent as cocaine. SKF-82958 (1.0 mg/kg) combined with cocaine (5.0 mg/kg) produced synergistic enhancement of BSR threshold lowering. The results show SKF-82958 to be *intensely rewarding* in its own right. Also, the fact that SKF-82958 enhances, rather than opposes, cocaine's rewarding properties suggests its therapeutic efficacy to treat cocaine dependence may be limited.

ACKNOWLEDGMENT: Supported by the Aaron Diamond Foundation.

SELF-ADMINISTRATION OF ETHANOL, COCAINE ALONE AND IN COMBINATION

M. J. Macenski and R. A. Meisch

Department of Psychiatry and Behavioral Sciences, University of Texas Houston - Health Science Center, Houston TX

Concurrent cocaine and ethanol self-administration may present special problems as this combination yields significant behavioral, physiological and biochemical interactions. In vivo, cocaine and ethanol yield a psychoactive metabolite cocaethylene, which has been shown to be at least as potent as cocaine. This project assessed the combination's reinforcing effects and the contribution of taste factors. Four rhesus monkeys were subjects. In the first study, monkeys had concurrent access to 0.4 mg/ml cocaine (C), 8% w/v ethanol (E), and 0.4 cocaine plus 8% ethanol (C+E) vs. Vehicle (V) and C+E vs. C, E and V. The combination was preferred to C, E, and V alone and was consumed in greater quantities that the single drugs alone. In a second study, monkeys had access to V, C, E and C+E under a progressive ratio schedule where the response cost was increased by one following each drug delivery. Break point was the largest ratio completed. Break point was greatest for C+E followed by E, C and V. These results matched the rank order of drug consumption in the previous study. In a final study, E was replaced with a saccharin (S) concentration which maintained more responding than E. Comparisons were completed as in the first study, with an additional C+E vs. C+S comparison. S, C and the combination were preferred to vehicle and the S+C combination was preferred to the single constituent solutions alone. Further, C+E was preferred over S+C. Results strongly support the idea that cocaine and ehanol in combination exert greater reinforcing effects that the single drugs alone and that the observed effects are not due to appetitive ethanol taste factors.

ACKNOWLEDGMENT: Supported by NIDA research grant DA11805 awarded to MJM.

EFFECTS OF D_1 vs. D_2 ANTAGONISTS ON TRANSITIONS IN BEHAVIORAL RESPONDING AND ACCUMBENS CELL FIRING DURING COCAINE SELF-ADMINISTRATION

R. M. Carelli and S. A. Deadwyler

Department of Psychology, University of North Carolina, Chapel Hill, NC and Department of Physiology/Pharmacology, Wake Forest University School of Medicine, Winston-Salem, NC

During cocaine self-administration in rats, lever pressing behavior (FR1) is characterized by an initial burst of responding during the early trials of the session (termed 'Load-Up'), followed by stable self-administration responding with regularly spaced inter-infusion intervals for the remainder of the session. We have previously reported that the spontaneous transition in behavioral responding from high to tow rates is cocaine dose-dependent. and corresponds to changes in nucleus accumbens (NA) firing from activity unrelated to the reinforced response, to one of four types of patterned discharges. The present study examined the potential involvement of dopaminc D_l vs. D_2 receptors in this process. Rats (n=8) were pretreated with either saline, the dopamine D_1 receptor antagonist SCH23390 (2.5-40 µg/kg, SC), or the dopamine D_2 receptor antagonist eticlopride (2.5-40 µg/kg, SC) 30 min prior to the cocaine (0.33 mg/inf) self-administration session. Results show that SCH23390 significantly increased the number of Load-Up responses at 10, 20, and 40 µg/kg and the number of responses following the Load-Up phase (ie., during the Session phase) at 10 and 20 µg/kg. Eticlopride dose-dependently increased the number of Session responses (10, 20, 40 µg/kg) but did not alter the number of Load-Up responses at any dose tested. The abrupt transitions in NA cell firing corresponded to the shift in behavioral responding across SCH23390 and etictopride doses. These findings indicate that the corresponding transitions in behavioral responding and NA activity are sensitive to manipulations of the dopamine D_l but not D_2 receptor subtype.

ACKNOWLEDGMENTS: Supported by NIDA grant DA10006 to RMC; DA0119 and DA06634 to SAD.

EFFECTS OF CP-154,526 ON INTRAVENOUS COCAINE SELF-ADMINISTRATION IN RATS

N. E. Goeders and G. F. Guerin

Departments of Pharmacology and Therapeutics and Psychiatry, LSU Medical Center, Shreveport, LA

Previous research from our laboratory has suggested the potential involvement of the hypothalamic-pituitary-adrenal (HPA) axis in cocaine reinforcement. In particular, we found that exposure to non-contingent electric footshock facilitated the acquisition of intravenous cocaine self-administration in rats. In another series of experiments, we demonstrated that surgical and pharmacological (i.e., ketoconazole, metyrapone pretreatment) adrenalectomies abolished the acquisition and attenuated the maintenance of cocaine self-administration, suggesting a role for corticosterone in cocaine reinforcement. Corticotropin-releasing factor (CRF) is released by the hypothalamus during stress and acts on the pituitary to induce the secretion of adrenocorticotropic hormone (ACTH). ACTH can then act on the adrenals to regulate the secretion of corticosterone. These experiments were therefore designed to determine the effects of pretreatment with CP-154,526, a centrally active, small molecule CRF receptor antagonist, on intravenous cocaine self-administration in rats. Adult male Wistar rats were trained to respond under a multiple, alternating schedule of food reinforcement and cocaine self-administration. During daily 2-hr sessions, the rats were allowed access to food presentations (delivered under a fixed-ratio 10 schedule) and cocaine self-administration (fixed-ratio 4) during alternating 15-min periods. Three doses of cocaine were tested, 0.125, 0.25 and 0.5 mg/kg/infusion. Prior to testing, the rats were exposed to multiple cocaine extinction (saline substitution) probes. Pretreatment with CP-154,546 (0-40 mg/kg, ip), 30 minutes before the start of the behavioral session, did not affect food-maintained responding. However, cocaine self-administration at all three doses was significantly attenuated, and in some cases completely eliminated, following pretreatment with CP-154,526. These data underscore a potential role for CRF receptors in cocaine reinforcement.

ACKNOWLEDGMENT: Supported by USPHS grant DA06013 from NIDA

ACUTE AND CHRONIC ADMINISTRATION OF 7-OH-DPAT DIFFERENTIALLY ALTERS COCAINE-SEEKING BEHAVIOR

R. A. Fuchs, T. V. Khroyan, L. T. L. Tran-Nguyen, and J. L. Neisewander

Department of Psychology, Arizona State University, Tempe, AZ

The D3-preferring agonist 7-OH-DPAT has been proposed as a substitution therapy for cocaine dependence. Thus, the present study examined the effects of 7-OH-DPAT on cocaine-seeking behavior, a measure of incentive motivation for cocaine. Rats were trained to press a lever for cocaine infusions (0.25 mg/kg/0.1 ml, IV) or received yoked saline infusions during daily 2-h sessions for 21 days. They were then withdrawn from the self-administration regimen and were given 7-OH-DPAT (0, 0.001, 0.01, 0.1, or 1.0 mg/kg, SC) daily on withdrawal days 7-22. They were tested for extinction of cocaine-seeking behavior (i.e., nonreinforced lever presses) following acute administration of 7-OH-DPAT on withdrawal day 7 and following chronic administration on withdrawal day 21 (15-22 h after their daily treatment). They were also tested for the effects of 7-OH-DPAT on the ability of cocaine (15 mg/kg, IP) to reinstate extinguished cocaine-seeking behavior on withdrawal day 22. Acute administration of low doses (0.01-0.1 mg/kg) of 7-OH-DPAT attenuated cocaine-seeking behavior, whereas the highest dose (1 mg/kg) initially attenuated and then enhanced cocaine-seeking behavior relative to controls. In contrast, chronic administration of 0.1-1.0 mg/kg 7-OH-DPAT enhanced cocaine-seeking behavior relative to controls. Furthermore, 1 mg/kg 7-OH-DPAT enhanced cocaine reinstatement of extinguished cocaine-seeking behavior. These results suggest that 7-OH-DPAT alters incentive motivation for cocaine, but may not be suitable for treatment of cocaine dependence since chronic administration may enhance motivation for cocaine.

ACKNOWLEDGMENTS: Supported by DA11064 and DA05816.

EFFECTS OF D_1 AND D_2 DOPAMINE AGONISTS ON COCAINE DISCRIMINATION AND SELF-ADMINISTRATION IN RATS

S. B. Caine, S. S. Negus, N. K. Mello, and J. Bergman

Alcohol and Drug Abuse Research Center, McLean Hospital–Harvard Medical School, Belmont, MA

The hypothesis was tested that treatments with D1-like and D2-like agonists differ in their effects on cocaine discrimination and self-administration in rats. Male rats were trained to discriminate cocaine (5.6 mg/kg IP) from saline, or to self-administer cocaine (0.01-0.1.0 mg i.v.) under a fixed ratio schedule. In discrimination studies, one group of rats (n=6) had approximately two years of cocaine discrimination training, whereas a second group (n=6) had only six months of training. In both groups, treatments with the D2 agonists quinelorane and 7-OH-DPAT dose-dependently and fully substituted for the cocaine stimulus, though full generalization occurred at doses that suppressed response rates. In contrast, treatments with D1 agonists (SKF 82958, SKF 77434, SKF 83959) produced partial substitution for the cocaine stimulus in the first group of rats, and full substitution in the second group of rats. To the degree that the agonists substituted for cocaine, pretreatments prior to cocaine injections generally produced additive effects. In rats trained to self-administer cocaine (n=8), substitution with the D2 agonists quinelorane or 7-OH-DPAT dose-dependently maintained responding at rates similar to or slightly below rates maintained by cocaine. In contrast, across a wide dose range, the D1 agonists SKF 82958 and SKF 77434 failed to maintain responding at rates similar to cocaine, and rarely maintained responding at rates significantly greater than those observed with saline substitution. Moreover pretreatments with the D1 agonists prior to cocaine self-administration produced downward shifts in cocaine self-administration dose-effect functions, whereas pretreatments with the D2 agonists produced leftward shifts in cocaine self-administration dose-effect functions. Overall the results suggest that D2 agonists enhance the discriminative stimulus and reinforcing effects of cocaine, whereas the behavioral effects of D1 agonists and cocaine may overlap to a lesser extent.

ACKNOWLEDGMENTS: Supported by NIDA grants DA07252, DA00101, and DA04059.

NEUROTRANSMITTER RELEASE DURING COCAINE SELF-ADMINISTRATION AND CUES IN RHESUS MONKEYS

C. W. Bradberry and S. R. Rubino

Department of Psychiatry, Yale University School of Medicine and the West Haven Veterans Administration Medical Center

In order to explore the effects of self-administered cocaine on extracellular neurotransmitter dynamics, we have developed methods for conducting microdialysis studies in chaired rhesus monkeys while they self-administer cocaine intravenously. Probes were inserted using chronic guide cannulae and magnetic resonance imaging into striatal and frontal cortical sites. The following day, the animal was chaired for 90 min prior to presentation of a cue signaling availability of a 0.5 mg/kg i.v. dose of cocaine under an FR10 lever response. The impact of cocaine on extracellular dopamine, 5-HT, and glutamate was determined in both regions. In addition, data from striatal DA determinations made at 2 min intervals for examination of the impact of cocaine, and cocaine-associated cues will be presented, as will data showing tolerance to repeated doses of cocaine in a given session, and the impact of cocaine over an extended number of months demonstrating progressive changes in the neurochemical impact of cocaine over time. These data represent the first results of extracellular neurotransmitter measurements in non-human primates during cocaine self-administration or cocaine-associated cues, and will complement results from other methods for studying the functioning primate brain such as neurophysiological recording and brain imaging methodologies.

ACKNOWLEDGMENTS: Supported by DA08073, DA10331, DA04060, and West Haven Veterans Administration Center for the Study of Alcoholism.

THE EFFECTS OF 6-OHDA LESIONS OF THE NUC ACC ON EXTRA-CELLULAR DOPAMINE DURING COCAINE SELF-ADMINISTRATION

J. E. Smith, G. M. Sizemore, T. R. Koves, and C. Co

Department of Physiology and Pharmacology, Wake Forest University School of Medicine, Winston-Salem, NC

Dopaminergic innervation of the nucleus accumbens (NA) has been demonstrated to be central to cocaine reinforcement processes. This experiment was initiated to investigate the basic mechanisms underlying the effects of 6-OHDA lesions of the NA on intravenous cocaine self-administration. Rats were trained to self-administer cocaine and received either sham treatment or 6-OHDA lesions of the NA and the effects of these treatments were assessed on drug intake and extracellular fluid levels of dopamine [DA]e in the NA using microdialysis. Catherized rats implanted with bilateral guide cannulae were allowed access to 3 different doses (0.17, 0.33 and 0.67 mg/inf) of cocaine during a single session. When responding stabilized, 6-OHDA lesions were produced by infusion of 8.0 µg of 6-OHDA in 2 µl of saline. A sham treated group received infusions of the vehicle. A second lesion or sham treatment occurred 48 hrs after the first. Microdialysis probes (2.0 mm) were inserted into the NA and artificial CSF was perfused at a rate of 0.5 µl/min. Samples were collected every 10 min beginning 1.5 hrs pre-session and ending 1.5 hrs post-session. The levels of [DA]e were assessed during the self-administration session on days 6, 15, 30 and 45 post lesion. On the 6th and 16th day post-lesion, baseline levels of DA were undetectable and remained so even when subjects self-administered cocaine. By the 30th day, when self-administration behavior had returned to prelesion levels, baseline DA levels could be detected and cocaine self-administration caused DA levels to increase slightly. By the 45th day DA levels before and after cocaine self-administration were similar to nonlesioned rats. These data indicate that self-administration of cocaine and [DA]e in the NA appear to be unrelated following 6-OHDA lesions.

ACKNOWLEDGMENTS: Supported by USPHS grants DA 03628, DA 06634, and DA 00114.

ORAL COMMUNICATIONS XI

ATTENTION DEFICIT HYPERACTIVITY DISORDER IN NICOTINE DEPENDENCE

M. Mengis, G. Humfleet, D. Hartz, and S. Hall

Department of Psychiatry, University of California, San Francisco and the San Francisco Veterans Affairs Medical Center, San Francisco, CA

Studies have reported a high prevalence of Attention Deficit Hyperactivity Disorder (ADHD) in substance abusers compared to the general population. The purpose of this investigation is to study the prevalence of ADHD in nicotine dependence and to investigate whether current adult ADHD symptoms or a history of childhood ADHD influences treatment outcome. We hypothesize that the prevalence of ADHD will be increased in treatment seeking subjects with nicotine dependence compared to the general population. We also hypothesize that subjects with a history of childhood ADHD or current adult ADHD symptoms will have a more severe dependence problem and worse treatment outcome. Subjects are screened from two main outcome studies on nicotine dependence which compare various treatment conditions including medication with bupropion or nortriptyline. Subjects are assessed for a history of childhood ADHD at baseline using the ADHD module of the Diagnostic Interview Schedule for the DSM-IV (DIS-IV). All subjects are also assessed for current adult ADHD symptoms at baseline, 12 and 24 weeks using the Brown Attention Deficit Disorder Scale for adults. Severity of nicotine dependence is measured by the Fagerstrom Tolerance Score and number of cigarettes smoked per day. Subjects are also assessed at weeks 12 and 24 on biologically confirmed abstinence from nicotine. Preliminary results in nicotine dependent subjects suggest that 13 percent of subjects have endorsed a history of childhood ADHD and 10 to 20 percent of subjects have endorsed current adult ADHD symptoms. These results suggest a higher prevalence of ADHD in nicotine dependent subjects compared to a prevalence of one to three percent in the general population.

PHARMACOKINETIC AND PHARMACODYNAMIC EFFECTS OF ORAL SNUFF IN HUMANS

R. V. Fant, J. E. Henningfield, R. A. Nelson, M. E. Chenoweth, and W. B. Pickworth

NIDA, Intramural Research Program, Baltimore, MD

The use of oral snuff has increased considerably since the 1970s with the most recent "Monitoring the Future" study finding that approximately 25% of adolescents (mostly males) had tried smokeless tobacco. The current study examined the pharmacokinetic and pharmacodynamic effects of four popular brands of oral snuff that deliver nicotine (Copenhagen, Skoal Original Wintergreen, Skoal Long Cut Cherry, Skoal Bandits Wintergreen) and a mint "snuff" product that does not deliver nicotine. The products were selected, in part, to represent a wide range of predicted nicotine delivery characteristics based on the pH and nicotine content of the products. Ten male adult smokeless tobacco users participated in five experimental sessions during each of which they received one of the five products. The snuff was kept in the mouth for 30 min during which the participant was allowed to expectorate ad libitum. Prior to snuff administration and at timepoints up to 90 min following administration, biochemical, physiologic, and subjective measures were collected. Each tobacco snuff product (except Skoal Bandits) produced plasma nicotine concentrations at least as high as those seen during cigarette smoking. High plasma concentrations (> 10 ng/ml) were observed within 10 min of administration of these products. Plasma nicotine concentrations were related to both nicotine concentration and alkaline pH of the products in solution. Of two products with similar nicotine concentrations, the product with a higher pH level produced substantially more rapid and elevated plasma nicotine levels. Ratings of drug strength, subjective ratings of drug effects, and cardiovascular effects increased as a function of plasma nicotine. The fact that plasma nicotine concentrations from oral snuff are at least as high as those produced by smoking is consistent with the known high abuse liability and dependence potential of these products.

SMOKING BELIEFS AND BEHAVIORS IN AFRICAN AMERICAN SMOKERS AND EX-SMOKERS

K. L. Jeffries-Leonard, L. L. Adams-Campbell** and E. G. Singleton*#*

***MayaTech Corporation, Silver Spring, MD, **Howard University, Washington, DC, and #Johns Hopkins University, Baltimore, MD**

The majority of African American smokers who want to stop smoking do not join cessation programs, and those who do seek help in breaking the habit are less successful at quitting than other racial groups. Focus groups were conducted with African American smokers and ex-smokers to determine if and what program improvements need to be made to increase program participation and enhance success rates. Consensus was that traditional smoking cessation programs are targeted to a "different type" of population which contribute to their overall lack of appeal. Smokers and ex-smokers were equally aware of the negative health consequences of smoking, so cessation programs focusing on health education could be less effective with this group. The main reason cited for smoking initiation was social desirability. Spirituality and religious beliefs reportedly motivated quit behavior. The notion of using more "nonconventional methods" was a constant theme. Results suggest that promoting cessation programs in ongoing religious activities and integrating ministers into the social support system would be effective ways of encouraging African American participation in smoking cessation programs.

COGNITIVE DESCRIPTORS OF SMOKING OUTCOMES

J. Mullennix, L. Farnsworth, R. Torrento*, S. Fisicaro*, and M. M. Kilbey**

University of Pittsburgh, Johnstown PA, and *Wayne State University, Detroit, MI

Cognitive expectancies related to nicotine dependence were investigated by examining the generation of smoking-related words. Randomly selected young adults (3,805) in the metropolitan Detroit area were contacted. Nine hundred thirty respondents that met our criteria (including that they smoked at least one cigarette in their lifetime) were selected to approximate the 1990 census distribution for the Detroit metropolitan area for gender, ethnicity, and level of education. Of these adults, 45.3 % were classified as current smokers; 65.3% of people with less than a high school education were current smokers, compared to only 18.3% of those having bachelor's degrees or beyond; 64.5% of current smokers with a high school degree or less regularly or always smoked their first cigarette of the day within 30 minutes of waking, compared to 35.5% of those with college coursework or a college degree. Each participant completed a series of questionnaires related to smoking and generated a list of smoking-related stimulus words. In terms of number of words generated, more words were generated as education level increased and with more words were generated by Caucasians compared to African Americans. The words were distilled into 39 different semantic categories containing five words each for the purposes of further analysis. Differences in words used within categories varied as a function of smoking status (current or non-current smoker) and smoking history (whether a person smoked daily for a month or more), with 12 of 39 categories affected by smoking status and 14 of 39 categories affected by smoking history. The results suggest that important differences in generating smoking-related words exists across different categories of smokers.

ACKNOWLEDGMENT: Supported by NIH (NIDA) grant R01 DA10583.

DEPRESSION HISTORY AND DEVELOPMENT OF MAJOR DEPRESSION FOLLOWING SMOKING CESSATION TREATMENT

J. Y. Tsoh, G. L. Humfleet, R. F. Muñoz, V. I. Reus, D. T. Hartz, and S. M. Hall

Department of Psychiatry, University of California, San Francisco, CA

Recent case studies have suggested some smokers may have an increased risk of major depressive episodes (MDE) following cigarette abstinence. This study examined the 12-month prevalence and predictors of MDE following smoking cessation treatment among 304 participants (57% female) from 2 clinical trials using different pharmacological agents: nortriptyline and nicotine gum. Participants in both trials also received psychological group treatment. MDE post treatment was assessed by the Inventory to Diagnose Depression (LDD) at each follow-up assessment. The 12-month prevalence of MDE following smoking cessation treatment was 14.1%. Multiple logistic regression analysis indicated depression history was a significant predictor of post treatment MDE among participants who had no spouse or partners (OR = 4.08; 95% CI = 1.59-10.51), but not among those who had partners. Other significant predictors were baseline Beck depression score (OR = 1.09; 95% CI = 1.03-1.14), age at smoking initiation (OR = 0.87; 95% CI = 0.78-0.97), and college education (OR = 3.03; 95% CI = 1.36-6.73). Abstinence status at end of treatment was found to have a significantly higher risk associated with post treatment MDE among participants in the trial using nicotine gum than participants in the nortriptyline trial (ORs: 4.34 vs. 0.73, p for interaction = 0.05). Clinical implications include the need for educating both treatment providers and patients about the risks of MDE following smoking cessation attempts. The results underscore the importance of careful management of depression post treatment while helping patients maintain abstinence.

ACKNOWLEDGMENTS: Supported by NIDA grants DA02538, DA09253, DA07250, and Career Research Scientist Award from the Veterans Administration.

DIFFERENCES IN DRUG USE AMONG METHADONE MAINTAINED TOBACCO CHIPPERS AND HEAVY SMOKERS

D. L. Frosch, S. Shoptaw, D. Nahorn, W. Ling, and M. E. Jarvik

Friends Research Institute, Inc., UCLA School of Medicine, Department of Psychiatry and Biobehavioral Sciences, SDSU/UCSD Joint Doctoral Program in Psychology, Los Angeles, CA

The objectives for the present study are to evaluate whether tobacco "chipping" occurs among methadone maintained tobacco smokers and to evaluate whether prospectively defined tobacco use levels associate differentially with illicit drug use in methadone maintained tobacco smokers. Participants were assigned into one of three groups: non-smokers (self-reported and verified by clinic staff, n=9); chippers (1-5 cigarettes per day at least 4 days per week, n=11); or heavy smokers (smoking 20+ cigarettes per day, n=11). Participants provided the following: 7 consecutive days of urine samples analyzed for metabolites of nicotine, heroin, and cocaine; concurrent collection of expired carbon monoxide; an ASI; a detailed smoking history; and were reimbursed $50. Results showed an ordered, stepwise relationship between smoking level and urinary cotinine corrected for creatinine, with nonsmokers having no cotinine in urine, chippers having a moderate amount, and heavy smokers having the highest values. Parallel associations were demonstrated between tobacco use groupings and expired carbon monoxide levels. Regarding illicit drug use, no urinary cocaine metabolite was detected for nonsmokers, while chippers showed 27.3% of samples with cocaine metabolite and heavy smokers had 57.1% of samples with cocaine metabolite in urine (X^2=55.60, df=4, p<.001). Similarly, opiate metabolite was detected in 13.9% of nonsmokers' urine samples, compared to 72.4% of chippers and 83.1% of heavy smokers (X^2=83.42, df=4, p<.001). These results demonstrate that the tobacco chipping phenomenon extends to methadone maintained tobacco smokers. Findings provide strong implication that tobacco use may represent a marker for other substance use among methadone maintained opiate dependent individuals.

ACKNOWLEDGMENTS: Supported by Smith/Kline Beecham, NIDA grant 1 R01 DA 09992.

THE EFFICACY OF THE NICOTINE PATCH IN RECOVERING ALCOHOLIC SMOKERS

P. L. Novy, J. R. Hughes, J. A. Jensen, D. K. Hatsukami*, and J. Huston*

University of Vermont, Burlington, VT and *University of Minnesota, Minneapolis, MN

Although smoking prevalence has been steadily declining in the general population, it remains high among active and recovering alcoholics. The purpose of the present study is to determine the efficacy of transdermal nicotine replacement among recovering alcoholic smokers, and to determine whether smoking cessation prompts relapse to alcoholism. Participants (N=117) were recruited from the general population through advertisements. They were eligible if they were alcohol dependent (DSM-IV criteria via CIDI-SAM), with their alcoholism in remittance for at least 30 days. On average, participants were abstinent from alcohol and other drugs for 4.7 years. Participants were randomly assigned to receive a 21 mg nicotine patch (N =62) or a placebo patch (N =55) for 6 weeks in a double blind fashion, followed by a 6 week tapering schedule. All participants received weekly group behavior therapy. The point prevalence quit rates at the end of week 12 for the active and placebo groups were 37% (N =22) and 26% (N =14), respectively, odds ratio = 1.7, n.s. The point prevalence quit rates at the end of week 24 for the active and placebo groups were 21 % (N= 13) and 19% (N= 10), respectively ,odds ratio = 1.2, n.s. The sustained quit rates at the end of week 24 for the active and placebo groups were 21% (N =13) and 15% (N=8), respectively, odds ratio = 1.6. n.s. Reported desire for alcohol did not appear to increase. Seven participants (6%) used alcohol, marijuana, or cocaine, but this occurred on one occasion only. Although our abstinence results are encouraging, larger studies or use of higher dose patches may be necessary to show efficacy in recovering alcoholics. Our alcohol relapse results are also encouraging, but need to be verified in studies that follow all participants, not just those abstinent.

ACKNOWLEDGMENTS: Supported by NIAAA grant AA-09430 and NIDA RSDA DA-00109.

SUCCESSFUL SMOKING CESSATION AMONG METHADONE-MAINTAINED TOBACCO SMOKERS

D. Nahom[1], S. Shoptaw[1]; D. Frosch[1], M. E. Jarvik[1,2], R. A. Rawson[1,2], and W. Ling[1,2]

[1]Los Angeles Addiction Research Consortium and [2]UCLA Department of Psychiatry

It has been reported that among substance abusers, opiate-addicted individuals have the highest rate of tobacco use (i.e., 70% to 98% smokers). Since tobacco smoking is predictive of morbidity and mortality in this high risk population, there is a critical need for smoking cessation treatment among opiate-addicted individuals. One objective of this project was to collect qualitative data to be used to design more effective smoking cessation treatments for this group of tenacious smokers. Part of a larger study evaluating behavioral therapies for optimizing transdermal nicotine patch treatment for smoking cessation, a total of 20 methadone-maintained opiate addicts who completed at least 6 weeks in the smoking cessation trial completed an ethnographic interview discussing their experiences in the trial. Results suggest that behavioral treatments, such as relapse prevention groups, are rated by women as more helpful for smoking cessation than by men. Subjects also report a decrease in illicit drug use as tobacco use decreases. Thus, while nicotine substitution is widely recognized as a useful treatment for tobacco dependence, behavioral treatments used in conjunction with this provide a feasible addition for successful smoking cessation treatment.

ACKNOWLEDGMENTS: Supported by NIDA grant 1RO1-DA09992-02 and Smith Kline Beecham.

ORAL COMMUNICATIONS XII

DIFFERENTIAL DYNORPHIN RELEASE WITH ISOMERIC CANNABINOIDS

M. Eads and S. P. Welch

Department of Pharmacology, Medical College of Virginia of Virginia Commonwealth Univeristy, Richmond, VA

Previous studies have shown that various cannabinoids induce an antinociceptive effect in rats. The concentration levels of dynorphin A, dynorphin B, or both seem to play a role in the mechanisms that cause the antinociceptive effect seen in rats after the intrathecal (i.t.) administration of various cannabinoids. The following studies examined the steroselectivity of two isomeric cannabinoids: levonantradol (levo) and dextronantradol (dextro). We examined if dynorphin A (1-17) or dynorphin B concentrations changed 10 minutes after intrathecal administration, and if an antinociceptive effect occurred. The concentration levels of dynorphin A (1-17) showed a 2-fold increase compared to the vehicle (DMSO) after i.t. injections of levo at lug / rat and at 5 µg / rat [DMSO, 3.0 ± 0.9 pg/ml; levo, 1µg 6.5 ± 1.9 pg/ml & 5 µg, 13.8 ± 8.8 pg/ml]. Levo produced a 2-fold increase in dynorphin B release [8.05 ± 2.4 pg/ml versus 4.04 ± 0.8 pg/ml for DMSO vehicle]. Dextro did not significantly alter the concentrations of dynorphins. Levo produced variable antinociceptive effects at 1 µg/rat [from 22 to 82% MPE]. At 5 µg/rat levo produced 56±13 % MPE. Dextro (30 1µg/rat) failed to produce antinociceptive effects. Due to variable responses, the data on dynorphin release failed to achieve significance. These data suggest that levonantradol and dextronantradol produce stereoselective antinociceptive effects, but there remains a trend toward a stereoselective effect on dynorphin release. With the addition of increased sample number the effects are anticipated to be significant.

ACKNOWLEDGMENTS: Supported by K02DA00186 and DA05274.

PERIPHERAL KAPPA OPIOID RECEPTORS IN THE MODULATION OF CAPSAICIN-INDUCED THERMAL NOCICEPTION IN RHESUS MONKEYS

M. C. Ko, E. R. Butelman, and J. H. Woods*

University of Michigan, Ann Arbor, MI and *Rockefeller University, New York, NY

Capsaicin produces burning pain followed by nociceptive responses such as allodynia and hyperalgesia in humans and rodents. The aim of this study was to investigate whether local administration of *kappa* opioids including U50,488, bremazocine, and dynorphin (1-13) can diminish capsaicin-induced nociception in rhesus monkeys (n=6) by utilizing a warm water tail withdrawal assay. Normally, the monkeys maintained their tails in 46°C water for 20 seconds (cutoff latency). Following s.c. administration into the tail, capsaicin (0.01-0.32 mg) dose-dependently produced allodynia manifested as reduced tail withdrawal latencies (2-3 sec). When coadministered with capsaicin (0.1 µg) into the tail, U50,488 (3.2-100 µg), bremazocine (0.1-3.2 µg), and dynorphin (1-13) (3.2-100 µg) dose-dependently attenuated capsaicin-induced allodynia. However, the locally effective doses of these *kappa* opioids, when applied S.C. in the back, did not inhibit capsaicin-induced allodynia. This indicates that the site of action of these *kappa* opioids is located in the tail. In addition, pretreatment with the selective *kappa* antagonist nor-binaltorphimine (0.32 mg) in the tail antagonized the local antinociceptive effects of U50,488 against capsaicin, but not that of bremazocine. These results suggest that peripherally located *kappa* receptors may diminish capsaicin-induced nociception in primates. The possibility of existence of *kappa* receptor subtypes in the periphery is being investigated currently.

ACKNOWLEDGMENT: Supported by USPHS grant 00254.

OPIOID ANTINOCICEPTION IN OVARIECTOMIZED MONKEYS: COMPARISON TO MALES AND EFFECTS OF ESTRADIOL

S. S. Negus and N. K. Mello

Alcohol and Drug Abuse Research Center, McLean Hospital—Harvard Medical School, Belmont, MA

Baseline nociception and opioid antinociception were compared in male and ovariectomized female rhesus monkeys using a warm-water tail-withdrawal assay of thermal nociception. In addition, the effects of estradiol replacement (0.002 and 0.01 mg/kg/day) were examined in the females. Preliminary data suggest that there were no differences between males and ovariectomized females in baseline thermal nociception across a wide range of temperatures (42-54°C). In addition, estradiol replacement did not alter baseline nociception in the females. The mu opioid agonists morphine (0.32-18 mg/kg) and fentanyl (0.0032-0.1 mg/kg) produced dose-dependent antinociceptive effects and comparable maximal effects in both males and ovariectomized females. However, both morphine and fentanyl were slightly more potent in the males, and estradiol replacement increased the potency of both mu agonists in the females. There were no sex differences or effects of estradiol on the pharmacokinetics of morphine. The kappa agonist U50,488 (0.1-3.2 mg/kg) also produced dose-dependent antinociceptive effects in both males and ovariectomized females. However, U50,488 was more potent and produced a greater maximal effect in the males. Estradiol replacement increased the potency and maximal effect of U50,488 in the females. These findings suggest that sex differences related to the hormonal milieu may influence opioid antinociception in primates.

ACKNOWLEDGMENTS: Supported in part by NIDA grants P50-DA04059 and K05-DA00101.

BU72 - A HIGH EFFICACY BUPRENORPHINE CONGENER

C. L. Neilan ♦#, S. M. Husbands, S. Breedon*, J. Broadbear ♦, J. W. Lewis*, J. H. Woods ♦, and J. R. Traynor ♦#*

Department of Pharmacology, University of Michigan, Ann Arbor, MI; and Departments of Chemistry, Universities of Bristol and Loughborough, UK

A morphinan-pyrrolidine derivative, BU72, has been developed as an alternative to methadone for the treatment of opiate abuse. At the cloned μ-opioid receptor expressed in C6 glioma ceils BU72 showed higher affinity (Ki = 0.06nM) than methadone (Ki = 5.85nM) or buprenorphine (Ki = 0.12nM). In the [^{35}S]GTPyS assay, BU72 acted as a full agonist and was considerably more efficacious than buprenorphine. In the mouse warm water tail-withdrawal assay, BU72 produced dose-dependent antinociception approximately 200 x more potent than methadone (EC50 BU72 = 0.07mg/kg). Similar results were obtained in the acetic acid induced writhing assay. Pre-treatment of mice with the non-competitive μ-opioid antagonist M-CAM (3.2mg/kg) completely suppressed the antinociceptive effect produced by BU72 whereas pre-treatment with either naltrindole or norBNI had no effect. Pre-treatment with a high dose of BU72 (10mg/kg) afforded long-lasting antinociception after which time antagonism of morphine was observed in both the tail withdrawal and writhing assays. Peak antagonism occurred at 72 hours, and in the writhing assay a maximal dose of morphine (3.2mg/kg) was still fully antagonized after 6 days. The data from the binding and antinociceptive studies indicate that BU72 is a μ-selective opioid agonist with subsequent antagonist properties. BU72 could be a useful lead to develop compounds with potential for the treatment of opiate abuse.

ACKNOWLEDGMENTS: Supported by DA 07315 and 00254.

BEHAVIORAL PHARMACOLOGY OF THE HIGHLY POTENT AND MU-SELECTIVE OPIOID RECEPTOR ANTAGONIST CTAP

S. E. Bowen, J. A. Moretti, C. L. Steinmiller, and A. M. Young

Department of Psychology, Wayne State University, Detroit, MI

CTAP (D-Phe-Cys-Tyr-D-Trp-Arg-Thr-Pen-Thr-NH_2) is a somatostatin derivative shown to be a selective antagonist for μ-opioid receptors. The present studies assessed CTAP's ability to antagonize the antinociceptive effects of μ opioids and to alter withdrawal in animals made acutely dependent to morphine (MS). In a 55°C warm-water tail-withdrawal assay, CTAP (0.1-10 ug; icv) dose-dependently antagonized the antinociceptive effects of MS (0.32-560 mg/kg; sc) and DAMGO (0.1-55 ug; icv). Furthermore, CTAP antagonized analgesic doses of MS (10 or 32 mg/kg; sc) for at least 3 hours. In other studies, CTAP and naltrexone (NTX) were evaluated for behavioral effects on response rates in rats trained under a FR30 schedule for food reinforcement. Cumulative doses of NTX and single doses of CTAP dose-dependently decreased response rates in rats pretreated (-4 h) with either saline or 5.6 mg/kg MS (sc), with NTX being equipotent by the sc or icv route. However, whereas MS pretreatment markedly enhanced sensitivity to cumulative doses of NTX (sc or icv), such pretreatment produced only a small increase in sensitivity to CTAP. Finally, CTAP (1.0-10.0 ug; icv) slightly attenuated the rate-decreasing effects of cumulative doses of sc but not icv NTX, in MS pretreated animals. Taken together these results suggest that effective μ antagonist doses of CTAP do not precipitate marked withdrawal in rats made acutely dependent on MS.

ACKNOWLEDGMENTS: Supported by NIDA grants DA 03796 and K02 DA00132.

7-OH-DPAT, BUT NOT QUINPIROLE, ATTENUATES THE ANTINOCICEPTIVE EFFECTS OF MU OPIOIDS

C. D. Cook, J. S. Rodefer, and M. J. Picker

Department of Psychology, University of North Carolina, Chapel Hill, NC

The present study evaluated the effects of the DA D3 agonist (±)-7-OH-DPAT and the D2 agonist quinpirole on the antinociceptive effects of mu opioids using a warm-water tail-withdrawal procedure in rats. The mu opioids morphine (0.3-10 mg/kg) and dezocine (0.03-3.0 mg/kg) produced dose-dependent increases in antinociception with maximal effects obtained at the higher doses tested. Pretreatment with 7-OH-DPAT (1.0-10 mg/kg) produced a dose-dependent attenuation of the antinociceptive effects of morphine and dezocine. At the highest dose of 7-OH-DPAT tested (10 mg/kg), the morphine dose-effect curve was shifted rightward by approximately 1.5 log units and the dezocine curve by greater than 2.3 log units. The (+)-isomer of 7-OH-DPAT (1.0-3.0 mg/kg) also shifted the morphine dose-effect curve to the right in a dose-dependent manner. The D2 agonist quinpirole (0.3-10 mg/kg) produced relatively small (<0.5 log units) rightward shifts in the morphine dose-effect curve, and these effects were not dose-dependent. At doses (0.1 and 1.0 mg/kg) larger than those previously reported to attenuate the effects of D2 agonists, the DA antagonist spiperone failed to alter the morphine dose-effect curve, but did reverse 7-OH-DPAT's effects on morphine antinociception. The present results demonstrate that 7-OH-DPAT attenuated mu opioid antinociception and that this effect was most likely mediated by activation of D3 receptors. The effects of 7-OH-DPAT were also differentiated from those produced by quinpirole, suggesting that these compounds produced their effects by activating different DA receptors.

ACKNOWLEDGMENTS: Supported by NIDA grants DA10277 and DA07244.

ACUTE BEHAVIORAL INTERJECTIONS BETWEEN OPIATES AND NMDA RECEPTOR ANTAGONISTS IN RATS

R. M. Swadley-Lewellen, K. Watorski, K. Warmoth, and K. A. Trujillo

Psychology Program, California State University, San Marcos, CA

NMDA receptor antagonists have been reported by several laboratories to inhibit tolerance to the analgesic effects of morphine without altering acute morphine analgesia. Others, however, have reported that NMDA antagonists enhance acute morphine analgesia. The present studies were undertaken to further explore the acute interactions between NMDA receptor antagonists and morphine in analgesia and locomotion. Male Sprague-Dawley rats (6/8 group) were injected with the NMDA antagonist MK-801 (0.1 or 0.3 mg/kg i.p.) followed 15-30 minutes later by morphine (3.0 or 10 mg/kg s.c.). The time course of analgesia was assessed by the tail-flick test and the time-course of locomotor effects assessed by a San Diego Instruments Flex Field photocell apparatus. As previously reported, MK-801 by itself produced no effect on the tail flick test. The low dose of MK-801, which is known to interfere with tolerance to morphine analgesia, did not alter the acute analgesic effects of morphine. The higher dose of MK-801, which has been reported to produce toxic interactions with morphine, significantly enhanced morphine analgesia. MK-801, by itself, produced a dose-dependent increase in locomotion, with a mild effect at the low dose and a potent increase at the higher dose. The higher dose also produced incoordination and ataxia. MK-801 dose-dependently increased locomotion in morphine treated animals, both inhibiting morphine-induced motor depression and enhancing morphine-induced motor facilitation. The resutls suggest potent interactions between NMDA receptors and opiates in analgesia and locomotion, particularly at doses that produce ataxic side effects.

ACKNOWLEGEMENTS: Supported by NIDA DA11803 and by CSU San Marcos

PATIENT-CONTROLLED ANALGESIA (PCA): EFFECT OF DRUG HISTORY ON MORPHINE SELF-ADMINISTRATION

A. Marco[1], M. K. Greenwald[2], and M. Higgins[3]

[1]Johns Hopkins University, Baltimore, MD; [2]Wayne State University, Detroit, MI; and [3]Vanderbilt University, Nashville, TN

This study evaluated the effect of drug history on morphine drug-seeking behavior, morphine consumption and pain reports in 9 consecutive, non-emergency cesarean section patients. Volunteers were interviewed on the day before surgery to obtain informed consent, a urine toxicology screen, drug use and psychiatric history, and baseline evaluation (repeated postsurgery) of pain signs/symptoms and mood state. Three subgroups of the 9 patients were: current illicit drug users (IDU, n=2; one methadone-maintained [40 mg] polydrug user and a cocaine user); tobacco users (NIC, 21 pack/day, n=3); and caffeine-only users (CAF, n=4). All patients were nicotine- and caffeine-deprived during the study. No preoperative medications were given. Standard intraoperative regional anesthesia was used (nonopioid, epidural). At first complaint of postsurgical pain, patients began PCA (loading: three 30-min periods of access to 3, 4 and 5 mg boluses q. 6 min; terminated when patient felt "comfortable") and continued 24 hr post-loading (maintenance: access to 1.5 mg boluses q. 6 nun). Hourly drug-seeking and consumption were recorded. Mean (M) 24-hr morphine-seeking was highest for IDU (M=432), intermediate for NIC (M=183), least for CAF (M=38). Morphine use (mg/kg/24hr) was highest for IDU (M=2.36), intermediate for NIC (M=1.80) least for CAF (M=0.64). Efficiency of responding for morphine analgesia (#bolus infusions ÷ #attempts) was highest for CAF (M=0.88), intermediate for NIC (M=0.51), least for IDU (M= 0.21). These data indicate that drug history can significantly (all group effects, $p < .005$) modulate morphine seeking, use and analgesia. Despite greater morphine use, pain severity remained high for IDU, moderate for NIC, but was low among CAF. These dramatic individual differences in PCA clinical outcome indicate the need for further research to optimize post-surgical analgesia (e.g., by increasing morphine bolus doses, providing nicotine replacement) among certain substance-using patients.

NMDA RECEPTOR BINDING AND ANTINOCICEPTIVE ACTIVITY OF ACETYLMETHADOLS AND METHADOLS

C. E. Inturrisi and A. L. Gorman

Department of Pharmacology, Cornell University Medical College, New York, NY

We have previously demonstrated that the d- and l-isomers of methadone exhibit low micromolar affinities for the [^{3}H]MK-801-labeled noncompetitive site of the NMDA receptor. d-Methadone also produces nonopioid antinociceptive activity after intrathecal (IT) administration as assessed during phase 2 of the formalin test or in the paw withdrawal test which measures NMDA-induced hyperalgesia (Shimoyama *et al.* JPET 283: 648, 1997). In addition d-methadone attenuates the development of morphine tolerance after IT or systemic administration. We have extended these studies to include the 1 and d isomers of acetylmethadol and a-methadol. The l-isomer of acetylmethadol is LAAM, the opioid maintenance drug, while the d-isomer is DAAM. The methadol isomers are 1-α-methadol which results from the reduction d-methadone and d-α-methadol which is derived from 1-methadone. Of these four compounds only DAAM had appreciable affinity for the MK-801 site on the NMDA receptor in rat forebrain with a Ki of 11 ± 1 μM compared 7.4 ± 1.2 for d-methadone. In addition, IT DAAM dose-dependently blocked IT NMDA-induced hyperalgesia. These results indicate that DAAM has NMDA receptor antagonist activity.

ACKNOWLEDGMENTS: Supported in part by NIDA grants DA01457, DA00198, and DA07274.

ANALGESIC EFFECTS OF ORAL MORPHINE IN METHADONE-MAINTAINED VS. NON-OPIOID DEPENDENT VOLUNTEERS

A. Bisaga, S. D. Comer, and M. W. Fischman

Substance Use Research Center, NYS PI and Columbia University, New York, NY

The analgesic effects of morphine (0, 5, 10, 20, and 40 mg p.o.) were evaluated in methadone-maintained (60-80 mg) individuals and healthy controls during an outpatient study. At the beginning of each experimental session, drug toxicologies on observed urines were performed to confirm the absence of illicit substances. Morphine was given one hr after the daily methadone dose in methadone-maintained individuals. Morphine doses were given in non-systematic, order both within and between participants in a double-blind manner. Immediately prior to, and at various time points after morphine administration, participants immersed their non-dominant arm into cold water (4°C). Dependent measures included latency to feel pain (threshold), latency to withdraw the forearm from the water (endurance), subjective ratings of pain measured immediately after arm withdrawal, pupil diameter, heart rate, and blood pressure. In addition, psychomotor task performance was assessed and subjective effects questionnaires were completed repeatedly during the sessions. Individual responsivity to the painful tonic stimulus of ice-cold water, and the effects of morphine on the experience of pain were highly variable. In the first six experimental subjects and four controls tested, baseline pain threshold was not different between the two groups, but pain endurance was longer in the control group. Morphine did not affect withdrawal latency or latency to feel pain in either group of participants. However, morphine reduced some subjective reports of pain in methadone and control subjects. Morphine produced minimal subjective effects in methadone-maintained subjects as opposed to robust subjective effects in non-opioid-dependent matched controls. These preliminary findings suggest that although methadone maintained subjects have blunted responses to the subjective and physical effects of opioids, cross-tolerance between methadone and morphine in terms of analgesic effects might be incomplete. These results provide useful information for clinicians treating pain in methadone-maintained individuals.

ACKNOWLEDGMENT: Supported by NIDA grant DA09236.

ORAL COMMUNICATIONS XIII

NEW KNOWLEDGE ABOUT FETAL ALCOHOL SYNDROME AMONG AMERICAN INDIAN TRIBES IN THE SOUTHWEST

P. A. May, J. P. Gossage, L. L. Ballinger, and M. M. Harris

University of New Mexico Ctr on Alcoholism, Substance Abuse, and Addictions, Albuquerque, NM

In a cooperative agreement with the U.S. Centers for Disease Control and Prevention (CDC) and building on earlier efforts, the authors have been working in three American Indian communities in New Mexico over the past four years to better understand the current epidemiology of FAS. The project includes: (1) training on the recognition of FAS for health care providers, teachers, and others; (2) networking to identify children who have FAS or other possible Alcohol-Related Birth Defects (ARBD) or Alcohol-Related Neuro-developmental Disorders (ARND); (3) obtaining referrals; (4) conducting special developmental clinics to diagnose FAS; and (5) interviewing the mothers of the children referred to these clinics to assess maternal risk factors. The data presented were designed to explain the goals, objectives and methodology of the project, and present results. Over 200 children were screened among children of all ethnic groups in New Mexico; of these 93 were American Indian from the three focal Indian communities. Sixteen (17.2%) of these children were found to have FAS which yields a prevalence rate of 2.14 per 1000 children born between October 1, 1984 and September 30, 1996. This rate compares favorably with North American estimates from studies using retrospective and prospective methods (2.2) and is also similar to rates (of 2.0 per 1000) found among southwestern Indians born 1969-1982. Minimal variance was found between the three communities, as the range in rates was 1.81 to 2.27. The American Indian rate in this study was, however, substantially higher than that found in the non-Indian New Mexico communities (0.31). Finally, the maternal risk rate for FAS was 1.84 per 1000 women of childbearing age (15-44 years) in the three Indian communities.

MATERNAL PRENATAL SUBSTANCE ABUSE AND INFANT VISUAL ATTENTION AT ONE MONTH POST DELIVERY

R. Tyler, J. Howard, and M. Espinosa

Department of Pediatrics, University of California, Los Angeles (UCLA), CA

The purpose of this study was to obtain baseline information on visual attention in infants who were prenatally exposed to drugs. Visual attention measures in early infancy are powerful predictors of later cognitive development in normal children and high risk groups of children. Fifty-five infants with prenatal cocaine exposure whose mothers were heavy drug users were brought into a laboratory at one month of age and were administered a visual attention measure. Each infant was placed in a comfortable infant seat. Three visual black and white images (a checkerboard, a drawn face, and a bulls eye) were shown sequentially. The average duration of looking directly at the visual stimulus was measured. Only data from the first stimulus, the checkerboard, could be analyzed since the majority of the infants began to cry and were unable to visually attend to the remaining stimuli. Two measures of maternal drug use were included: the ASI and the urine toxicology screen at birth. Birthweight and gestational age were also included as a potential factor influencing visual attention. The ASI, birthweight, and gestational age were not related to visual attention. However, a positive urine toxicology screen at the time of delivery was significantly related to a longer length of visual fixation. Shorter fixation times have been found to be later associated with better cognitive development. Further research is necessary to understand the long term developmental implications.

FOCUSED ATTENTION AND DISTRACTIBILITY IN TODDLERS PRENATALLY EXPOSED TO COCAINE

I. J. Feldman, R. L. Freedland, J. M. Gardner, B. Z. Karmel, and S. C. Gartenberg

NYS Institute for Basic Research in Developmental Disabilities, Staten Island, NY

Focused attention, the ability to select and sustain attention to an object, is vital to learning and is associated with later cognitive measures. To obtain information about the environment, it is necessary to both a)shift attention between stimuli, and b)focus attention more narrowly on a single stimulus. Using a modification of Ruff's procedure, 16 month-olds (n = 39) played with a series of toys for 3 2-minute trials while distracters (computer-generated animation) were presented for 4-s. durations at random intervals. One group was prenatally exposed to cocaine (CE: n=18) as determined by maternal report, maternal or infant urine toxicology, and/or infant meconium toxicology. The other group was not exposed to cocaine or any other drugs of abuse (Non-CE: n=21). All were term and healthy at birth. Looking behavior was analyzed from videotapes to differentiate casual looking from deep (focused) attention. Although CE and non-CE toddlers spent the same overall time looking at the toy for the first two minutes, CE toddlers evidenced a different pattern of attention. Their attention was characterized by a rapid increase that plateaued and began to decrease over the last two minutes. Non-CE toddlers evidenced a linear increase in attention across trials. CE toddlers spent significantly more time in non-focused attention than the non-exposed toddlers ($p < .05$). There were no group differences in distractibility. Differences in the ability to sustain attention became apparent after the fourth minute when CE toddlers showed a trend towards a shorter duration of focused attention to the toy, that was due to a significantly shorter duration of each focused epoch ($p < .04$). In summary, the attentional performance of CE toddlers suggests that differences in the arousal-modulated attention mechanism of the neonate may continue in development in the guise of difficulty maintaining sustained attention, and this is hypothesized to underlie a number of behavioral and academic difficulties in later years.

ACKNOWLEDGMENTS: Supported by NIDA grants R-01-DA-06644, K-21-DA-00236, and NICHD grant R-01-HD-21784.

THE BRAZELTON NEONATAL BEHAVIORAL ASSESSMENT SCALE AND PLAY IN PRENATALLY DRUG-EXPOSED TODDLERS

L. Beckwith, J. Howard, R. Tyler, and M. Espinosa

Department of Pediatrics, University of California, Los Angeles, CA

The purpose of this study was to determine whether the BNBAS at 1 month was predictive of later play behavior of 18 month old toddlers who were prenatally exposed to drugs. Seventy-one children and their caregivers were studied from pregnancy through 18 months of age. All mothers were heavy drug users with the primary drug of abuse being cocaine. The BNBAS was administered and scored at 1 month in the laboratory, using the cluster system developed by Lester *et al.* (1982). At 18 months, the child and caregiver returned to the laboratory where a videotaped play assessment was conducted. The child's play behavior was rated on seven scales by a researcher blind to the BNBAS findings. These seven scales coded different aspects of the maturity of the child's play including amount of mouthing of toys, amount of thematic play, and the inclusion of caregiver in the play. Other predictors included maternal drug use as measured prenatally by the ASI, by a urine toxicology screen at birth, as well as birthweight since it reflects neonatal status. The BNBAS was found not to be related to maternal drug use or birthweight. However, BNBAS did predict differences in levels of maturity in play at 18 months. Four of the six clusters (orientation, motor, range of state, regulation of state) were found to be significantly related to four of the play scales. These findings extend into toddlerhood results from previous studies showing that neonatal behavioral organization accounts for significant differences in later competencies.

INHIBITORY CONTROL OF COCAINE-EXPOSED INFANTS AT THREE YEARS

R. Geva, J. M. Gardner, B. Z. Karmel, I. J. Feldman, and R. L. Freedland

NYS Institute for Basic Research in Developmental Disabilities, Staten Island, NY

Neurotoxic effects of prenatal exposure to cocaine can result in atypical development of the limbic-striatal-prefrontal axis. Cerebral damage involving this pathway has been associated with inhibitory control (IC) deficits on neuropsychological testing. We hypothsized that cocaine-exposed (CE) children could exhibit IC deficits manifest by poor ability to control, plan, execute, and modify intentional motor acts. Cognitive development and IC were evaluated in two groups of healthy term infants at 34 mos. One group (n=31) was exposed to cocaine prenatally as determined by maternal report, maternal or infant urine toxicology, or infant meconium toxicology. The other group (n=57) was not exposed to cocaine or any other controlled substance. Griffiths Mental Development Scales were used to evaluate overall cognitive competence as well as individual profiles of ability. CE children, although within the normal range, had lowered scores on all Griffiths Scales except Personal-Social. A Rapid Sequential Alteration Naming Task (RSANT) and a Graphomotor Task (GMT) were designed to evaluate IC at this age. Completion time and perseverative errors were scored. Performance on RSANT by CE children was marked by more perseverative errors and slowed processing relative to the contrast group, even when the Speech and Language and the Performance Scales of the Grifiths were used as covariates. On the GMT, CE children made perseverative errors (Type 1 & 2) more frequently than the contrast goup, even with Griffith' Eye-Hand Coordination Scale covaried. CE children also were more affected by the increasing demand for effortful inhibition across the 4 GMT levels. They showed more errors even at the lower levels of required effort. These findings indicated effects from prenatal cocaine exposure on IC in healthy term children with normal cognition as manifest by verbal and manual perseverative errors and prolonged processing speed at 34 months, thereby potentially affecting later language, information processing. and motor integration.

ACKNOWLEDGMENTS: Supported by the March of Dimes Foundation grant #12-FY96-98-0543, NIDA grants R-01-DA06644 and K-21-DA00236, and NICHD grant R-01-HD21784.

PARENTING PRACTICES AND BEHAVIOR PROBLEMS AMONG CHILDREN OF COCAINE-DEPENDENT OUTPATIENTS

C. J. Wong, C. Stanger, J. Katmon, and S. T. Higgins

Substance Abuse Treatment Center, University of Vermont, Burlington, VT

Children of drug abusers are at risk for behavioral, social and academic problems. Children of parents receiving treatment for drug abuse score higher on the Child Behavior Checklist (CBCL) for the anxious/depressed, delinquent, and aggressive behavior syndromes. We examined the relationship between parenting practices among cocaine and opiate dependent mothers and their children's behavior problems. The CBCL and Alabama Parenting Questionnaire (APQ) were administered to cocaine-dependent outpatients who parented 74 children between the ages of 4-18 yrs. Weexamined whether CBCL syndrome scores were significantly associated with parenting practices on the APQ. Higher scores on the withdrawn, anxious/ depressed, attention problems, and aggressive syndromes were associated with lower parental involvement scores ($p<.01$). Higher withdrawn, delinquent, and aggressive syndrome scores were significantly associated with lower positive parental interaction scores ($p<.05$). Higher delinquent sydrome scores were associated with lower parent monitoring scores ($P<.05$). Higher somatic complaints, attention. delinquent and aggressive syndrome scores were associated with higher inconsistent parenting scores ($p<.05$). Lastly, higher attention and aggressive syndrome scores were associated with higher corporal punishment scores ($p<.05$). These results provide useful information for the development of effective parenting interventions for cocaine-dependent parents.

THE RELATIONSHIP BETWEEN MATERNAL REJECTION AND ADOLESCENT SUBSTANCE USE

S. Reyland, M. Chawarski, and R. Schottenfeld

Yale University School of Medicine, Department of Psychiatry

The objective of this study was to assess the relationship of between maternal rejection and substance use in a sample of 140 (females = 86, males = 54) adolescents enrolled in an inner-city high school and middle school located in the Bronx borough of New York City. The mean age of the sample was 15 (SD =1.8), with a range of 11-19. This study utilized a cross-sectional design to assess five variables: (1) frequency of alcohol and marijuana use was measured using two frequency questions; (2) parental acceptance, as measured by the Parental Acceptance-Rejection Questionnaire (Rohner, 1984); (3) age; (4) sex and, (5) ethnicity. Logistic regression revealed that alcohol and marijuana involvement was best predicted by maternal rejection and age. In addition, gender also predicted marijuana use. The results of a Chi Square revealed that for adolescents, over the age of 15, the relationship between maternal rejection and substance use was stronger than for adolescents under the age of 15. Results of this study can be used to guide prevention and intervention curriculums that focus on issues of adolescent substance use.

ACKNOWLEDGMENT: Supported by NIDA Research Training Grant T32DA07238.

SUBSTANCE USE FROM TEEN TO ADULT YEARS: RISK FACTORS FOR TEEN MOTHERS

M. D. Cornelius, H. Lebow, L. Goldschmidt, and N. L. Day

Departments of Psychiatry and Epidemiology, University of Pittsburgh School of Medicine, Pittsburgh, PA

In an ongoing study, teen mothers were interviewed about their drug use the year prior to pregnancy, during pregnancy, and six years postpartum. The current data represent 88 of the first 415 teen mothers who have been followed for six years and who are now young adults. Their average age is 22.7 years (20 - 25); 26% are Caucasian and 74% are African-American. As teenagers, 53% smoked cigarettes the year before pregnancy, 74% used alcohol, and 38% used marijuana. By the third trimester of pregnancy, alcohol and marijuana use dropped to 8% and 3%, respectively, however; tobacco use increased to 59%. Six years postpartum, 61% were tobacco users, 90% used alcohol, and 33% used marijuana. Using logistic regression analyses, significant predictors of heavier tobacco use (10+ cigarettes/day) in early adulthood were: Caucasian race, attention problems (YSR, Achenbach, 1991) and somatic problems (YSR) as measured when the mothers were teenagers. Significant predictors of early adulthood heavier drinking (2+ drinks per day) were: Current average daily tobacco use, current average daily marijuana use, and higher scores on the hostility measure (Spielberger, 1970). Significant predictors of heavier marijuana use (1+ joints/week) were: Current average daily alcohol use, and higher scores on the depression measure (CES-D). Mothers who used two or more of these substances in adulthood had significantly more hostility and depressive symptoms, less satisfaction with social support, lower income, and were non-married and non-working. At the six year follow-up, 94% of the women had more children after the proband offspring. Therefore, future offspring continued to be exposed to maternal substance use, and those at highest risk for exposure were offspring of mothers with other characteristics that may indicate less optimal environments for children.

ORAL COMMUNICATIONS XIV

BIOEQUIVQLENCE OF LIQUID AND TABLET FORMULATIONS OF BUPRENORPHINE

M. C. Chawarski, R. S. Schottenfeld, J. Pakes, and P. G. O'Connor

Department of Psychiatry, Substance Abuse Center, Yale University School of Medicine, New Haven, CT

Background: Current buprenorphine dosing recommendations for agonist maintenance treatment are based on studies using sublingual liquid buprenorphine, but tablet formulations will replace the liquid formulation. Prior studies suggest that bioequivalence of tablets is 50-60% of liquid. **Objective:** To evaluate peak plasma levels (C_{Max}), trough levels (C_{24h}), and 24 hour area under the concentration curve ($AUC_{()-24h}$) during maintenance on sublingual liquid or tablet formulations, when patients received tablet doses that were twice as high as liquid doses. **Methods:** Sixty subjects were enrolled and assigned randomly to 3 sublingual (SL) daily buprenorphine dose pairs: a) 8 mg SL liquid and 16 mg SL tablets, b) 12 mg SL liquid and 24 mg SL tablets, and c) 16 mg SL liquid and 16 mg SL tablets. All subjects were first administered two weeks of maintenance on the liquid formulation followed by two weeks of maintenance on the corresponding dose of tablets. Subjects and research staff were kept blind to dose but not to formulation. Six plasma samples from each subject were obtained on two occasions-after at least 10 days of maintenance on the liquid formulation and after at least 10 days of maintenance on the tablet formulation. Plasma samples were obtained prior to medication dispensing, and then 1, 2, 4, 6 and 24 hours following administration of the daily buprenorphine dose. **Results:** Plasma results are available on 46 subjects. Preliminary analysis of available plasma concentrations show a large inter- and intrasubject variability of plasma concentrations, with greater variability for tablets than for liquid buprenorphine (based on 95% CI). Based on C_{Max} results, the tablets are about 60%-75% equivalent of liquid buprenorphine. The results of trough plasma levels (C_{24h}) indicate that tablets are about 100% equivalent of liquid buprenorphine. Finally, based on $AUC_{()-24h}$ results tablets are about 75-80% equivalent of liquid buprenorphine. These results are substantially higher than reported earlier.

ACKNOWLEDGMENTS: Supported by NIH grants DAO9250 and DAO9803.

DOSE PROPORTIONALITY OF SUBLINGUAL BUPRENORPHINE AND NALOXONE TABLETS

R. T. Jones, R. Upton, E. Lin, S. G. Welm, and J. Mendelson

Drug Dependence Research Center, Langley Porter Institute, University of California, San Francisco

Sublingual buprenorphine in combination with naloxone is a promising treatment for opiate dependence. This study evaluated the dose proportionality of sublingual tablet dose formulations of 4 to 16 mg of buprenorphine combined with naloxone in a 4:1 ratio in eight opiate-experienced, but not dependent, subjects. Plasma and urine buprenorphine and naloxone levels were measured by LC/MS/MS, standard pharmacokinetic parameters were determined, and opiate-specific subjective and physiologic effects measures were obtained. Mean buprenorphine AUC and Cmax increased with dose of buprenorphine, but dose-corrected AUC for the 16 mg dose alone or in combination with naloxone was less than the AUC for the 4 mg dose. Naloxone was not found to alter the pharmacokinetic characteristics of buprenorphine. There were no phannacodynamic differences between preparations or doses, and no opiate withdrawal occurred with sublingual naloxone in this population of opiate users. The sublingual buprenorphine and naloxone combinations (4:1 ratio) have a similar profile to buprenorphine for all the effects measured in this study. This tablet formulation appears to be adequately absorbed and potentially effective in the treatment of opiate dependence. Acceptability as a treatment medication was highest for the buprenorphine (4 mg) and naloxone (1 mg) tablet formulation.

ACKNOWLEDGMENT: Supported in part by NIDA Contract 271-90-7307.

PHARMACOKINETIC COMPARISON OF THE BUPRENORPHINE SUBLINGUAL LIQUID AND TABLET

K. J. Schuh, C. R. Schuster, and C. E. Johanson

Department of Psychiatry and Behavioral Neurosciences, Wayne State University School of Medicine, Detroit, MI

Buprenorphine is a μ opioid partial agonist being developed as a treatment for opioid dependence. Buprenorphine is usually administered as a sublingual liquid held under the tongue for 5 min but it is now being developed as a sublingual tablet for clinical use. However, the relative bioavailability of these two dosage forms is unknown. The present study compared participants plasma concentrations after daily maintenance on three buprenorphine liquid doses and one tablet dose. Fourteen opioid-dependent individuals (11 males, 3 females) participated. Participants were maintained on ascending doses of 2, 4, and 8 mg liquid, then 8 mg tablet, then descending doses of 4 and 2 mg liquid. For 7 participants, plasma samples were collected after maintenance on the liquid doses for at least 14 days and the tablet dose for at least 7 days. For the other 7 participants, plasma samples were only collected during ascending doses. These participants were maintained on each dose for at least 10 days. Plasma samples collected 15 min before the daily dose on three consecutive days were averaged to obtain trough concentrations. During the second day samples were also collected 30, 60, 120, 180, 240, and 360 min after the dose. At this time, samples from only the first 7 participants have been analyzed. Preliminary results indicate a dose-related increase in plasma buprenorphine concentrations when the liquid doses were administered. Five of the 7 participants had higher plasma concentrations after administration of the 8 mg liquid compared with the 8 mg tablet. The mean concentrations after the 8 mg liquid and tablet were 5.46 and 2.95 ng/ml, respectively. The plasma concentrations produced by the 8 mg liquid were overly influenced by the high concentrations from 2 participants. However, the buprenorphine tablet produced plasma concentrations lower than an equal dose liquid.

ACKNOWLEDGMENT: Supported by NIDA grant DA00254.

BUPRENORPHINE/NALOXONE COMBINATION TABLET: EFFECTS IN NON-DEPENDENT OPIOID ABUSERS

E. C. Strain, K. B. Stoller, S. L. Walsh, and G. E. Bigelow

Department of Psychiatry, Johns Hopkins University School of Medicine, Baltimore, MD

Buprenorphine is an opioid partial agonist being developed for opioid dependence treatment. To reduce the risk of buprenorphine abuse, a combination tablet with naloxone is being developed. This capitalizes on the poor SL but good parenteral bioavailability of naloxone, so that the indicated route (SL) will result in a buprenorphine effect but illicit use by injection will precipitate withdrawal in opioid-dependent people. However, it is not known if adding naloxone might alter buprenorphine's effects in non-dependent opioid abusers. Therefore, this inpatient laboratory study assessed the effects of buprenorphine/naloxone combination tablets in non-dependent opioid abusers. In twice-weekly experimental sessions participants received double-blind SL tablets as well as intramuscular (IM) injections. Study conditions were: buprenorphine/naloxone combination (1/0.25, 2/0.5, 4/1, 8/2, 16/4 mg SL tablets), hydromorphone alone (2, 4 mg IM), buprenorphine alone (4, 8, 16 mg SL tablets), or placebo. During sessions, physiological status was recorded continuously, and tasks assessing psychomotor, subjective and objective status are repeatedly performed. Results for subject-rated, observer-rated, and physiological measures showed hydromorphone produced typical opioid agonist-like effects, as did sublingual doses of buprenorphine alone and buprenorphine/naloxone. These effects for buprenorphine and buprenorphine/naloxone were dose-related, and there was no evidence that agonist-like effects of buprenorphine were attenuated by the addition of naloxone. These results suggest the addition of naloxone to buprenorphine does not alter the effects of buprenorphine in non-dependent opioid abusers, when taken by the sublingual route, and the possibility of abuse by the SL route in this population.

ACKNOWLEDGMENTS: Supported by grants R01 DA08045, K02 DA00332, K05 DA00050, and T32 DA07209 from NIDA.

BUPRENORPHINE TREATMENT OF HEROIN DEPENDENCE IN A PRIVATE PRACTICE SETTING

R. B. Resnick, E. Resnick, C. Pycha, and M. Galanter

Division of Alcoholism and Substance Abuse, New York University Medical Center, New York, NY

The recent upsurge in heroin use makes it important to develop new strategies with which to deliver effective and acceptable treatments to the expanding numbers of heroin addicts who are unwilling to accept currently available treatments. We have shown previously that many of this group will accept treatment with buprenorphine when offered in a medical office facility. Two open clinical trials (detoxification and maintenance) explored buprenorphine treatment conducted on a fee-for-service basis in a private psychiatric practice. In a detoxification protocol, 29 of 40 subjects (72.5%) completed buprenorphine administration (10-34 days) and started placebo. At three months follow-up, seven subjects (17.5%) were opioid-free and at 12 months, four subjects (10%) remained abstinent. These findings are comparable to the outcomes reported for methadone and in-patient detoxification. In a maintenance protocol, 23 subjects, dependent on $50-150/day heroin (mean: $75/day), received 5-16 mg/day buprenorphine and weekly counseling for up to 14 months. Take-home doses were not permitted, but by increasing the dose most subjects were able to reduce frequency of visits from daily to 3-4 times per week. A community pharmacy administered buprenorphine during periods of staff vacations. Heroin use was monitored by self-report and urine drug screens for those who claimed to be abstinent. Subjects were middle-class; ages 20-52 years (mean 36.1 years); 20 subjects were either employed (N= 16), living with an employed spouse (N= 3) or attending school (N= 1). Criminality was absent in all but one subject. Three subjects had irregular attendance and were terminated in <2 months. Twenty subjects received buprenorphine for 6-14 months, with no heroin use in 16 subjects and occasional use in four subjects. Follow-up showed a high relapse rate after program termination. Only four subjects detoxified from buprenorphine and were abstinent 6 months after termination. Considering its appeal to heroin addicts who refuse other treatments, expanding buprenorphine to private practice settings has potentially significant public health benefits with minimal risk to public safety, making it an important treatment option for further study.

TREATMENT OF HEROIN DEPENDENT POLY-DRUG ABUSERS WITH CONTINGENT VOUCHERS AND BUPRENORPHINE

K. K. Downey, J. A. Hopper, M. Henderson, E. Corby, T. Helmus, and C. R. Schuster

Wayne State University School of Medicine, Department of Psychiatry and Behavioral Neurosciences, Clinical Research Division on Substance Abuse

This study was designed to develop a more effective treatment program for heroin-dependent poly-drug abusers by combining Voucher-Based Reinforcement Therapy (VBRT) with a buprenorphine and cognitive-behavioral treatment program. Previous studies have used VBRT to target a specific drug; the present study targets poly-drug use. The three treatment conditions are standard VBRT as described by Higgins *et al.* (1994), a VBRT condition in which voucher values are reduced (rVBRT) by about 1/3, and a yoked control (YC) condition. All subjects are also exposed to a contingency management procedure in which each accurate prediction of urinalysis results yields a $2.50 voucher. To date, 42 subjects have been enrolled, 13 dropped out early, and 29 have been radomized. We have been encountering an early drop-out rate significantly higher than expected, as compared to retention rates in our methadone maintenance clinic. These preliminary results suggest that VBRT yields better retention than rVBRT and YC, but is not clearly superior in terms of treatment outcome. It was expected that the rVBRT condition would yield results similar to those achieved by VBRT, but this has not been evident. Results suggest that VBRT's efficacy may be compromised when targeting poly-drug abuse, although the approach may still make a difficult treatment population more accessible for receiving needed services. Subjects have been predicting urinalysis results with 92% accuracy. This suggests that clinic toxicology costs may be reduced via effective contingency management procedures to reduce the necessity for frequent urinalysis.

ACKNOWLEDGMENT: Supported by NIDA grant 5 RO1 DA 10816-02.

PILOT OPEN-LABEL SAFETY STUDY OF BUPRENORPHINE (BUP) DURING PREGNANCY

R. E. Johnson, D. S. Svikis, W. B. Kissin, G. Alpan, J. Bienstock, E. J. Cone*, A. S. Golden, N. A. Haug, G. R. Huggins, L. Jansson, M. E. Lantz, D. Wilkins**, and D. R. Jasinski

Johns Hopkins University School of Medicine, *NIH/NIDA/IRP, Baltimore, MD and **University of Utah, Salt Lake City, UT

Methadone (M) is recommended for treating pregnant opioid dependent women. Although neonates of M maintained mothers have significantly improved birth outcomes compared to those born to heroin dependent mothers, they often exhibit neonatal abstinence symptoms (NAS) requiring costly medical intervention. The minimal opioid abstinence syndrome observed following abrupt termination of BUP in adults suggests that neonates of BUP maintained mothers may demonstrate fewer NAS than neonates of mothers maintained on M. The purpose of this study was to assess maternal safety, pharmacokinetic (PK) and dose adequacy (DA) parameters and neonatal birth outcome, PK, and NAS to establish the feasibility of a randomized controlled trial (RCT) comparing M and BUP. Three pregnant (24-26 weeks) women (opioid and nicotine dependent; HIV negative; otherwise drug free) were maintained on BUP sublingual tablets (8-12 mg/day). No clinically significant abnormalities were observed on maternal safety measures. Pre- and post- delivery maternal BUP plasma (P) levels ranged from 124-485 ng/L and 115-789 ng/L, respectively. Breast milk (BM) BUP level (489 ng/L; n=1) showed a BM/P ratio of 1. DA scores showed BUP was "Holding" the women well; they "Liked" the medication and had minimal "Heroin Craving" and feelings of being "Hooked". All neonates were full-term and birth outcome measures were within normal limits. Mean cord, plasma, and urine BUP levels were 118 (n=3), 97 (n=1), and 1132 (n=1) ng/L, respectively. BUP levels in meconium (n=1) were 1.3, 3.6, and 35.4 ng/g for the first 3 stools, respectively. Onset, peak, and duration of NAS were 4-36, 16-72, and 115-120 hours, respectively. The two NAS most often observed were tremors and hyperactive moro. Peak NAS scores ranged from 6-13 (max. possible = 48). NAS required no medical treatment. It is concluded that: 1) BUP is sufficiently safe for both mother and fetus to warrant a RCT comparing BUP and M, and 2) BUP exposed neonates experience NAS (possibly confounded by nicotine) that may be milder and of shorter duration than observed with M.

ACKNOWLEDGMENTS: Supported by Reckitt & Colman, VACSP/NIDA, DA 09258, and DA 07209.

THRICE WEEKLY VS. DAILY BUPRENORPHINE MAINTENANCE

R. S. Schottenfeld, P. G. O'Connor, J. Pakes, M. Chawarski, and M. Pantalon

Department of Psychiatry, Yale University School of Medicine and The APT Foundation

Background: Alternate day and thrice weekly buprenorphine (BUP) is well tolerated by opioid-dependent patients and leads to substantial reductions in illicit opioid use. **Objective:** To compare the efficacy of daily vs. three times per week (3x/wk) BUP for the maintenance treatment of opioid dependence. **Study Design:** Random assignment, double blind clinical trial comparing BUP SL liquid daily (16 mg/70 kg) and 3x/wk (34 mg, 34 mg, and 44 mg/70 kg). Outcome Measures include retention, results of 3x/wk urine testing for opioids and cocaine, and self-report measures of illicit opioid use. Subjects (n=92) meeting DSM-IV criteria for current opioid dependence and age 18-64 years were randomly assigned to 12 weeks maintenance on daily (n=45) or 3x/wk (n=47) BUP after 3-day induction. The two groups were comparable at baseline on social, demographic and drug use measures. **Results:** Retention in the daily and 3x/wk conditions averaged 71% and 77%. Rates of opioid-positive urine tests decreased significantly from baseline in both groups (Wald chi square = 281.5, df5, p<.001) and averaged 56.3% (daily) and 57.3% (3x/wk). There were no significant differences in the proportion of subjects achieving 3 or more consecutive weeks of abstinence from illicit opioids in the daily and 3x/wk conditions (37.8%, 42.6%) or in rates of cocaine-positive urine samples (48.9%, 44.7%). There were also no significant differences between the groups in self-reported number of bags of heroin used on Sundays (48-72 hours following the Friday dose in subjects in the 3x/wk condition), or in medication compliance (92%, 91%). Rates of opioid-positive urine tests were significantly lower among subjects who remained abstinent from cocaine for 3 or more weeks compared to those who did not abstain (49%. 68%; Wald chi square =8,8, dfl, p<.005). **Conclusions:** Daily and 3x/wk BUP dosing led to substantial and comparable reductions in illicit opioid use, at equivalent weekly BUP doses. The finding of no significant differences in medication compliance or self-reported daily illicit opioid use suggest that subjects did not respond adversely to placebo medication days in the 3x/wk condition.

ACKNOWLEDGMENTS: Supported by DA09803 and DA09250.

EFFICACY OF AND PREFERENCE FOR 3-DAY VS. DAILY DOSING WITH THE BUPRENORPHINE-NALOXONE COMBINATION TABLET

L. Amass, J. B. Kamien, and S. K. Mikulich*

Department of Psychiatry, Addiction Research and Treatment Services, University of Colorado School of Medicine, Denver, CO and *BioPsych Consulting, Denver, CO

A combination buprenorphine-naloxone tablet containing 8 mg of buprenorphine and 2 mg of naloxone can be administered effectively on a less than daily basis. This study determined the clinical efficacy of, and preference for, daily and 3-day dosing schedules using the combination tablet, Opioid-dependent outpatients (N=24) entered a triple crossover trial blinded for dose magnitude. Twenty-one days of daily combination tablet administration were compared to two different 21-day periods of 3-day (MWF) tablet administration. Under one 3-day schedule (3-day clinic), clients ingested 16, 16, and 24 mg of the combination tablet at the clinic each Mon., Wed. and Fri., respectively. On the other 3-day schedule (3-day take-home), clients received an 8 mg tablet every Mon., Wed. and Fri. and 8 mg tablets to take at home on days between clinic visits. Outcome measures included treatment retention, medication compliance, drug use and self-reports. Fifty-four percent (13/24) of patients completed the study. Of the 11 subjects who dropped out, 5 did so during daily dosing and the rest were evenly distributed between the two 3-day dosing conditions. More doses were taken under the 3-day schedules (p=.007). There were no significant differences across conditions in rates of illicit drug use, with 45% of urine samples positive for opioids across the entire treatment period. Subjects "liked" both 3-day schedules more than the daily schedule (p=.002), and ratings of "good" were higher for the 3-day take-home as opposed to 3-day clinic condition (p=.04). Eighty-five, 77 and 67 % of subjects would continue on the 3-day take-home, 3-day clinic and daily dosing schedules if they could, respectively. Almost all of the subjects (91%) rated 3-day take-home as the best schedule while 82% rated daily dosing as least preferred. These data suggest that reducing clinic attendance improves medication compliance and increases client satisfaction without impacting illicit drug use. Moreover, a 3-day dosing schedule with take-homes is preferred to a 3-day schedule without take-homes.

ACKNOWLEDGMENT: Supported by NIDA grant DA11160.

A MULTI-SITE EFFICACY EVALUATION OF A BUPRENORPHINE/NALOXONE PRODUCT FOR OPIATE DEPENDENCE TREATMENT

P. J. Fudala[1], T. P. Bridge[2], S. Herbert[2], C. N. Chiang[2], and D. B. Leiderman[2] for the BUP/NX Collaborative Study Group

[1]Department of Veterans Affairs/University of Pennsylvania, Philadelphia, PA and the [2]National Institute on Drug Abuse, Medications Development Division, Rockville, MD

Hypothesis: A combination product containing both buprenorphine (BUP) and naloxone (NX) is expected to be undesirable for parenteral abuse by opiate (OP)-dependent individuals but safe and efficacious for OP-dependence treatment. **Objective:** Determine the efficacy and safety of a BUP/NX sublingual tablet formulation as an office-based therapy for OP-dependence treatment. **Methods:** A multicenter trial (8 sites, 326 pts total). Pts were OP dependent, seeking substitution therapy, men and women, and between 18 and 59 years of age. During the first, 4-week efficacy-assessment phase, pts were randomly assigned to either daily 1) placebo, 2) BUP 16 mg, or 3) BUP 16 mg/NX 4 mg given as a sublingual tablet. Pts attended the clinic 5 days weekly (M-F) and received take-home study medication doses on weekends and clinic holidays. They were compensated ($10/day) for time spent completing study-mandated assessments; pts were NOT paid for taking study medication. Pts completing the first study phase were given the opportunity to continue in a second, open-label, 48-week phase focusing on the collection of additional safety data. Primary Outcome Measures: 1) Urine samples negative for OPs, 2) Pt-reported craving for Ops. Principal Secondary Outcome Measures: 1) Clinician- and 2) Pt-reported global impression ratings. **Results:** The first phase of the study was terminated early due to the conclusive demonstration of the efficacy of BUP/NX as compared to placebo. Both BUP/NX and BUP were associated with a significantly greater proportion of urine samples negative for OPs, less OP craving, and higher global impression ratings than placebo. **Summary:** This study is expected to be considered pivotal with regards to a New Drug Application for BUP/NX.

ACKNOWLEDGMENT: Supported by NIDA through the VA Cooperative Studies Program.

VOLUME LOSS IN THE BRAIN STEM OF CHRONIC HEAVY DRINKERS: A PRELIMINARY MRI STUDY

D. Langleben, C. Bloomer, G. Fein, and D. J. Meyerhoff

Magnetic Resonance Unit, VA Medical Center 114M, University of California San Francisco, San Francisco, CA

The brain stem contains centers involved in reward mechanisms, which are important in addiction. The effect of chronic alcohol on brain stem size has not been studied in-vivo. We used quantitative MRI to compare volumes of the brain stem in 10 light/non-drinking men (LD) and 12 heavy drinking men (HD) of similar age. LD subjects drank 17 ± 9 drinks/month and HD subjects 234 ± 182 drinks/month for at least 2 years prior to study. Four of the 10 LD subjects and two of the six HD subjects were HIV-seropositive. Subjects with focal abnormalities on brain MR were excluded. MRI was performed on a Siemens 1.5 T system. A home-written computer program was used to determine from 3D T1-weighted oblique coronal 1.5 mm thick slices reconstructed in the sagittal plane a) the volume of the brain stem and b) the area of the brain stem on a midsagittal slice (separated into midbrain, pons, and medulla). Brain stem measures were normalized to the intracranial volume that was determined from 3 mm thick contiguous axial spin-echo images and included gray and white matter, ventricular and sulcal CSF. ANOVA was used to evaluate alcohol and HIV effects on MRI brain stem measures with a two-factor fully-crossed design. The brain stem volume in HD was reduced by 6% ($p < 0.03$). The midsagittal MRI revealed reduced areas of the total brain stem (12%), the midbrain (15%) the pons (10%), and the medulla (12%) in HD compared to LD (all $p < 0.004$). No HIV effects were observed for any of the brainstem measures. The area of the midsaggital slice of the brain stem was correlated with brain stem volume ($r = 0.66$, $p < 0.001$). The number of drinks/months over lifetime was negatively correlated with midsagittal slice areas of the midbrain ($r = -0.75$, $p < 0.0001$) and the whole brainstem ($r = -0.66$, $p < 0.001$) but not with those of pons or medulla. These preliminary results suggest that a) the brain stem of chronic alcohol abusers is reduced in size, b) the midbrain is preferentially affected by chronic alcohol and c) midsagittal slice brain stem area is a reasonably good measure of whole brain stem volume.

COCAINE-INDUCED CEREBRAL BLOOD VOLUME REDUCTION IN WOMEN IS A FUNCTION OF MENSTRUAL CYCLE PHASE

M. J. Kaufman[1,2], J. M. Levin[1,2], L. C. Maas[1], T. J. Kukes[1], R. A. Villafuerte[1], S. B. Hsia[1], J. H. Mendelson[2], S. E. Lukas[2], B. M. Cohen[1], and P. F. Renshaw[1]

[1]Brain Imaging Center and [2]Alcohol & Drug Abuse Research Center, McLean Hospital, Harvard Medical School, Belmont, MA

Cerebral perfusion has been shown to be abnormal in cocaine-dependent subjects, with men developing more blood flow abnormalities than women (Levin *et al.,* 1994). This suggests that the vascular effects of cocaine might be influenced by gonadal steroid hormones. This study evaluated whether the cerebral vasoconstrictive effects of acute cocaine differ in women as a function of menstrual cycle phase. Cocaine-induced cerebral vasoconstriction, detected as reduced cerebral blood volume (CBV), was evaluated with dynamic susceptibility contrast MRI (DSC MRI). Nine healthy women (28 ± 2 years old) reporting occasional cocaine use (7 ± 2 lifetime exposures) participated. Subjects underwent DSC MRI scans during the follicular (days 5 - 8) and luteal (days 18 - 22) menstrual cycle phases. The global CBV detected in an axial brain slice after cocaine (0.4 mg/kg, i.v.) during these phases averaged 103 ± 10% and 88 ± 5% of baseline, respectively ($p < 0.05$, paired t-test). No menstrual cycle phase differences in plasma cocaine levels were noted. The luteal phase CBV reduction was less than found in men administered the same cocaine dose (-19%). The apparently smaller vasoconstrictive effect of cocaine in women may be attributable to estrogen, and may in part explain the gender differences in cocaine's cerebrovascular effects. The larger CBV effect of cocaine in women during the luteal phase may be attributable to progesterone, which is present in high levels only during this phase. Progesterone has been implicated in increasing cocaine's toxicity, possibly by altering heart muscle tone. If progesterone also increases cerebrovascular smooth muscle tone, it may in combination with cocaine result in greater vasoconstriction when compared to the follicular phase.
Reference: Levin, J.M., *et al., J Nucl Med ,* 35: 1902-1909, 1994.

ACKNOWLEDGMENTS: Supported by NIDA grants DA09448, DA00329, DA00297, DA00064, DA00343, and DA04059.

PET IMAGING OF DOPAMINE D2 RECEPTORS IN GROUP-HOUSED MONKEYS: EFFECT OF SOCIAL RANK AND COCAINE

O. Prioleau, S. H. Nader, J. Lile, K. A. Grant, R. H. Mach, H. D. Gage, J. R. Kaplan, R . Ehrenkaufer, D. Morgan, and M. A. Nader

Departments of Pharmacology, Radiology and Comparative Medicine, Wake Forest University School of Medicine, Winston-Salem, NC

The goal of the present research is to develop a nonhuman primate model of vulnerability to cocaine abuse. This research utilizes the noninvasive imaging procedure Positron Emission Tomography (PET), socially-derived stress in group-housed macaques and intravenous cocaine self-administration methodology. Initially, all monkeys (n=20) were individually housed and baseline locomotor activity, cortisol levels and PET studies with the dopamine D2 ligand [^{18}F]fluoroclebopride (Mach et al., Synapse 24: 322, 1996) were performed. Next, monkeys were housed in social groups (N=4/pen) and after 3 months PET scans were redetermined. Baseline PET data showed that the mean D2 binding potential, which is a ratio of B_{max}/K_d (Logan *et al.,* J Cer Bld Flw 10:740, 1990), was 2.59±0.06. Cortisol measures and D2 binding potentials obtained while the monkeys were individually-housed did not correlate with eventual social status (dominant vs. subordinate). After 3 months of chronic social stress, D2 binding potential for the dominant monkeys was significantly higher than the binding potential for the subordinate monkeys (3.03 vs. 2.69). These data, utilizing a within-subjects design, replicate and extend previous findings in cynomolgus monkeys using a group design (Grant et al., Synapse 29: 80-83, 1998). We will determine to what extent differences in social rank and D2 receptor levels influence acquisition, maintenance and relapse to cocaine addiction.

ACKNOWLEDGMENTS: Supported by NIDA grants DA 10584 and DA 08468.

PET rCBF STUDIES OF SINGLE AND MULTIPLE DOSE COCAINE

E. Rubin, R. Van Heertum, E. D. London*, R. Foltin, N. Nunes, H. D. Kleber, and M. W. Fischman

Columbia University, New York, NY and *IRP, NIDA, Baltimore, MD

We are using $H_2{}^{15}O$-PET to correlate regional cerebral blood flow (rCBF) with subjective effects in two placebo-controlled cocaine administration procedures with cocaine-dependent subjects. Each study measures rCBF every 15 min. On study Day 1, rCBF is measured after a single IV dose of cocaine (32mg/70kg); on study Day 2. we track rCBF across four such doses (1 dose/15 min), a schedule which promotes acute tolerance to euphoriant effects. Global-normalized rCBF measurements are guided by coregistered MRI. Subjects (n=4) report appropriate placebo and drug-related subjective effects during these protocols, and display acute subjective tolerance with multiple drug doses. For selected time points, brain regions, and subjective effect scales, significant correlations between rCBF and euphoria are seen. On Day 1, 17 min after a single cocaine injection, CBF in right basal ganglia (RBG) is negatively correlated with "High", "Stimulated", and "Good drug effect" (r's -.97 to -.99, all $p<.02$). At the same time point, rCBF for right inferior frontal cortex (RIFC) correlates positively with "High" and "Good drug effect" ($r=.95$, both $p<.05$). On Day 2, following four cocaine doses, significant correlation is again seen 17 min post-dose between rCBF for RBG and "Good drug effect", but now this correlation is positive ($r=.99$: $p<.01$). On Day 2, rCBF for RIFC no longer correlates with euphoriant effects. While preliminary, these results suggest that activity in specific brain regions correlates with euphoria, and that these correlations change as tolerance develops.

ACKNOWLEDGMENTS: Supported by NIDA P50 DA09236 and NIH RR00645.

LIMBIC AND CORTICAL ACTIVATION SPECIFIC TO CUE-INDUCED COCAINE CRAVING

H. Garavan, A. S. Bloom, L. L. Sperry, J. Pankiewicz, D. Ward, R. C. Risinger, T. Salm, and E. A. Stein

Medical College of Wisconsin, Milwaukee, WI

Cues associated with cocaine produce craving in cocaine addicts. To better understand this phenomenon, we employed fMRI to identify brain regions showing altered brain activity when addicts are shown videotapes of cocaine users smoking crack cocaine. A second tape of nature scenes identified brain regions responsive to nonspecific video content, while a third, containing explicit sexual content, served to identify regions affected by arousing content. Thirteen cocaine addicts (mean age: 34) with a mean 11 years of cocaine use served as subjects. The effectiveness of each tape to induce feelings of craving was assessed through physiological measurements and retrospective verbal reports. Each 12 minute scan consisted of a 3 minute baseline period, a 4 minute video and a 5 minute visuospatial working memory task. The latter served as a distracter to reverse or attenuate any video-induced craving or arousal and also allowed an assessment of the effects of cue-induced craving on cognitive performance. fMRI signals acquired over the time-course of each video were modeled with beta distributions on a per voxel basis. In general, those EPI signals that increased did so within 1 minute after video onset and remained elevated for the duration of the tape. Area-under-the-curve analyses comparing addicts to controls with no cocaine history, reveal widespread differences in signal increases in response to the cocaine tape. Areas that discriminated addicts from controls in the cocaine tape, but not in the sex tape, included superior frontal, right caudate, left amygdala, and a substantial pons, cerebellar peduncle and cerebellum network. These structures may comprise part of a neural network subserving specific memory driven emotional responses experienced by addicts that is distinct from generalized arousal.

ACKNOWLEDGMENT: Supported by NIDA grant DA09465.

ORAL COMMUNICATIONS XVI

THE EFFECT OF ASCORBIC ACID AND ALPHA-TOCOPHEROL ON METHAMPHETAMINE TREATED NEUROGLIOMA CELLS

*C. Providence, E. M. Knight, W. L. West, and J. Cadet**

Center for Drug Abuse Research, Howard University, Washington, DC; and *Molecular Neuropsychiatry Section, IRP, NIDA, NIH, Baltimore, MD

In previous studies methamphetamine (METH), an analog of amphetamine produced degeneration of selective dopaminergic neurons. METH neurotoxicity is thought to be mediated via oxidative stress. In this report, dose-dependent *in vitro* techniques were used to further assess the role of oxidative stress in METH-induced neurotoxicity, and to test if the antioxidants ascorbic acid and alpha-tocopherol could protect independently or additively against the deleterious effects of the drug in neuroglioma cells obtained from a human male. Using lactate dehydrogenase assay, cellular illumination, and DNA electrophoresis, a concentration of 3mM METH caused an increase in the cellular destruction by DNA smearing and cellular swelling reminiscent of necrosis, and a toxicity of 77.70 ± 1.65%. This toxicity was reduced significantly ($P<0.0001$) to 22.63 ± 0.33% with a dose of 0.01mM ascorbic acid, but patterns of DNA laddering and smearing were seen on the agarose gel for this combination. Alpha-tocopherol, at a concentration of 1mM, also provided protection by lowering the toxicity of the drug to 29.87 ± 3.05% ($P<0.0001$), and by reducing the DNA smearing caused by METH. In combination, ascorbic acid in high concentrations and alpha-tocopherol in low concentrations provided a significant protection against METH-induced neurotoxicity. These observations provide further support for the involvement of oxidative stress in the toxic effect of METH, and the role of antioxidants in combating oxidative stress. These findings provide useful information in addressing substance abuse and nutrition.

ACKNOWLEDGMENT: Supported entirely by the Intramural Research Program of the NIDA, NIH, Baltimore, MD.

METHAMPHETAMINE AND OXYGEN RADICALS: EFFECTS ON TRYPTOPHAN HYDROXYLASE AND SEROTONIN TRANSPORTERS

A. E. Fleckenstein, J. M. Kokoshka, R. R. Metzger, D. G. Wilkins, J. W. Gibb, and G. R. Hanson

Department of Pharmacology and Toxicology, University of Utah, Salt Lake City, UT

Methamphetamine (METH) administration causes formation of reactive oxygen species *in vivo,* suggesting that proteins susceptible to oxidative modification may be particularly affected by the stimulant. Hence, effects of METH on two serotonin-related proteins susceptible to oxidative inactivation, tryptophan hydroxylase (TPH) and the serotonin transporter (SERT), were assessed. METH administration caused a rapid decrease in the activity of TPH, the rate-limiting enzyme in the synthesis of serotonin. This decrease was reversed completely by exposing the METH-impaired enzyme to a reducing environment, suggesting that the decrease in TPH activity was a reversible oxidative consequence of oxygen radical formation. METH administration also caused a rapid and selective decrease in SERT activity, as assessed in striatal synaptosomes prepared from METH-treated rats. This effect was attributable to a decreased V_{max} of [^{3}H]serotonin uptake, and was not caused by residual METH introduced by the original subcutaneous injection. Consistent with an oxidative event, both the METH-induced decrease in TPH and SERT activity recovered to control levels 24 - 36 h after dosing. These data support the hypothesis that ROS may mediate some of the pharmacological effects of METH, which have important implications for the physiological regulation of serotonergic systems.

ACKNOWLEDGMENTS: Supported by USPHS grants DA00869, DA04222, and DA11389.

'ICE SMOKING' AND DAILY EPISODES OF ALCOHOL INTOXICATION: DATA FROM A NATIONAL SAMPLE OF METHAMPHETAMINE SMOKERS

C. D. M. Furr, J. Delva, and J. C. Anthony

Department of Mental Hygiene, The Johns Hopkins University, School of Hygiene and Public Health, Baltimore, Maryland, USA

This study estimates the degree to which recent and frequent alcohol intoxication might influence the occurrence of methamphetamine smoking ('ice'), with matching and regression adjustment for other potentially important confounding variables (e.g., sex, education, other drug use). Both theory and research linking earlier alcohol use with later psychostimulant use motivate this investigation. The focus on 'ice smoking' stems from recent national and international concern about this form of psychostimulant use. For this study, a nationally representative sample of 101 ice users and 816 non-users were matched on neighborhoods from which they were sampled as part of the 1993 National Household Survey on Drug Abuse. The conditional form of logistic regression was used to estimate the strength of association and to hold constant suspected confounding variables. Recent ice smoking was five times more common among persons with recent daily alcohol intoxication versus those at lower drinking levels—before and after adjusting for age, sex, race, education, and other drug use (estimated odds ratio = 5.1; p=0.01). Otherwise, ice smoking did not vary across levels of drinking (p>0.10). This epidemiologic evidence of a strong association between daily intoxication and ice smoking can be used to guide methamphetamine prevention and intervention efforts toward a population subgroup of special importance-namely, drinkers who become intoxicated every day. Ice smoking also might promote daily drinking to the point of intoxication. This hypothesis can be pursued in future field studies, and also in controlled laboratory investigations.

ACKNOWLEDGMENT: Supported by NIDA training grant T32-DA07292.

COCAINE VS. METHAMPHETAMINE USERS: DIFFERENCES IN DEMOGRAPHICS, DRUG USE PATTERNS, AND TREATMENT RESPONSE

A. L. Copeland and J. L. Sorensen

Department of Psychiatry, University of California, San Francisco, San Francisco, CA

Although the number of methamphetamine patients in drug treatment programs in western states has greatly increased in recent years, few empirical studies describe this population and its potentially unique treatment needs. Among major western cities, San Francisco has the second highest rate of methamphetamine admissions. At the Stimulant Treatment Outpatient Program (S.T.O.P.) at San Francisco General Hospital, methamphetamine patients receive the same treatment as cocaine patients. This allowed us to examine potential differences among these 2 populations regarding demographics, drug use patterns, and treatment compliance. These hypothesized differences were based on preliminary studies, clinical observation, and the pharmacological and environmental differences between cocaine and methamphetamine. We conducted a retrospective chart review of the 345 S.T.O.P. admissions from January 1995-December 1997. As predicted, preliminary analyses revealed an increase in methamphetamine patients over the 3-year period, and that these patients were more likely to be male, Caucasian, and gay or bisexual. Methamphetamine patients were more likely to be HIV+ (59% vs. 31%), have a psychiatric diagnosis (49% vs. 28%), and be on psychiatric medications (30% vs. 15%). These patients were also significantly more likely to be engaging in high-risk drug use behaviors, such as using and sharing needles. Despite these demographic and drug use differences, these 2 populations did not differ in treatment compliance, as measured by clinic attendance, drug-free urines, and successful completion of treatment. These findings suggest that highly specialized treatments for methamphetamine patients may not necessarily be needed. Resources may instead be directed toward addressing their dual diagnosis issues by providing ancillary services.

ACKNOWLEDGMENT: Partially supported by Grant P50DA09235.

COGNITIVE PERFORMANCE OF METHAMPHETAMINE ABUSERS

C. Domier[1,2], S. L. Simon[1,2], R. Rawson[1,2,3], and W. Ling[1,2,3]

L. A. Addiction Research Center, [2]Long Beach VA Medications Development Unit, and [3]Matrix Institute on Addictions, Los Angeles, CA

There is ample evidence for neurotoxicity associated with repeated exposure to amphetamine. On the other hand, amphetamine has been found to enhance both recognition and recall memory performance in humans and methamphetamine (MA) has been found to increase their processing speed. Our question was, "Where in the continuum between enhanced performance and cognitive deficits do currently using MA abusers fall?" To answer this question 76 currently using MA abusers and an equivalent comparison group were given a battery of cognitive tests. The battery includes recall, recognition, Digit Symbol, Trail Making A & B, Stroop Wisconsin Card Sort, backward digit span, and the FAS test of verbal fluency. MA abusers were significantly more impaired on Trail Making B (t_{112}=2.66, p=.009) and Digit Symbol (t_{112}=4.64,p<.001) than the comparison group. There were also reliable differences between recall for pictures (t_{111}=3.25, p=.002) and for words (t_{112}=3.71, p<.001). The pattern of results found with the Stroop Color Word Test (normal word scores, normal color scores, and low color word scores) is generally associated with isolated pre-frontal injuries, and is associated with early forms of brain atrophy second to chronic drug use. The only reliable difference (t_{92}=207, p=.04) between the MA group and the comparison group on the WCST was obtained for the 'learning to learn' measure. There were no significant differences between the two groups on either the FAS test of verbal fluency, or on the backward digit span test. There were surprisingly few clear associations between performance on cognitive tests and patterns of abuse. Age, gender, psychiatric and medical problems were of no predictive value in determining performance on any task.

ACKNOWLEDGMENTS: Supported by inter-agency agreement no. 1 YO1 DA 50038-00 between NIDA and the Department of Veterans Affairs.

HIV RISK BEHAVIORS OF METHAMPHETAMINE USERS

V. Gulati[1], A. Huber[1,2], C. Reback[1,3], S. Shoptaw[1,2], T. Freese[1], and R. Rawson[1,2]

[1]LA Addiction Treatment Research Center, Long Beach VA MDRU, and Van Ness Recovery House Prevention Division, Los Angeles, CA

This study compares HIV-related high-risk sexual behaviors in two cohorts of methamphetamine users in Southern California: a predominantly heterosexual sample in Rancho Cucamonga, California (RC) which is located in San Bernadino County, and a sample of gay/bisexual male methamphetamine users in Hollywood, California (HW). At both of these sites, parallel treatment evaluation projects are ongoing, using similar outcome measures and similar treatment interventions. Fifty-eight (RC=38, HW=20) treatment-seeking users completed screening which included an evaluation of HIV-related sexual and methamphetamine-use behaviors. Findings indicate a strong connection between methamphetamine abuse and HIV-risk behaviors. Injection behaviors were more prevalent in the Hollywood sample (HW=65% vs. RC=18%). However, both groups reported high-risk sexual behaviors including sex while intoxicated (HW=79%, RC=58%), sex with one or more partners without using condoms (HW=65%, RC=21%). The HW sample seemed to be more concerned about their HIV risk than the RC sample. The majority (79%) of the participants in the Hollywood sample repotted concern about their sexual behavior while only 8% of the RC sample reported similar concern. Additionally, 100% of the HW sample had been tested for HIV, but only 58% of the RC sample had been tested. Given the level of HIV risk in these populations, it is critical that drug abuse treatment clinics provide HIV prevention interventions that focus on both drug-use and sex behaviors.

ACKNOWLEDGMENTS: NIDA grants 1 R01 DA 1103 and 1 R01 DA 10923.

ELECTRON MICROSCOPIC (EM) EVALUATION OF THE CARDIAC TOXICITY ELICITED BY 3,4-METHYLENEDIOXYMETHAMPHETAMINE (MDMA)

J. B. Delcarpio, J. M. Moerschbaecher, and K. J. Varner

Departments of Cell Biology and Anatomy and Pharmacology, LSU Medical Center, New Orleans, LA

We recently found using light microscopy that the daily injection of (MDMA) or methamphetamine (METH) for 28 days showed areas of focal necrosis in the papillary muscles, atria and ventricles. The purpose of this study was to characterize the ultrastructural changes in myocardial cells produced by the repeated administration of MDMA (20 mg/kg, s.c.) or METH (1 mg/kg, s.c.). Male Sprague-Dawley rats (275-300 g) were treated with MDMA or METH or 28 days. Age and weight-matched control rats received saline injections. After treatment, the rats were sacraficed and the hearts perfused with 2% glutaraldehyde/paraformaldehyde. The hearts were cut into lmm cubes, embedded in Epon-Araldite, sectioned, and stained with heavy metals and examined in a JEOL 1210 transmission EM. Electron microscopic analysis revealed that MDMA treatment produced myofibrillar disruption associated with contraction band necrosis in ventricular and papillary myocytes. Dilatation and disruption of the sarcoplasmic reticulum and transverse tubular system were observed in atrial and ventricular myocytes. Mitochondrial changes included swollen cristae and matrix disruption. In addition, increases in fibroblasts and interstitial collagen deposition were observed. Treatment with METH yielded similar results. These results are consistent with morphological findings at the light microscopic level and show that repeated administration of MDMA and METH can produce significant ultrastructural changes in cardiac myocytes.

ACKNOWLEDGMENTS: Supported by NIDA grants DA 08255 and DA 04775.

ORAL COMMUNICATIONS XVII

nNOS KNOCKOUT MICE ARE RESISTANT TO COCAINE- AND METHAMPHETAMINE-INDUCED SENSITIZATION

Y. Itzhak, J. L. Martin, and P. L. Huang

University of Miami School of Medicine, Miami, FL and Massachusetts General Hospital, Charlestown, MA

In the present study, we investigated whether mice deficient in the neuronal nitric oxide synthase (nNOS) gene are protected from cocaine- and methamphetamine (METH)-induced behavioral sensitization. Homozygote nNOS(-/-), heterozygote nNOS(+/-) and wild type mice were administrated either cocaine (15 mg/kg) or saline for 5 days. Animals' locomotor activity in response to cocaine or saline administration was recorded on day 1, 5 and 15, after a 10 day drug free period. Male nNOS(-/-) were responsive to the acute effect of cocaine (day 1), but they developed neither a sensitized response to the drug nor conditioned locomotion. Heterozygote nNOS(+/-), and wild type mice developed sensitization to cocaine as well as conditioned locomotion. The disposition of [^{3}H]cocaine in brain of the various mouse strains examined was similar. Administration of METH (5 mg/kg x 3) to nNOS(+/-) and wild type mice resulted in depletion of striatal dopaminergic markers and robust locomotor sensitization to a subsequent METH injection. However, homozygote nNOS(-/-) were protected against both METH-induced dopaminergic neurotoxicity and behavioral sensitization. These findings indicate that deletion of the nNOS gene provided protection against the development of behavioral sensitization to psychostimulants.

ACKNOWLEDGMENTS: Supported by NIDA DA08584 (YI) and NINDS NS33335 (PH).

COCAINE-INDUCED CONVULSIONS: SEROTONIN RECEPTOR DENSITY APPEARS TO MEDIATE GENETIC SENSITIVITY

L. E. O'Dell, M. J. Kreifeldt, F. R. George, and M. C. Ritz

Amethyst Technologies, Inc., Scottsdale, AZ

Research in our laboratory has demonstrated that the initiation of cocaine-induced convulsions is related to cocaine inhibition of serotonin (5-HT) reuptake and that serotonin$_2$ (5-HT$_2$) receptor antagonism attenuates this effect. We have also demonstrated that C57BL/6J and C57BL/6ByJ mice differ significantly in sensitivity to cocaine-induced convulsions (ED_{50} = 61.0 and 104 mg/kg, respectively). We hypothesized that this differential sensitivity to cocaine-induced convulsions in C57BL/6J and C57BL/6ByJ mice may be due to differences in 5-HT$_2$ receptor density and that cinanserin, a potent 5-HT$_2$ antagonist, might differentially influence cocaine-induced convulsions in these strains. ^{3}H-Ketanserin binding in the amygdala, brainstem, cerebellum, frontal cortex, hippocampus, hypothalamus, midbrain, and striatum was measured. In addition, the effect of cinanserin on cocaine-induced convulsions was assessed. The results indicate that the density of 5-HT$_2$ receptors is higher in the C57BL/6ByJ relative to the C57BL/6J mice across all brain regions. The magnitude of these differential densities suggests important physiological relevance to behavioral effects mediated by 5-HT neurotransmission. Consistent with this notion, cocaine-induced convulsions were completely blocked by 10 mg/kg of cinanserin in the C57BL/6J mice, whereas a higher dose of 30 mg/kg was necessary to block this effect in the C57BL/6ByJ mice. These results are consistent with our previous findings that cocaine inhibition of 5-HT reuptake plays an important role in the initiation of cocaine-induced convulsions. Further, sensitivity to this effect of cocaine appears to be mediated by post-synaptic 5-HT$_2$ receptor density.

ACKNOWLEDGMENTS: Supported by DA 07767 and DA07767-03S1.

COCAINE-INDUCED CONVULSIONS: SEROTONIN UPTAKE INHIBITION MODULATES GENETIC SENSITIVITY

M. C. Ritz, L. E. O'Dell, M. J. Kreifeldt, and F. R. George

Amethyst Technologies, Inc., Scottsdale, AZ

Research in our laboratory has demonstrated that the initiation of cocaine-induced convulsions is related to cocaine inhibition of serotonin (5-HT) reuptake. We have also demonstrated that C57BL/6J and C57BL/6ByJ mice differ significantly in sensitivity to cocaine-induced convulsions (ED_{50} = 61.0 and 104 mg/kg, respectively). We hypothesized that this differential sensitivity to cocaine-induced convulsions in C57BL/6J and C57BL/6ByJ mice may be due to differences in 5-HT transporter density and that fluoxetine, serving as a potent indirect 5-HT agonist, might differentially influence cocaine-induced convulsions in these strains. ^{3}H-Paroxetine binding in the brainstem, cerebellum, frontal cortex, hippocampus, midbrain, and striatum was measured. In addition, the effect of fluoxetine on cocaine-induced convulsions was assessed. The results indicate that there were no differences in the density of 5-HT transporter sites or the affinity of the labeled ligand between strains. However, fluoxetine produced a more robust increase in cocaine-induced convulsions in C57BL/6ByJ relative to C57BL/6J mice. These findings suggest that 5-HT effects at postsynaptic receptors may mediate the differential increase in cocaine-induced convulsions following fluoxetine administration in these mouse strains. This is consistent with our finding that C57BL/6ByJ mice have a higher density of 5-HT_2 receptors and that these mice require a higher dose of a 5-HT_2 antagonist to block cocaine-induced convulsions relative to C57BL/6J mice. Thus, postsynaptic 5-HT_2 receptors appear to play an important role in the initiation of cocaine-induced convulsions.

ACKNOWLEDGMENTS: Supported by DA 07767 and DA07767-03S1.

CONDITIONED FOS EXPRESSION ELICITED BY A COCAINE SELF-ADMINISTRATION ENVIRONMENT

D. A. Baker,[1] R. A. Fuchs,[1] L. T. L. Tran-Nguyen,[1] A. J. Palmer,[1] J. F. Marshall,[2] R. J. McPherson,[2] and J. L. Neisewander[1]

[1]Department of Psychology, Arizona State University, Tempe AZ and [2]Department of Psychobiology, University California-Irvine, Irvine CA

Cocaine and cocaine-paired environmental stimuli elicit craving in humans and reinstate cocaine-seeking behavior in rats. This study examined cocaine-seeking behavior (responding in the absence of cocaine reinforcement) and Fos expression in the central and basolateral amygdala (CeA and BlA) following exposure to a cocaine-paired environment and a priming injection of cocaine. On days 1-15, animals were trained to press a lever for cocaine or received yoked saline administration. On days 16-36, cocaine was not available and rats received daily exposures to either the self-administration environment (i.e., extinction training) or an alternate environment. Extinction training was employed to decrease the salience of environmental conditioned stimuli. On day 37, all rats were placed into the self-administration environment and tested for cocaine-seeking behavior for 90 min. Some of the rats were further tested for reinstatement of cocaine-seeking behavior following a cocaine priming injection (15 mg/kg, IP) for an additional 90-min. All rats were sacrificed within 2-hr of testing. Extinction training attenuated both spontaneous and cocaine-reinstated cocaine-seeking behavior. The cocaine priming injection enhanced Fos expression only in the CeA regardless of group. Conditioned enhancement of Fos expression was observed only in the B1A as an increase in animals with no extinction training relative to controls, but no difference between animals with extinction training and controls. We are currently investigating Fos expression in other regions.

ACKNOWLEDGMENTS: Supported by DA 11064, DA05816, and DA 10249.

COCAINE-INDUCED BIOCHEMICAL NEUROADAPTATIONS AND BEHAVIORAL CORRELATES IN LEWIS AND FISCHER (F344) RATS

C. N. Haile, N. Hiroi, E. J. Nestler, and T. A. Kosten

Department of Psychiatry, Yale University School of Medicine, New Haven, CT

Lewis (LEW) and Fischer (F344) inbred rat strains offer an ideal model to study correlations between brain chemistry and behavior. Previous work has shown that the LEW strain is more responsive to drugs of abuse across a wide variety of behavioral paradigms compared to the F344 strain. The mesolimbic dopamine system, which plays an important role in drug reinforcement, also differs between these strains at baseline and in response to chronic morphine treatment. Differences in this system may be associated with innate differences observed in drug preferring behaviors between strains. Interestingly, proteins regulated by chronic morphine exposure in the F344 remain unchanged in the LEW. This study examined whether chronic cocaine treatment induced similar changes in brain neurochemistry in F344, but not in LEW. Male LEW and F344 (N=12ea) rats were pretreated with cocaine (15mg/kg) or saline twice a day for 14 days. In the F344, chronic cocaine induced an increase in tyrosine hydroxylase (TH) and glial fibrillary acidic protein immunoreactivity in the ventral tegmental area and decreased TH in the nucleus accumbens (NAc). In contrast, these proteins were unaltered in the LEW. However, a robust increase in chronic fos-related antigens (cFRAs) was observed in the NAc of both strains. In order to correlate changes in brain chemistry with behavior, LEW and F344 rats were habituated to a locomotor apparatus then underwent similar pretreatments (cocaine or saline). Subsequent locomotor activity in response to an acute cocaine injection (7.5mg/kg) was then measured. All groups showed a significant increase in locomotor activity to cocaine compared to baseline. However there was no difference between cocaine pretreated LEW and F344 groups (P=0.44). These results suggest that once protein specific neuroadaptations are initiated through cocaine pretreatment in the F344, similar behavioral responses to cocaine are observed between these strains.

ACKNOWLEDGMENT: Supported by NIDA grant DA04060.

COCAINE CONDITIONED PLACE PREFERENCE IS RETAINED IN DOPAMINE-TRANSPORTER AND IN SEROTONIN-TRANSPORTER KNOCKOUT MICE

G. R. Uhl", C. Wichems*[+], *Z. Zeng*, X.-F. Li*, K. Itokawa*, R. S. Revay*, K.-P. Lesch*[++], *D. L. Murphy*[+], *and I. Sora**

Molec. Neurobiol.*, NIDA-IRP*, Lab. of Clinical Sci., NIMH-IRP[+], NIH, Dept. Psychiatry, Univ. of Wuerzburg, Germany[++] and Depts. Neurol. & Neurosci., JHUSM*", Baltimore, MD

Several lines of evidence have provided support for a role of the dopamine transporter (DAT) as a primary site for cocaine reward. Psychostimulant structure-activity relationships document good fits between these drugs' rewarding properties and their abilities to block the dopamine transporter, while poorer correlations are noted with activities at other transporters. Dopaminergic lesions blunt cocaine reward. Psychostimulants enhance dopamine release from dopaminergic circuits. Indirect lines of evidence support the idea that cocaine's inhibition of serotonin uptake could also provide an alternative and plausible molecular site for contributions to cocaine reward. To test the dopamine- or serotonin-transporter-dependence of cocaine reward, we have constructed DAT and 5-HTT knockout mice and assessed cocaine conditioned place preferences in these DAT knockouts and in 5-HTT knockout mice. We now report that both transgenic mice without DAT and mice without 5-HTT retain cocaine conditioned place preferences. These results have substantial implications for understanding cocaine actions and for strategies to produce anti-cocaine medications.

CHRONIC ADMINISTRATION OF HIGH DOSES OF ANABOLIC ANDROGENIC STEROID NANDROLONE DECANOATE ALTERS HPA ACTIVITY AND LEVELS OF mRNAs FOR CRF AND POMC IN THE MALE RAT AMYGDALA

Y. Zhou[1], P. Johansson[2], A. Ho[1], F. Nyberg[2], and M. J. Kreek[1]

'Laboratory of the Biology of Addictive Diseases, The Rockefeller University, NY, USA and 2Department of Pharmaceutical Biosciences, Division of Biological Research on Drug Dependence, Uppssala, Sweden

Clinical studies show that long-term and high dose abuse of anabolic sndrogenic steroids (AAS) leads to profound disruptions in levels of sex hormones and development of psychiatric symptoms. Little is known about the effects of chronic administration of AAS on hypothalamic-pituitary-adrenal (HPA) activity or brain corticotropin-releasing factor (CRF) or pro-opiomelanocortin (POMC) expression. In the present study, we examined CRF and POMC mRNA levels in the hypothalamus and amygdala, and type I CRF receptor (CRF, receptor) and POMC mRNA levels in the anterior pituitary, as well as adrenocorticotropin immunoreactivity (ACTH-ir) and corticosterone levels in the blood, in male rats after chronic (14 days) daily intramuscular injections of an AAS (nandrolone decanotey ND) at 15 and 45 mg/kg doses. Measurements 1 day after 14 days of ND administration at 45 mg/kg showed a significantly decreased level of both ACTH-ir and corticosterone in the blood, coupled with a reduction of both CRF mRNA levels in the hypothalamus and POMC mRNA levels in the anterior pituitary, with no changes of anterior pituitary CRF, receptor mRNA levels. Also, a significant decrease in POMC mRNA levels was found in the hypothalamus and in the amygdala at 45 mg/kg. In contrast, a significant increase in CRF mRNA levels was observed in the amygdala 1 day after chronic ND administration at 45 mg/kg, with no effect at 15 mg/kg. These results show that there is a disruption of HPA activity, and an alteration of both POMC and CRF mRNA expression in the brain after chronic high dose administration of ND, suggesting that both effects may contribute to some of the psychiatric symptoms following long-term AAS abuse.

ACKNOWLEDGMENTS: Supported by grants from NIH/NIDA Research Center Award P50-DA05130 and a Research Scientist Award (NIH/NIDA DA00049) MJK.

ORAL COMMUNICATIONS XVIII

RATIO SIZE AND UNIT DOSE MODIFY THE EFFECTS OF GBR 12909 PRETREATMENT ON FOOD- AND COCAINE-MAINTAINED RESPONDING

D. Stafford and J. R. Glowa

Department of Pharmacology and Therapeutics, Louisiana State University Medical Center at Shreveport, LA

In previous reports from our laboratory, pretreatment with the dopamine-selective reuptake inhibitor GBR 12909 decreased rates of responding maintained by cocaine at doses that had little or no effect on food-maintained responding, and this effect was influenced by the unit dose of cocaine. That is, selective reductions in cocaine-maintained responding were most likely to be observed when relatively small unit doses were available. Data from other laboratories have demonstrated that the effects of pharmacological pretreatments can also be modified by the number of responses required to produce drug delivery (i.e., fixed-ratio (FR) size). In the present study, the effects of GBR 12909 in three rhesus monkeys were assessed on a multiple schedule of food and cocaine delivery, and the response requirements (FR 10, FR 56, or FR 100) for cocaine delivery and unit dose of cocaine (56.0, 30.0, 10.0, or 5.6 ug/kg/inj) were varied across conditions. Pretreatment with GBR 12909 selectively decreased cocaine-reinforced responding when the response requirements for cocaine delivery were relatively large and the unit dose of cocaine was relatively small. When the response requirements for cocaine delivery were relatively small and the unit dose was relative large, selective reductions of cocaine-maintained responding were greatly diminished or eliminated. These results add to a growing body of data demonstrating that environmental variables play an important role in determining the effects of pharmacological pretreatments on cocaine self-administration.

ACKNOWLEDGMENT: Supported by NIDA grant DA 09820.

THE REINFORCING EFFICACY OF 2ß-PROPANOYL-3ß-(4-TOLYL)-TROPANE (PTT) VS. COCAINE IN RHESUS MONKEYS

M. A. Nader, K. A. Grant, C. L. Hubbard, T. Moore, A. Birmingham, and H. M. Davies[+]

Department of Pharmacology, Wake Forest University School of Medicine, Winston-Salem, NC and [+]Department of Chemistry, SUNY Buffalo

Earlier work in monkeys has shown that PTT maintained low rates of self-administration, yet had cocaine-like discriminative stimulus effects for up to 8 hrs (Nader *et al.,* JPET 280:541-550, 1997; Birmingham *et al.,* Psychopharmacology, 136: 139-147, 1998). The purpose of the present study was to determine the reinforcing efficacy of PTT vs. cocaine in monkeys that could choose between the two drugs. Rhesus monkeys (n=3), surgically prepared with indwelling double-lumen intravenous catheters, were trained to respond under a mutually-exclusive choice procedure similar to that described by Woolverton and Johanson (JEAB 41: 35-43, 1984). Cocaine (saline, 0.03-0.3 mg/kg/inj) and PTT (saline, 0.01-0.03 mg/kg/inj) were available under a fixed-ratio (FR) 30 schedule and were signaled by different colored lights. Each choice trial was separated by a 10-min timeout and session length was 7 hrs or the completion of 30 trials. When the choice was between 0.3 mg/kg/inj cocaine and saline, 25-27 trials were completed per session with approximately 85% of the trials resulting in cocaine presentation. When 0.01 mg/kg/inj PTT was the alternative to cocaine, neither cocaine preference nor total trials completed in a session were altered. When the choice was between 0.03 mg/kg/inj PTT and cocaine (0.03 or 0.3 mg/kg/inj), tested in two monkeys, cocaine preference decreased to approximately 50% and the total trials completed decreased to less than 10 per session. When the choice was between saline and 0.03 mg/kg/inj PTT, less than 3 trials were completed per session. These preliminary results suggest that PTT availability decreased the reinforcing efficacy of cocaine.

ACKNOWLEDGMENT: Supported by DA 06634.

PHARMACOLOGICAL EFFECTS OF NOVEL 3α-(DIPHENYLMETHOXY)TROPANE AND BENZTROPINE, ANALOGS

J. L. Katz, S. Izenwasser, R. H. Kline, A. C. Allen, and A. H. Newman

Psychobiology Section, National Institute on Drug Abuse, Intramural Research Program, National Institutes of Health, Baltimore, MD

The pharmacological effects of a series of 3α-(diphenylmethoxy)tropane analogs were assessed. Like cocaine, these compounds displaced [^{3}H]WIN 35,428 binding from rat caudate and had affinities ranging from approximately ten-fold greater than cocaine (Ki=11.8 nM), to relatively low affinity (Ki=2000 nM). Like the parent compound benztropine, the analogs displaced [^{3}H]pirenzepine from muscarinic M1 receptors with affinities ranging from 2 to 120 nM. Cocaine produced dose-related increases in locomotor activity in Swiss-Webster mice, whereas the 3α-(diphenylmethoxy)tropane analogs generally had efficacies lower than cocaine. Compounds with fluoro-substituents in the phenyl rings generally were among those with efficacy approaching that of cocaine. Those with chloro- and bromo-substituents were markedly less efficacious, despite having affinities for the dopamine transporter comparable to those of the corresponding fluoro-substituted compounds. The 3α-(diphenylmethoxy)tropane analogs were also examined in rats trained to discriminate saline from cocaine (10 mg/kg, i.p.) injections. Cocaine produced a dose-related increase in responding on the cocaine-appropriate lever, reaching 100% at 10 mg/kg. Only the 4',4''-difluoro-substituted analog produced effects similar to those of cocaine, the other compounds showed markedly reduced efficacy compared to cocaine. Drug interaction studies showed that the antimuscarinics, atropine and scopolamine, potentiated rather than attenuated the locomotor stimulant and discriminative-stimulus effects of cocaine, indicating that antimuscarinic effects of the 3α-(diphenylmethoxy)tropane analogs did not contribute to their diminished cocaine-like activity. Because none of the analogs studied showed evidence that they were, like cocaine, binding to more than one site on the dopamine transporter, and because the structure-activity relationships among these drugs were distinctly different from those obtained with cocaine analogs, these data suggest that the 3α-(diphenylmethoxy)tropane analogs are accessing a different binding domain than that accessed by cocaine, resulting in a behavioral profile that is distinct from that of the cocaine-like dopamine uptake inhibitors.

BEHAVIORAL EFFECTS OF PHENYLTROPANE COCAINE ANALOGS: RTI-31, RTI-32, AND RTI-55

W. M. Meil, M. D. Schechter, F. I. Carroll, and J. W. Boja*

Northeastern Ohio Universities College of Medicine, Rootstown, OH and *Research Triangle Institute, Research Triangle Park, NC

One potential therapeutic approach to cocaine dependence involves the use of compounds with high affinity for and that dissociate slowly from the dopamine transporter. The ability of three phenyltropane cocaine analogs, RTI-31, RTI-32, and RTI-55, to produce cocaine-like behavioral effects was investigated in male, Sprague-Dawley rats. After stable cocaine self-administration (0.33, 0.66 mg/kg/inf, 3h daily sessions) was achieved, rats were pretreated (IP) with RTI-31 (0.025-0.2 mg/kg), RTI-32 (.02-2.0 mg/kg), RTI-55 (0.025-0.2 mg/kg) 1 h prior to cocaine self-administration. Pretreatment with these compounds produced a dose-dependent decrease in cocaine self-administration. Pretreatment also significantly attenuated operant responding for food at some, but not all doses. Doses of RTI-31 (.025, 0.05 mg/kg), RTI 32 (0.6, 1.2 mg/kg), and RTI-55 (0.05, 0.1 mg/kg) which each attenuated cocaine self-administration also produced conditioned place preference. The ability of these phenyltropanes to produce behavioral sensitization of locomotor activity was also investigated. Rats received 10 injections of RTI-31 (0.1, 0.5 mg/kg), RTI-32 (0.5, 1.5 mg/kg), or RTI-55 (0.1, 0.5 mg/kg) over 12 days followed by locomotor activity measurement for 1 h. Repeated administration of each compound tended to augment locomotor activity and stereotypy at lower doses. Higher doses of these compounds produced a decrease in locomotor activity, as well as an increase in stereotypy. In all tests RTI-32 was less potent than RTI-31 and RTI-55 suggesting that the CH_3 paraphenyl substitution renders cocaine analogs behaviorally less potent. These results suggest that these compounds possess cocaine-like behavioral effects, including the ability to attenuate cocaine self-administration and to produce conditioned place preference and behavioral sensitization.

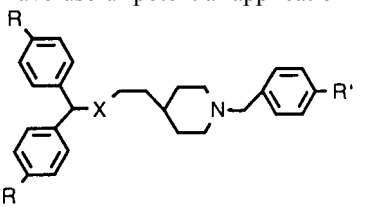
ACKNOWLEDGMENT: Supported by NIDA grant DA05827-01.

SYNTHESIS AND BIOLOGICAL EVALUATION OF NEW-GENERATION N-ANALOGS OF PIPERIDINE DERIVATIVES OF GBR 12909-RELATED COMPOUNDS

A. K. Dutta and M. E A. Reith

Organix Inc, Woburn, MA and University of Illinois, Peoria, IL

The replacement of the benzhydrylic oxygen-atom of our previously developed dopamine transporter (DAT)-specific ligands 4-[2-(diphenylmethoxy)ethyl]-1-[(4-fluorophenyl)methyl]piperidine, **1a** and 4-[2-[Bis(4-fluorophenyl)-methoxy]ethyl]-1-benzylpiperidine, **1b** by an nitrogen atom, resulted in the development of the N-analogs 4-[2-(Diphenylmethylamino)-ethyl]-1-[(4-fluorophenyl)methyl]piperidine, **4a** and 4-[(Bis(4-fluorophenyl)-methylamino)-ethyl]-1-[benzyl]piperidine, **4b.** Biological evaluation of these novel compounds in rat striatal tissue and in HEK-293 cells expressing the cloned human transporters demonstrated high potency and selectivity of these compounds for the DAT. Thus the potency of the compound **4a** for the DAT was 9.4 nM and 30 nM in rat striatal tissue and in the cloned transporter cells, and its binding selectivity for the DAT compared to the serotonin transporter (SERT) for these two systems was 62 and 195 respectively. The compound **4b** similarly exhibited high potency and selectivity for the DAT. Thus, these novel N-analogs represent more polar new-generation piperidine congeners of GBR 12909. They might have useful potential application in developing a pharmacotherapy for cocaine dependence.



1a; R = H, R' = F, X = O
1b; R = F, R' = H, X = O
4a; R = H, R' + F, X = NH
4b; R = F, R' = H, X = NH

ACKNOWLEDGMENT: Supported by NIDA grant DA08647 (AKD).

NONAMINES: A NEW VIEW OF COCAINE RECOGNITION SITES ON MONOAMINE TRANSPORTERS

B. K. Madras, G. M. Miller, A. J. Fischman, A. Bonab, B. F. O'Dowd, S. R. George, and P. C. Meltzer

Harvard Medical School, Southborough, MA, Massachusetts General Hospital, Boston, University of Toronto, Canada, Organix, Woburn, MA

The dopamine transporter is a significant target of cocaine in the brain. Without exception, therapeutic and other monoamine transporter inhibitors contain an amine nitrogen. Drug design has been guided by a prevailing premise that an amine nitrogen, corresponding to the amine of dopamine, is required for binding to the transporter. Nonamines, novel compounds in which the amine nitrogen is replaced by an oxygen or a carbon atom, do not support this model. In vitro, several nonamines, are potent, selective and effective monoamine transport inhibitors. The monoamine O-1109 bound to the dopamine transporter (DAT) with high affinity (IC_{50}: 1.16 ± 0.15 nM) and > 700-fold selectivity for the dopamine over the serotonin transporter (SERT). The enantiomerically pure 8-oxa analog, O-1059 (IC_{50}: 4.59 ± 0.57 nM; > 450-fold DAT:SERT transporter selectivity) and the racemic 8-carba analog also bound with similar affinity (IC_{50}: 5.50 ± 0.72 nM) and > 900-fold transporter selectivity. These results indicate that neither ionic nor hydrogen bonding are needed for high affinity binding or blockade of the dopamine transporter. The pharmacological specificity of [3H]O-1059, is virtually identical to [3H]WIN 35,428 (CFT). Several nonamines enter the brain and produce biochemical and behavioral effects comparable to those produced by cocaine. These novel compounds require significant revisions of prevailing views of drug binding to a principal target of cocaine in brain. Their biological activity suggests that they may offer unique opportunities for developing a new generation of therapeutic drugs.

ACKNOWLEDGMENTS: Supported by NIDA DA06303, DA11558, DA09462, DA4-8309, RR00168, and DA00304.

GBR12909 DECANOATE (DL699): SUSTAINED DECREASE IN DOPAMINE TRANSPORTER BINDING IN RAT BRAIN

R. B. Horel*, M. H. Baumanu*, K. C. Rice#, D. B. Lewis#, F. I. Carroll$, and R. B. Rothrman*

***NIDA, NIH, Baltimore, MD; #NIDDK, NIH, Bethesda, MD; and $RTI, Res Triangle Park, NC**

The illicit use of methamphetamine (METH) is a major health concern, and medications for METH dependence have not been developed. Recent findings suggest that a decanoate analog of GBR12909 (DL699) can antagonize *in vivo* effects of METH and might therefore be a potential treatment agent. In the present study, we used quantitative autoradiographic methods to assess the long-term effects of DL699 on binding to dopamine transporters (DAT) and serotonin transporters (SERT). On day 1, groups of rats received single i.m. injections of DL699 or its sesame oil vehicle. On days 6 and 13, groups of rats were decapitated and their brains collected. Coronal sections (20 μm) were cut from the frozen brains. Binding of the radiolabeled cocaine analog, [^{125}I]RTI-55 (10 pM), was carried out under DAT selective ([^{125}IRTI-55 + 50 nM citalopram) and SERT selective ([^{125}I]RTI-55 + 100 nM GBR12935) conditions. Sections were subsequently exposed to film, and densitometry was used to quantitate binding in specific brain regions. DL699 pretreatment significantly decreased DAT binding, without affecting SERT binding, in the caudate nucleus and nucleus accumbens on days 6 and 13. The present findings show that a single injection of DL699 can produce long-term and selective reductions in DAT binding in the brain. The DL699-induced decrease in DAT binding may explain the persistent *in vivo* effects of DL699 reported to occur in rats and monkeys. DL699 or similar agents may be useful pharmacological adjuncts in the treatment METH dependence.

ACKNOWLEDGMENT: Supported by NIDA IRP.

CHRONIC METHYLPHENIDATE ADMINISTRATION PRODUCES ALTERATIONS IN DOPAMINE TRANSPORTERS THAT ARE DIFFERENT FROM COCAINE

A. E. Coy[1], D. French[1], B. Ladenheim[2], R. J. Loeloff[1] J. L. Cadet[2], and S. Izenwasser[1,3]

[1]Psychobiology and [2]Molecular Neuropsychiatry, NIDA, IRP, Baltimore, MD and [3]Dept. of Neurology, Univ. of Miami Sch. of Med., Miami, FL

Continuous infusion of cocaine produces partial behavioral tolerance to its locomotor activating effects, while daily injections produce sensitization. Methylphenidate binds with a similar affinity to cocaine at the dopamine transporter, but has a much lower affinity for the serotonin transporter than does cocaine. This study was done to compare the effects of chronic methylphenidate with chronic cocaine. The pattern of locomotor activity over a seven day treatment period was significantly different from cocaine. Methylphenidate elevated activity on each day, compared to saline, yet neither tolerance to a continuous infusion of the drug, nor sensitization to repeated daily injections was produced. We have previously shown that neither of these treatments with cocaine produces significant alterations in dopamine transporter density one day after the end of treatment. In contrast, methylphenidate injections significantly decreased dopamine transporters in rostral caudate putamen, with no change in nucleus accumbens. Continuous infusion of methylphenidate had no effect on dopamine transporters in either brain region. These findings provide further evidence that different classes of dopamine uptake inhibitors may interact with the dopamine transporter in qualitatively different manners. Furthermore, it is possible that the inhibition of serotonin uptake by cocaine may contribute to the patterns of behavioral activity that are seen during chronic treatment.

ACKNOWLEDGMENT: Supported by the NIDA Intramural Research Program.

CHANGES IN ALPHA-2 ADRENERGIC RECEPTOR FUNCTION AFTER REPEATED COCAINE INJECTIONS IN RATS

M. H. Baumann, A. B. Milchanowski, and R. B. Rothman

NIDA, NIH, Baltimore, MD

Withdrawal from long-term cocaine abuse produces major-depressive-like symptoms which may involve alterations in monoamine function. Ironically, few studies have examined the effects of chronic cocaine on central noradrenergic (NE) transmission. In the present study, we examined the effects of repeated cocaine injections on neuroendocrine responses evoked by the alpha-2 adrenergic receptor agonist clonidine (CLON). It is well known that CLON increases pituitary growth hormone (GH) secretion by a central mechanism involving activation of postsynaptic alpha-2 adrenergic receptors. Rats previously fitted with indwelling jugular catheters received injections of cocaine (15 mg/kg, i.p., bid) or saline for 7 days. At 42 h and 8 days after treatment, rats were challenged with CLON (25 μg/kg, i.v.) or saline, and serial blood samples were withdrawn. Plasma was assayed for GH and corticosterone by RIA. Prior cocaine exposure did not affect basal levels of either hormone. Cocaine-pretreated rats displayed a significant reduction in CLON-induced GH secretion at 42 h, and this blunted response was still apparent 8 days later. In contrast, corticosterone responses to CLON were similar regardless of pretreatment. These data suggest that withdrawal from repeated cocaine administration may be accompanied by desensitization of postsynaptic alpha-2 adrenergic receptors. It is noteworthy that patients with major depression also exhibit blunted GH responses to CLON. Thus, the possibility that altered NE transmission contributes to cocaine withdrawal symptomatology deserves further investigation.

ACKNOWLEDGMENT: Supported by NIDA IRP.

ORAL COMMUNICATIONS XIX

DOPAMINE/OPIATE INTERACTIONS: COCAINE CONDITIONED PLACE PREFERENCE AND MORPHINE LOCOMOTOR ENHANCEMENTS DECREASE IN MU OPIATE RECEPTOR KNOCKOUT MICE

I. Sora*, X.-F. Li*, Z. Zeng, S. Kinsey*, N. Kitanaka*, J. Kitanaka*, N. Goodman*, H.-F. Liu *, M. Fun ada *, G. Elmer†, and G. R. Uhl*‡

Molec. Neurobiol.*, Preclinical Pharmacol.†, NIDA-IRP, NIH and Depts. Neurol. and Neurosci., JHUSM‡, Baltimore, MD

Opiates and psychostimulants display rewarding and locomotor stimulant properties. Dopamine system/opiate system interactions could have substantial impacts on both sorts of properties of both types of drugs. We have investigated these responses in mice with genetic disruption of the mu opioid receptor gene. Cocaine conditioned place preferences were significantly reduced in mu knockouts. Morphine-induced conditioned place preferences, morphine-induced locomotor stimulation were both virtually absent from homozygous mice which lack mu-opioid receptors. Heterozygous mice with half of wild-type levels of mu-opioid receptor expression display less morphine-induced locomotion. Heterozygotes have even signficantly greater morphine conditioned place preference than wild-type mice. Preliminary intravenous self-administration studies suggest that only the wild-type mice show dose-related changes in behavior. These data support substantial roles for mu receptors in the rewarding properties of not only opiates but also psychostimulants. They suggest that virtually all of the morphine-induced locomotor enhancement that can be seen with moderate morphine doses is mu-receptor dependent. These data support models of complex interactions between endogenous opiate and dopamine systems, reward and locomotion.

DIFFERENTIAL ANTAGONISM OF KAPPA AGONISTS SUGGESTS KAPPA RECEPTOR MULTIPLICITY IN SQUIRREL MONKEYS

K. R. Powell* and S. G. Holtzman

Department of Pharmacology, Emory University School of Medicine, Atlanta, GA

Distinctions between the receptors mediating the behavioral effects of various kappa-opioid agonists have been suggested in antagonists studies using both general and kappa-selective opioid antagonists. In the present study, the effects of 8 kappa agonists of the benzomorphan and arylacetamide chemical families were examined for their effects in squirrel monkeys responding under a fixed interval 3-min schedule of stimulus termination/avoidance. The abilities of the general opioid antagonist naltrexone and the kappa-selective opioid antagonist norbinaltorphimine (norBNI) to antagonize the response-decreasing effects of 3 of these kappa agonists were evaluated. Six of the 8 kappa agonists decreased significantly and dose-dependently total number of responses and response rates, A dose of 1 mg/kg of naltrexone and a dose of 3 mg/kg of norBNI were tested in combination with bremazocine, CI 977, and U69,593. All 3 kappa agonists were antagonized by naltrexone, but only bremazocine and U69,593 were antagonized by norBNI. Naltrexone was significantly more potent than norBNI at antagonizing CI 977 and U69,593, but naltrexone and norBNI were equipotent at antagonizing bremazocine. Furthermore, pK_B values indicate that naltrexone was 8-fold more potent at antagonizing U69,593 and CI 977 than bremazocine. These results suggest that these effects of kappa agonists may not be mediated by a homogenous receptor population.

ACKNOWLEDGMENTS: Supported by NIDA grants DA 00541, K05 DA 00008, and F32 DA 05709.

(+)-TIFLUADOM AND U69593 ACT ON DIFFERENT KAPPA- SITES IN THE GUINEA PIG CAUDATE: FURTHER EVIDENCE FOR THE EXISTENCE OF KAPPA RECEPTOR SUBTYPES

S. O. Heyliger, K. L. McCullough[1], C. Jackson[2], K. C. Rice[3], and R. B. Rothman[1]

[1]NIDA, NIH, Baltimore, MD; FAMU, [2]Tallahassee, FL; and [3]NIDDK, NIH, Bethesda, MD

There is strong evidence supporting the existence of multiple kappa receptors. Previous studies proposed that U69593 and (+)-tifluadom act on different kappa receptor subtypes, kappa 1 (k_1) and kappa 2 (k_2), respectively. In this study, we investigated the effects of the kappa selective antagonist nor-binaltorphimine (Nor-BNI) on U69593- and (+)-tifluadom-induced receptor mediated stimulation of [^{35}S]-GTP-y-S binding in the guinea pig caudate. The IC_{50} value of Nor-BNI in the presence of a stimulating concentration of U69593 (1000 nM) was 0.19 ± 0.02; while the IC_{50} for Nor-BNI in the presence of (+)-tifluadom (1000 nM)was 13.9 ±1.62 nM. The mu-opioid receptor antagonist CTAP (10,000 nM) significantly reduced (+)-tifluadom- induced increase of [^{35}S]-GTP-y-S binding in rat brain sections and guinea pig brain membranes, indicating that (+)-tifluadom is a mu agonist. Under conditions in which the mu agonist activity of (+)-tifluadom was blocked by 1000 nM the Ki value for Nor-BNI at the U69593 site was 0.036 ±.004 nM, whereas, its Ki value for the (+)-tifluadom site was 0.27 ±. 015nM. These results suggest that (+)-tifluadom and U69593 stimulate pharmacologically different sites. This study provides functional evidence in support of kappa receptor heterogeneity.

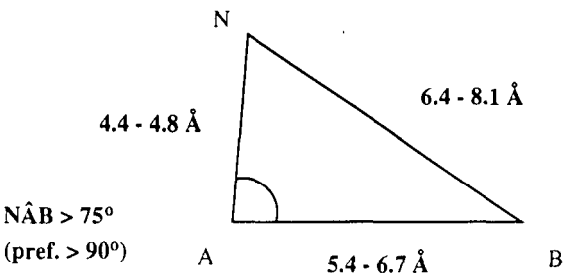
ACKNOWLEDGMENT: Supported by NIDA IRP.

PROGRESS IN THE DEVELOPMENT OF THE LMC DELTA OPIOID RECOGNITION PHARMACOPHORE

A. Coop and A. E. Jacobson

Laboratory of Medicinal Chemistry, National Institute of Diabetes, Digestive and Kidney Diseases, NIH, Bethesda, MD

A recognition pharmacophore for the delta opioid receptor has been developed *de novo* which is in essential agreement with that previously determined by Loew *et al.* (1997). Using different software (Tripos' Sybyl vs Quanta/CHARMm) and different data (Palmer *et al.* 1997) than those used by Loew, we find that a lesser intramolecular distance between the aromatic ring and hydrophobic area than that previously noted may be indicative of receptor selectivity (AB <6 Å). Although the vast majority of delta selective ligands (such as the indolomorphinans) satisfy the LMC pharmacophore, one notable exception is the highly selective agonist SNC80 which possesses an unusually large AN distance. In addition, it was shown that in the biologically important protonated forms, the proton on the terminal nitrogen of SNC80 occupies a different region of 3D space to the proton on the nitrogen of the indolomorphinans. This work shows that there are major differences between the indolomorphinans and SNC80, and suggests that they possess different binding modes. Reference list available on request from senior author.



MEMORY-IMPROVING SIGMAl RECEPTOR LIGANDS MODULATE INTRACELLULAR CA^{2+} MOBILIZATION IN NG-108 CELLS

T. P. Su and T. Hayashi

Unit on Cellular Pathobiology, Molecular Neuropsychiatry Section, Intramural Research Program, National Institute on Drug abuse, NIH, Baltimore, MD

Sigmal receptors have been implicated in the modulation of learning and memory in several animal models of amnesia as well as in drug abuse. However, the exact biochemical mechanism subserving sigmal receptors is essentially unknown. Because sigma receptors have been suggested to reside in close proximity to IP_3 receptors which are known to affect the intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$, we examined here using cultured cells (NG-108-15) if sigmal ligands such as (+)pentazocine [(+)PTZ] and PRE-084 might affect intracellular Ca^{2+} mobilization. Bradykinin (BK) induced an increase in $[Ca^{2+}]_i$ and the increase was found to be potentiated by a pretreatment of the cells with (+)PTZ (100 nM) for a period of at least 10 min. (+)PTZ (100 nM) thus administered was able to potentiate the BK-induced increase in $[Ca^{2+}]_i$ to 200% of that of the control. This effect of (+)PTZ was unaffected by the depletion of extracellular Ca^{2+} and could be antagonized by sigmal antagonists haloperidol (100 nM) and NE-100 (1 μM). The pretreatment of (+)PTZ with NG-108 cells also potentiated the depolarization (75 mM KCL)-induced $[Ca^{2+}]_i$ increase. The latter effect by (+)PTZ was antagonized by NE-100 and was abolished when cells received an administration of thapsigargin which depletes intracellular Ca^{2+} stores. PRE-084 (1 μM), on the other hand, did not affect the KCL-induced changes in $[Ca^{2+}]_i$, but reversed the inhibition caused by nifedipine on the KCL-induced increase of $[Ca^{2+}]_i$. These results indicate that sigmal receptors might modulate intracellular Ca^{2+} mobilization via two different modes of action: one related to the intracellular Ca^{2+} storage and the other to the plasma membrane. Our results suggest therefore a multiplicity of action exerted by sigmal receptors and that sigmal receptors may play an important role in intracellular signal transduction.

ACKNOWLEDGMENTS: Supported by Intramural Research Program, NIDA and Basic Neurobiological Systems Research Branch, DBR, NIDA.

FURTHER STUDIES ON THE ANTIPRURITIC ACTIVITY OF ICI 204448 IN MICE

G. B. Kehner and A. Cowan

Department of Pharmacology, Temple University School of Medicine, Philadelphia, PA

Using a recently described animal model of itch (Kuraishi et al. Eur J Pharmacol 275:229, 1995) we have demonstrated that peripherally selective kappa agonists antagonize focused scratching induced by compound 48/80 in mice. As an extension to these studies, we have characterized further the antipruritic activity of IC 204448, a standard peripherally selective kappa agonist (Shaw *et al.* Br J Pharmacol 96:986, 1989). Male Swiss mice (24-28 g; n = 11-17) were divided into 4 groups and pretreated s.c. (at T=.15 hr) with either norbinaltorphimine (norBNI, 20 mg/kg), the kappa receptor antagonist, or distilled water and given ICI 204448 (5 mg/kg) or saline (s.c.) at T=0 min. All mice received 50 μg (100 μl) of compound 48.80 s.c. into the back of the neck at T=20 min and neck scratches were counted for 30 min. NorBNI per se had no marked effect on compound 48/80-induced scratching. ICI 204448 (as expected at this dose level) reduced the indigence of scratching over twofold; and norBNI attenuated this antipruritic action of ICI 204448. These results underscore the important role kappa receptors play in mediating the scratch reflex induced by compound 48/80 in mice. Additional experiments with separate groups of mice (n-6-12) have revealed that the antipruritic activity associated with 5 mg/kg of ICI 204448 is essentially maintained at T=40-70 min (57.5±5.5% inhibition of scratching) and T=80-110 min (50.1±6.6% inhibition), begins to fade at T=160-190 min (36.9±9.6% inhibition) and is over at T=320-350 min (5.5±5.5% inhibition). Thus, ICI 204448 provides stable antagonism of compound 48/80-induced scratching for about 2 hr., a satisfactory duration of action for further pharmacological analysis.

ACKNOWLEDGMENT: Supported by NIDA grant DA-07237.

μ OPIOID RECEPTOR PHOSPHORYLATION: BASAL INCREASES IN MORPHINE TOLERANT RATS

J. B. Wang, H. B. Deng, and Y. Yu

Department of Pharmaceutical Sciences, School of Pharmacy, University of Maryland, Baltimore, MD

Although μ opioid receptors are acutely phosphorylated when expressing cells are exposed to morphine, phosphorylation's role in μ receptor desensitization, opiate tolerance and opiate dependence is not clear. We examined μ receptor phosphorylation in brain slices dissected from normal rats and rats treated chronically with morphine. Thalamic and striatal slices were incubated with [^{32}P]orthophosphoric acid. μ receptor is immunoprecipitated using a specific polyclonal anti-μ serum, and phosphoprotcins resolved using SDS-PAGE. A 66 kDa phosphoprotcin band was detected, which is similar in size to μ receptor purified from rat brain by ligand affinity and other methods. This band's intensity was ca 4-fold more prominent when slices were incubated with DAMGO for 20 min, and displayed significant increases after as little as 5 min treatment. Phosphorylation increases were blocked by naloxone pretreatment. Thalamic slices taken the day after 7 days' treatment with a regimen of 10 mg/kg morphine, three times a day, displayed greater phosphorylation than slices from saline-injected controls. These enhanced "basal" levels were accompanied by retained ability to further stimulate receptor phosphorylation after acute DAGO treatment on the slices. These results indicate that μ receptor phosphorylation status has been altered in morphine tolerant rat, which could contribute to biochemical processes involved in producing behavioral tolerance of opiate drugs.

ACKNOWLEDGMENT: Supported in part by PhRMA Faculty Development Award (JBW).

ROLE OF NEURONAL CA^{++} IN MORPHINE TOLERANCE IN MICE

F. L. Smith, D. L. Dombrowski, and W. L. Dewey

Department of Pharmacology and Toxicology, Medical College of Virginia of Virginia Commonwealth University, Richmond, VA

Numerous studies indicate that opioid analgesic tolerance involves a disruption in Ca^{++} homeostasis. The hypothesis was tested that both Ca^{++} influx and Ca^{++} release from intracellular pools maintains the expression of morphine tolerance. Placebo and morphine pelleted mice were injected i.c.v. with the Ca^{++} chelator EGTA at a dose not affecting morphine antinociception, in order to determine whether chelation of extracellular Ca^{++} would reverse tolerance in mice. EGTA (10.7 nmol) almost completely reversed tolerance. Antagonizing Ca^{++} channels with either nifcdipine (14.4 nmol) or omega-conotoxin GVIA (1.7 pmol) i.c.v. significantly reversed tolerance at doses having no effect in placebo pelleted mice. The role of intracellular Ca^{++} was investigated using the membrane permeable intracellular Ca^{++}chelators BAPTA-AM and EGTA-AM i.c.v. The partial but non-significant reversal of tolerance by BAPTA-AM (13.1 nmol) could be due to its extremely limited solubility. EGTA-AM reversed the antinociceptive tolerance to morphine. Finally, 1,4-dihydropyridine-sensitive Ca^{++} channels are known to stimulate Ca^{++}-induced-Ca^{++}-release (CICR) from Ca^{++}/caffeine sensitive microsomal pools that possess ryanodine receptors. We examined whether blocking Ca^{++} release from these pools with ryanodine (10.1 nmol, i.c.v.) would reverse morphine tolerance. Ryanodine also reversed morphine tolerance. Thus, CICR appears to contribute to the maintenance of tolerance. In summary, morphine tolerance appears to be associated with a change in Ca^{++} influx and Ca^{++} release from Ca^{++}/caffeine sensitive pools.

ACKNOWELDGEMENT: Supported by NIDA grant DA01647.

ORAL COMMUNICATIONS XX

NEUROSTEROIDS MODULATE THE EFFECTS OF BENZODIAZEPINES ON LEARNING

E. M. Nakamura-Palacios, P. Lambert, P. J. Winsauer, and J. M. Moerschbaecher

Department of Pharmacology, LSU Medical Center, New Orleans, LA

A multiple schedule was used to evaluate the effects of triazolam, flunitrazepam and the neuroactive steroid CO 6-0549, alone and in combination, on learning and performance of discriminations in monkeys. In the learning task, the subject acquired a different discrimination each day, while in the performance task the discrimination was the same each day. Responding was maintained by food presentation. Both triazolam and flunitrazepam produced dose-related decreases in the overall rate of responding under each task. The percentage of errors under the learning task was increased in a dose-related manner by both drugs, while the percentage of errors in performance was unaffected except at the highest doses. Both the rate-decreasing and error-increasing effects of each drug were antagonized by flumazenil. When administered alone, CO 6-0549 also decreased overall response rates in each task but increased percentage errors only in learning and only at higher doses. Doses of CO 6-0549, which had no effect on either rate or accuracy of responding when administered alone, potentiated both the rate-decreasing and error-increasing effects of triazolam under both the learning and performance tasks. Together, these results indicate some similarities in the actions of the benzodiazepines and neurosteroids when administered alone, and a significant interaction when administered in combination, in terms of their effects on complex behavioral processes.

ACKNOWLEDGMENT: Supported by DA04775

DISCRIMINATIVE STIMULUS EFFECTS OF BENZODIAZEPINE-SITE LIGANDS IN SQUIRREL MONKEYS

C. A. Paronis and J. Bergman

Behavioral Pharmacology Program, Harvard Medical School, ADARC/McLean Hospital, Belmont, MA

These studies sought to further characterize in monkeys the effects of putative full and partial benzodiazepine-like agonists by examining the midazolam-like discriminative stimulus (S^D) effects of several drugs that previously have been shown to increase punished responding. Squirrel monkeys (n=3-4) were first trained to respond under a schedule of stimulus-shock termination and then to discriminate midazolam from saline using a two-lever choice procedure. The training dose of 0.3 mg/kg midazolam is a dose of midazolam that produces peak antisuppressant effects on punished responding and all test drugs were examined over ranges of doses that have antisuppressant effects in squirrel monkeys. Midazolam (0.03–1.0 mg/kg) dose-dependently engendered responding on the midazolam-associated lever in all monkeys, as did diazepam (0.1-3.0 mg/kg), lorazepam (0.03-1.0 mg/kg), alprazolam (0.03-0.3 mg/kg) and flunitrazepam (0.01-0.3 mg/kg). Among the three putative partial agonists studied, imidazenil (0.003-0.1 mg/kg) produced intermediate levels, approximately 30-35%, of midazolam-appropriate responding in all monkeys, however, neither bretazenil (0.003-0.1 mg/kg) nor panadiplon (0.1-3.0 mg/kg) produced >10% midazolam-appropriate responding. These results suggest that antisuppressant effects of benzodiazepine-site ligands do not necessarily predict midazolam-like S^D effects in non-human primates. Subsequent studies examined the antagonism of the discriminative stimulus effects of midazolam by flumazenil. The effects of midazolam were dose-dependently antagonized by flumazenil, indicating that the S^D effects of midazolam are most likely mediated by benzodiazepine-site mediated effects. However, inspection of the data from individual subjects reveals that the effects of flumazenil are highly variable in different animals, suggesting that these data are not suitable for quantitative (Schild) analysis.

ACKNOWLEDGMENTS: Supported by NIH grants DA11453, DA03774, and MH07658.

DISCRIMINATIVE-STIMULUS EFFECTS OF BRETAZENIL IN RHESUS MONKEYS DISCRIMINATING BETWEEN MIDAZOLAM AND VEHICLE

S. Lelas, L. R. Gerak, and C. P. France

Department of Pharmacology, Louisiana State University Medical Center, New Orleans, LA

The present study was undertaken to characterize discriminative-stimulus effects of benzodiazepine (BZ) ligands in rhesus monkeys discriminating between triazolam or midazolam and vehicle. Four rhesus monkeys discriminated between 0.1 mg/kg of triazolam and vehicle in a single-cycle procedure on a fixed-ratio 5 schedule of stimulus-shock termination. Triazolam dose-dependently increased responding on the drug-appropriate lever, an effect dose-dependently reversed by flumazenil. Two BZ agonists, diazepam and midazolam, as well as the barbiturate pentobarbital, dose-dependently substituted for triazolam, whereas the non-competitive NMDA antagonist ketamine did not. The same animals were then trained to discriminate between 0.56 mg/kg of midazolam and vehicle under a multiple-cycle procedure (average of 8 additional sessions). Midazolam, diazepam, lorazepam, flunitrazepam, as well as pentobarbital, substituted for midazolam, whereas ketamine did not. Flumazenil did not substitute for midazolam and dose-dependently shifted the midazolam and diazepam dose-effect curves to the right. Bretazenil, a putative low-efficacy BZ agonist, did not substitute for midazolam in 3 out of 4 monkeys; in those three monkeys it shifted the midazolam dose-effect curve to the right, and in the remaining monkey the curve was shifted to the left. The present data support the hypothesis that the discriminative-stimulus effects of triazolam and midazolam are mediated by the same type of BZ receptor. These data also show that bretazenil has lower efficacy than midazolam at this BZ receptor. This procedure may be useful in identifying BZ agonists acting at different BZ receptor subtypes; these compounds would only partially substitute for the midazolam discriminative stimulus.

ACKNOWLEDGMENT: Supported by DA09157

IS THE FLUMAZENIL DISCRIMINATIVE STIMULUS A MEASURE OF BENZODIAZEPINE WITHDRAWAL IN DIAZEPAM-TREATED MONKEYS?

L. R. Gerak and C. P. France

Department of Pharmacology, Louisiana State University Medical Center, New Orleans, LA

Chronic treatment with positive γ--aminobutyric acid$_A$ ($GABA_A$) modulators can result in physical dependence. Previously, the discriminative stimulus effects of flumazenil in diazepam-treated monkeys were shown to be pharmacologically selective for neutral and negative $GABA_A$ modulators. The generality of this finding as well as the relationship between flumazenil-lever responding and benzodiazepine withdrawal were assessed in the current study. Four rhesus monkeys received 5.6 mg/kg/day of diazepam (p.o.) and discriminated 0.32 mg/kg of flumazenil (s.c.) while responding under a fixed ratio 5 schedule of food presentation. Suspension of diazepam treatment for 3 days resulted in a time-related shift in responding from the vehicle lever to the flumazenil lever, and flumazenil-lever responding was reversed by diazepam or pentobarbital. In diazepam-treated monkeys, bretazenil substituted for flumazenil. Moreover, the flumazenil dose-effect curve was shifted 3 to 10-fold to the right of the control curve following administration of 10.0 mg/kg of either diazepam or pentobarbital. Flumazenil-lever responding in diazepam-deprived monkeys suggests that the flumazenil discriminative stimulus is related to withdrawal. In addition, drugs that are likely to precipitate withdrawal in diazepam-treated subjects, including negative, neutral or low-efficacy positive $GABA_A$ modulators, substitute for flumazenil. Positive modulators with more efficacy are likely to reverse withdrawal and, consequently, they do not substitute for, but rather, attenuate the discriminative stimulus effects of flumazenil. These results attest to the utility of this procedure for evaluating dependence, possibly leading to improved treatment of anxiety-related disorders that require long-term administration of benzodiazepine agonists.

ACKNOWLEDGMENT: Supported by USPHS grant DA09157.

FLUMAZENIL DISCRIMINATION BY HUMANS: EFFECTS OF MIDAZOLAM AND CAFFEINE

B. J. Smith, W. K. Bickel, and S. A. Rogers

Departments of Psychiatry and Psychology , University of Vermont

Participants (n=8) were trained to discriminate flumazenil (0.56 mg/70 kg, i.v.) from saline. They were then tested with doses of flumazenil (0, 0.32, 0.56, 1.0 mg/70 kg, i.v.), midazolam (0, 0.10, 0.56, 1.0 mg/70 kg, i.v.), and caffeine (75 mg/70 kg, i.v.) under a novel-response drug discrimination procedure. Under the novel-response procedure, participants are offered a response alternative appropriate for effects unlike either training drug. Flumazenil produced a dose-dependent increase in flumazenil-appropriate responding as well as increased ratings on some self-report measures (e.g., visual analog ratings of drug-induced high and strength of drug effect). Midazolam also produced a dose-dependent increase in flumazenil appropriate responding. In addition, midazolam produced novel responding at the intermediate and highest test doses. Midazolam increased self-report ratings sensitive to sedative effects (e.g., PCAG subscale of the ARCI) and overall drug effects, and decreased performance on the DSST. Caffeine produced mostly saline-appropriate responding and had little effect on self-report measures. These data support previous research suggesting agonist effects of flumazenil and further suggest that the discriminative stimulus effects of flumazenil are similar to, but not identical to, those of a traditional benzodiazepine.

BEHAVIORAL EFFECTS OF TRIAZOLAM: INFLUENCE OF GENDER AND MENSTRUAL CYCLE PHASE

T. H. Kelly, C. S. Emuriau, C. A. Martin, L. R. Hays, K. M. Muse, S. J. Legan, and J. F. Wilson

Departments of Behavioral Science (THK, CSE, JFW), Psychiatry (CAM, LRH), OB/GYN (KMM), and Physiology (SJL), College of Medicine, University of Kentucky, Lexington, KY

This study examined the effects of gender and menstrual cycle phase on the behavioral effects of triazolam. Six male and six female healthy adults, blind to the study drug, gave written consent and participated on three consecutive days per week over eight consecutive weeks (i.e., across successive menstrual cycles). Menstrual cycle activity was monitored prior to the study, and study days for women were selected to coincide with four cycle phases (early follicular, late follicular, early luteal and late luteal). On study days, subjects consumed a standard meal at 5:30 P.M., received drug at 6:30, and completed 20-minute sessions consisting of computerized performance tasks and visual-analog scale (VAS) ratings of drug effect 0, 0.5, 1, 2, 3, 4 and 5 hours after drug administration, and upon waking the next morning. Each of 3 doses (0, 0.2 and 0.4 mg/70 kg) was administered orally 1 day each week in random order. Blood samples were collected prior to the first day of each week to monitor HPG hormone levels. Triazolam altered VAS ratings of drug effect and performance on all tasks, including response rates during a psychomotor performance task, acquisition efficiency during a learning task, time estimation and performance accuracy during a delayed matching-to-sample task. Gender differences in drug effects were observed on VAS ratings of drug effect, acquisition efficiency during the learning task, and systolic blood pressure, with the magnitude of drug effects being consistently greater in males. Interactions between the behavioral effects of triazolam and phase of the menstrual cycle were also observed on acquisition efficiency, with the magnitude of drug effects being greater during the luteal cycle phases. No evidence of residual next-day effects was obtained on any measure. These results indicate that the behavioral effects of triazolam on selected dimensions of performance, on verbal reports of drug effect, and on systolic blood pressure differ between males and females, and that triazolam-induced impairment of acquisition varies across the menstrual cycle.

ACKNOWLEDGMENT: Supported by NIDA grant DA 09098.

FLUNITRAZEPAM AND TRIAZOLAM: A COMPARISON OF BEHAVIORAL EFFECTS AND ABUSE LIABILITY

R. R. Griffiths and M. Z. Mintzer

Johns Hopkins University School of Medicine, Baltimore, MD

Flunitrazepam (FLU) is a benzodiazepine hypnotic whose recent abuse rates are reported to be exceptionally high relative to those of other benzodiazepines worldwide. The present double-blind, crossover study evaluated the acute behavioral and subjective effects of orally administered FLU (2, 4, and 8 mg/70 kg) relative to those of the benzodiazepine hypnotic triazolam (TRZ; .25, .5, and 1 mg/70 kg) in 14 sedative drug abusers on a residential research unit. Both FLU and TRZ produced dose-related decrements in performance, and increases in many participant- and observer-rated measures. Effects of FLU had an earlier onset and a longer duration than those of TRZ. Although there was evidence that the FLU doses selected for study were somewhat higher overall relative to the selected TRZ doses, the differences between FLU and TRZ which emerged from analysis of the participant-rated measures collected 24 hours after drug administration (next-day) were particularly striking. On three next-day measures (i.e., good effects, take again, worth), the highest FLU dose produced effects that were significantly greater than those of the highest TRZ dose, and on two next-day measures (i.e., liking and take again), all tested FLU doses produced effects greater than any TRZ dose. The highest FLU dose, but no TRZ dose, significantly increased the maximum dollar value at which participants chose drug over money in a Drug vs. Money Choice Procedure. These results suggest that FLU may have a greater abuse liability than TRZ when abuse liability is assessed 24 hours after drug administration.

ACKNOWLEDGMENT: Supported by NIDA grant DA03889.

INFLUENCE OF AGE ON THE BEHAVIORAL EFFECTS OF DIAZEPAM

A. M. Fredenburg, C. S. Emurian, C. A. Martin, L. R. Hays, K. M. Muse, S. J. Legan, J. F. Wilson, and T. H. Kelly

Departments of Behavioral Science (AMF, CSE, JFW, THK), Psychiatry (CAM, LRH), OB/GYN (KMM), and Physiology (SJL), College of Medicine, University of Kentucky, Lexington, KY

This study examined the effects of age and gender on the behavioral effects of diazepam. Healthy adult males and females, blind to the study drug, gave written consent and participated on three consecutive days per week over 8 consecutive week intervals. Six males and 6 females between 18-45 and 6 males and 8 females between 55-65 years of age completed the study. On study days, subjects consumed a standard meal at 5:30 P.M., received drug at 6:30, and completed 20-minute sessions consisting of computerized performance tasks and visual-analog scale (VAS) ratings of drug effect 0, 0.5, 1, 2, 3, 4 and 5 hours after drug administration, and upon waking the next morning. Each of 3 doses (0, 5 and 10 mg/70 kg) was administered orally 1 day each week in random order. Baseline differences on many dimensions of task performance were observed as a function of age. Diazepam altered task performance, including response rate during a psychomotor performance task, acquisition efficiency during a learning task, time estimation and performance accuracy during a delayed matching-to-sample task, as well as VAS ratings of 'Feel Drug,' 'High,' 'Sedated' and 'Sleepy.' The magnitude of drug effect on VAS ratings of Sedated' and 'Sleepy,' and response rate during the learning task was greater in the 18-45 age group. In contrast, the magnitude of drug effect on acquisition efficiency during the learning task was greater in the 55-65 age group. Age differences in the time course of drug effect were also observed on VAS ratings of 'Feel Drug,' 'Sedated' and 'Sleepy,' and response rate during the learning task, with onset of drug effects occurring more slowly in the 55-65 age group, particularly with females. A significant gender by age interaction with dose effects was observed for VAS ratings of 'High.' No evidence of residual next-day effects was obtained on any measure. These results indicate that the behavioral effects of diazepam on some dimensions of performance and verbal reports of drug effect vary as a function of both age and gender.

ACKNOWLEDGMENT: Supported by NIDA grant DA 09098.

TRAZODONE, ZOLPIDEM, AND TRIAZOLAM: ACUTE BEHAVIORAL EFFECTS AND ABUSE POTENTIAL

C. R. Rush, R. W. Baker, and K. Wright

Department of Psychiatry, University of Mississippi Medical Center, Jackson, MS

The present study examined the acute behavioral effects and abuse potential of trazodone (100-300 mg), a triazolopyridine antidepressant, zolpidem (15-45 mg), an imidazopyridine hypnotic, triazolam (0.25-0.75 mg), a triazolobenzodiazepine hypnotic, and placebo in 10 male volunteers with histories of alcohol and drug abuse. Trazodone was included because antidepressants are being used more frequently to treat sleep disorders, but it is unclear whether these compounds have a unique behavioral pharmacological profile relative to benzodiazepine hypnotics. Zolpidem was included because it is the most commonly prescribed hypnotic and purportedly has a unique benzodiazepine-receptor binding profile. Trazodone, zolpidem and triazolam generally produced comparable dose-related performance impairment and sedation. These findings suggest clinically equivalent drug doses were tested. The effects of trazodone on subject-rated items thought to measure abuse potential (e.g., Willing to Take Again) were significantly less than those observed with triazolam. By contrast, zolpidem and triazolam produced comparable effects on these measures. These data suggest that trazodone has less abuse potential than triazolam, and may be a viable alternative to benzodiazepine hypnotics in individuals with histories of alcohol or drug abuse. By contrast, despite its unique benzodiazepine-receptor binding profile, the acute behavioral effects and abuse potential of zolpidem are comparable to those of triazolam.

ACKNOWLEDGMENT: Supported by NIDA grant DA 09841.

ORAL COMMUNICATIONS XXI

KINETICS OF 5-HT_{1A} AND 5-HT_{2A} RECEPTOR TURNOVER IN ADULT RAT PROGENY EXPOSED PRENATALLY TO COCAINE

G. Battaglia, A. Vicentic, T. M. Cabrera-Vera, W. Pinto, and F. Garcia

Department of Pharmacology, Loyola University Chicago, Maywood, IL

Prenatal exposure to cocaine alters postsynaptic 5-HT_{1A} and 5-$HT_{2A/2C}$ serotonin receptor function in the absence of changes in receptor density. Steady-state receptor densities (Bmax) are dependent on intracellular rate constants of receptor production (r) and degradation (k). We have shown (Mol. Pharm. 46:1111-1119, 1994) that serotonin (5-HT) receptor subtypes with comparable Bmax values exhibit marked differences in r and k, suggesting differences in intracellular processes regulating receptor density. The objective of this study was to determine if prenatal exposure to cocaine could alter the underlying kinetic constants (i.e. r & k), and hence, turnover, of 5-HT_{1A} and 5-HT_{2A} receptors. Pregnant Sprague-Dawley rats (12/group) received either 0.9% saline or 15mg/kg (-)cocaine (s.c., b.i.d.) from gestational days 13-20. Adult male progeny were given a single injection of either vehicle or the irreversible receptor antagonist EEDQ (10mg/kg). Cortical 5-HT_{1A} and 5-HT_{2A} receptor densities were determined at various post-treatment times (0-14 days). Calculation of rate constants for receptor production and degradation, from the recovery data, indicated that prenatal exposure to cocaine did not alter r, k or the half-life of receptor repopulation for either 5-HT receptor subtype. These data suggest that prenatal exposure to cocaine did not alter the *overall* intracellular processes governing cortical 5-HT_{1A} or 5-HT_{2A} receptor repopulation or final Bmax values. It remains to be determined: (1) if these data are generalizable to other brain regions, and (2) whether recovery of receptor function after inactivation is altered by prenatal cocaine exposure.

ACKNOWLEDGMENT: Supported by NIDA grant DA 07741.

COCAINE SELF-ADMINISTRATION IN JUVENILE RHESUS MONKEYS EXPOSED PRENATALLY TO COCAINE

L. L. Howell, A. J. Kitchens, and C. M. Webb

Neuroscience Division, Yerkes Regional Primate Research Center, Emory University, Atlanta, GA

The present study characterized the reinforcing effects of cocaine in juvenile rhesus monkeys, ages 4-5 years, after prenatal exposure to cocaine (0.3 mg/kg/hr) from day 24 post-conception throughout gestation. Intravenous drug self-administration was initiated with a l-response fixed-ratio schedule (FR 1), and the ratio value was increased over successive sessions until the schedule value was FR 20. Subsequently, drug injections were delivered under a second-order fixed-interval 600-sec schedule with FR 20 components. Cocaine-exposed (N=4) and pair-fed controls (N=4) exhibited similar rates of acquisition for the maintenance dose (0.1 mg/kg) of cocaine. Moreover, there was no significant difference among treatment groups in sensitivity to the reinforcing effects of cocaine when a range of cocaine doses (0.01-1.0 mg/kg) was substituted for the maintenance dose. Pretreatment with the D_2-selective antagonist, raclopride (0.01-0.56 mg/kg), dose-dependently attenuated the reinforcing effects of cocaine in all subjects. There was no significant difference among treatment groups in susceptibility to antagonism by raclopride. The results demonstrate that prenatal exposure to cocaine had no long-term consequences on sensitivity to the reinforcing effects of cocaine via intravenous self-administration.

ACKNOWLEDGMENTS: Supported by USPHS grants DA-06264, DA-05346, and RR-00165.

THE PLACENTA AS A TARGET OF COCAINE ACTION

J. S. Meyer, L. P. Shearman, and A. M. McReynolds

Neuroscience and Behavior Program, University of Massachusetts, Amherst, MA

As norepinephrine (NE) and serotonin (5-HT) transporters have been found in human placental membranes, blockade of these transporters may underlie some of cocaine's adverse effects on pregnancy outcome and fetal development. The present studies examined NE and 5-HT uptake sites in gestational day (GD) 20 rat placenta with respect to binding characteristics, localization, and response to maternal cocaine treatment. Saturation analyses of [^{3}H]nisoxetine binding to normal placental membranes revealed a single binding site with a mean K_d of 1.0 nM and a B_{max} of 1.24 pmol/mg protein. Drug competition experiments supported the conclusion that [^{3}H]nisoxetine was labeling an NE transporter. 5-HT transporter studies were conducted using both [^{3}H]paroxetine and the cocaine congener [^{125}I]RTI-55. Whereas [^{125}I]RTI-55 saturation analyses yielded curvilinear Scatchard plots that could be resolved into high- and low-affinity components, [^{3}H]paroxetine bound to a single site with a mean K_d of 0.09 nM and a B_{max} of 96 fmol/mg protein. *In vitro* autoradiography of placental sections showed maximum [^{3}H]nisoxetine binding in the junctional zone, but maximum [^{125}I]RTI-55 binding in the labyrinth. Immunocytochemical studies revealed the presence of immunoreactivity for the 5-HT transporter and for 5-HT itself in all areas of the placenta, although the cellular staining within each area was heterogeneous, In the final experiment, 3 days of continuous maternal cocaine treatment led to a large up-regulation of [^{3}H]nisoxetine binding sites, but no change in [^{125}I]RTI-55 binding. In conclusion, 1) the near- term rat placenta expresses a much higher density of NE than 5-HT uptake sites, 2) these sites are differentially distributed in the placenta, and 3) the NE transporter is selectively influenced by cocaine exposure. The functional roles of placental monoamine uptake remain to be elucidated.

ACKNOWLEDGMENT: Supported by NIDA grant DA-06495.

A MODEL OF PRENATAL ALCOHOL EXPOSURE: SLEEP TIME RESPONSE TO FIRST ADULT ETHANOL CHALLENGE

T. Badger, M. Saviers, E. Glasier, M. Ronis, R. Hakkak, F. Scalzo, D. Irby, J. Beltson, and C. Weatherford

Department of Pediatrics, University of Arkansas for Medical Sciences, Arkansas Children's Hospital Research Institute, Little Rock, AR

Undernutrition has often been a major problem with previous rat models of *in utero* drug exposure. We have developed a rat model to study the effects of ethanol and other drugs on prenatal and postnatal rat development. In this model, pregnant rats are fed by total enteral nutrition (TEN), a diet delivery method by which a liquid diet containing all known required nutrients is infused directly into the stomach. TEN provides a means of delivering the appropriate dose of ethanol and the calculated level of all nutrients, thus allowing the study of the direct effects of ethanol independent of nutrition. This system can also be used to study virtually any drug with very slight modifications. In the present study, isocaloric diets, either with or without ethanol (12-13 g/kg/d), were infused during the last 16 d of gestation. Pups were allowed to grow untreated until age 75 d. They were fasted 24 h and infused intragastrically with a bolus of 4 g/kg ethanol and observed over the next several hours while monitoring blood ethanol levels. Offspring of mothers given ethanol during pregnancy had shorter times to first sleep and slept longer than control rats ($P < 0.05$). These results suggest that when nutrition is carefully controlled, in utero ethanol exposure alters CNS responses to the first exposure as adults.

ACKNOWLEDGMENT: Supported by NIAAA grant 08645

EFFECT OF PRENATAL Δ^9-TETRAHYDROCANNABINOL EXPOSURE ON THE HYPOTHALAMO-PITUITARY-ADRENAL (HPA) AXIS OF RAT OFFSPRING

L. L. Murphy and W. K. Walsh

Department of Physiology, Southern Illinois University School of Medicine, Carbondale, IL

The major psychoactive component in marijuana, Δ^9-THC, is a potent stimulator of ACTH and corticosterone (B) release in the adult animal. In the current study, the HPA response to THC in the pregnant rat and the effect of prenatal THC exposure on the HPA axis of the offspring were investigated. Pregnant Sprague-Dawley rats were administered either sesame oil vehicle or THC (1 or 5 mg/kg bw at 0900 and 1700h daily; po) on gestational days (GD) 14-19. In dams sacrificed at 1000h on GD19, there was a significant increase in maternal B levels following treatment with the high THC dose compared to vehicle-treated rats. In contrast, there was a significant decrease in fetal B levels with the high THC dose. Other dams gave birth and when offspring were between 75 and 90 days of age, they were subjected to either a 10 min-restraint stress or a dexamethasone (DEX) suppression test. Restraint stress produced significant elevations in ACTH and B levels in all animals, however; the magnitude and duration of hormone release were significantly greater in male rats exposed to the high THC dose when compared to vehicle controls. Furthermore, female rats which had been exposed to the high THC dose exhibited a greater suppression of ACTH levels following DEX (2µg/kg b.w.; sc) treatment relative to vehicle-exposed offspring. These results indicate that exposure to THC during late gestation alters the adult offspring's HPA response to positive or negative feedback signals. The ability of THC to alter glucocorticoids in the dam and fetus may play a role in this THC effect.

ACKNOWLEDGMENT: Supported by NIDA grant 10368.

PERINATAL OPIOIDS REDUCE STRIATAL NERVE GROWTH FACTOR (NGF)

S. E. Robinson, V. W. Wu, Q. Mo, and J. P. Schwartz

Department of Pharmacology and Toxicology, Medical College of Virginia of Virginia Commonwealth University, Richmond, VA

Methadone (m) maintenance is a standard method of managing pregnant heroin addicts, and the partial agonist buprenorphine (b) is under consideration for the same use. In the rat, perinatal exposure to methadone disrupts the development of striatal cholinergic neurons. Because NGF stimulates the expression of the cholinergic phenotype in the striatum, we determined whether perinatal opioid exposure reduces striatal NGF content. On day 7 of gestation, pregnant Sprague Dawley CD rats under methoxyflurane anesthesia were implanted subcutaneously with 28 day osmotic minipumps which delivered sterile water (w), methadone HCI (9 mg/kg/day) or buprenorphine HCI (1.5 mg/kg/day). Within 24 hr of parturition. litters were culled to 10, with equal numbers of males and females. and cross-fostered, resulting in the following prenatal/postnatal exposure groups: w/w, m/w, w/m, m/m, b/w, w/b, and b/b. On postnatal day 10, pups were decapitated, and striata were dissected and pooled for NGF analysis. All treatment groups receiving opioids perinatally exhibited a significant reduction in striatal NGF content. as compared to offspring of the control dams implanted with water-filled minipumps ($F=13.30$, $p < 0.0001$ by 1-way ANOVA and post-hoc Dunnett's test). These results indicate that perinatal opioid exposure reduces striatal NGF content. which may be responsible for the delayed expression of the cholinergic phenotype. Hence, use of μ-opioid agonists or partial agonists should be approached with care in pregnant women, as changes in NCF content may perturb the development of cholinergic neurons, and may contribute to the behavioral changes observed in the offspring of opioid-exposed mothers.

ACKNOWLEDGMENT: Supported by NIDA grant DA09399.

BUPRENORPHINE MAINTENANCE IN PREGNANT OPIATE ADDICTS

G. Fischer, R. Jagsch, C. Nagy, C. Lennkh, H. Eder, W. Gombas, and M. Langer

Department of General Psychiatry; University of Psychiatry, Vienna, Austria

It is a well known fact that maternal opiate use during pregnancy is associated with a long list of problems in the pregnant woman as well as in the fetus, neonate and young infant. Relevant pharmacological treatment for the latter individuals has not yet been established. Methadone maintenance therapy improves the situation for mother and child but cannot prevent the neonatal abstinence syndrome (NAS). Eleven opiate dependent pregnant addicts (mean age 24 years), with a mean duration of opioid dependence of 55,09 months, were enrolled in an open standardized treatment study with maintenance therapy of sublingual buprenorphine. Induction period to a daily dose of 8 mg sublingual buprenorphine (SD + 2,8; range 4-10) was performed on an in-patient basis during the mean duration of pregnancy of 27 weeks (SD + 5,4; range 17-36). Prior to buprenorphine all subjects were stabilized either on methadone (n=8; mean daily dosage of 40,4 mg) or on slow-release morphine (n=3; mean daily dosage of 400mg). Buprenorphine was well tolerated during pregnancy. Eleven healthy neonates were born during the 39,5th week of pregnancy (SD + 1,8; range 36-42), the mean birth weight being 2984 gramm (SD + 381,32; range 2290-3700) and with a weak occurence of an opioid related NAS (five did not show any NAS, six a weak). We propose that the partial agonistic profile of buprenorphine, in contrast to the full opiate agonistic properties of methadone, morphine and heroin, accounts for the absence, respectively weak NAS following buprenorphinc therapy.

PATTERNS OF WEIGHT GAIN IN A POPULATION OF COCAINE-DEPENDENT PREGNANT WOMEN

S. M. Bahl, R. Elk, and S. E. Williams

Department of Psychiatry and Behavioral Sciences, School of Allied Health Sciences, UT-Houston Health Science Center, Houston, TX

The focus of this study was to assess the nutritional status and patterns of weight gain in cocaine-dependent pregnant women who were participating in a comprehensive treatment program. Subjects were pregnant women who were 28 weeks gestation or less, with a primary diagnosis of cocaine dependence, or opiate dependence with secondary cocaine dependence. They were randomly assigned to one of three treatment groups and were subjected to a baseline treatment that included a combination of behavioral and group therapy sessions. Patients were also required to attend the Substance Abuse Prenatal Clinic once a week and the Treatment Research Clinic twice a week, providing a urine sample at each of these visits. All subjects were weighed at each visit. Additional nutrition information was also obtained. Results indicate that the body mass index (BMI) was significantly lower than normal for at least 25% of the sample studied. More than 15% had a BMI that was considerably higher than normal. Weight gain patterns were not in the acceptable range for several subjects, These findings have important implications as prepregnancy weight-for-height and serial weight measurements are the only anthropometric measurements with documented clinical significance.

ACKNOWLEDGMENT: Supported by NIDA RO1 DA-08438.

THE EFFECT OF REPORTED DRUG USE ON PLACENTA WEIGHT, DNA, RNA AND PROTEIN CONTENT OF AFRICAN AMERICAN SUBJECTS

E. M. Knight, M. Navahandi, C. H. Edwards, U. J. Oyemade-Bailey, O. Westney, G. Nolan, W. L. West, A. A. Johnson, O. J. Cole, L. Kessee, G. Narula, H. Laryea, J. F. Diaz, and L. Westney

Center for Drug Abuse Research, Dept. of Pharmacol., Dept. of Nutr. Sc., Div. of Allied Health Sc., Howard University, Washington DC

The placenta is associated with the transport of nutrients to the fetus. Therefore, for positive pregnancy outcome, the physiology of the placenta has been identified as a contributing variable. The data presented are from a group of African American subjects who were enrolled in a nutrition program project (NPP) and therefore had access to pre-natal care. The use of reported licit and illicit drugs was obtained from a questionnaire. At delivery, the placenta variables analyzed were nucleic acids (RNA and DNA) and protein which were compared between reported substance abusers and non abusers. The data show that placenta weight was positively correlated with the pregnancy outcome variables: head circumference ($n = 42$, $r = 0.46$, $P = 0.002$), birth length ($n = 42$, $r = 0.44$, $P = 0.003$), birth weight ($n = 42$, $r = 0.53$, $P = 0.035$), and ponderal index ($n = 42$, $r = 0.33$, $P = 0.035$). The reported use of substances of abuse had no significant effect on the placenta weight, the nucleic acids, and protein content of the placenta ($P > 0.05$). It appears that in this population prenatal care alleviated the negative effects of drug use on the placenta variables.

ACKNOWLEDGMENTS: Supported by NICHD P013HD17104-05, Eng, NIH and NIDA 0004.

ORAL COMMUNICATIONS XXII

ORAL ETHANOL SELF-ADMINISTRATION IN RHESUS MONKEYS

J. A. Vivian[1], J. D. Higley[2], M. Linnoila[2], and J. H. Woods[1]

[1]Department of Pharmacology, University of Michigan Medical School, Ann Arbor, MI and [2]Laboratory of Clinical Studies, National Institute on Alcohol Abuse and Alcoholism, Poolesville, MD

Previous research has revealed that oral ethanol serves as a reinforcer in non-human primates, and that ethanol consumption may be negatively correlated with CSF concentrations of the serotonin metabolite 5-HIAA and affected by parental rearing. In this study, three cohorts of 15-20 rhesus monkeys (Macaca mulatta) were socially housed and given 1-hr single spout access to an aspartame-sweetened ethanol (8.4% v:v) solution. The twelve monkeys (group 1) that consumed the most ethanol under these conditions were subsequently housed individually and given 2-hr two-spout access to a range of ethanol concentrations (0.25-160%) concurrently with water. These monkeys showed a marked preference for ethanol over water; ethanol consumption was fourfold greater than that of a second group of twelve monkeys (group 2) that were not chosen for an ethanol preference, but simply purchased from a commercial vendor. In addition, CSF 5-HIAA was obtained and found to lower in monkeys from group 1 (43.5±2.0 ng/ml) than in group 2 (66.3±4.9 ng/ml). These results indicate that consumption of sweetened ethanol in a social housing condition may predict later preference and consumption for unsweetened ethanol over water in individual housing conditions, and that low concentrations of CSF 5-HIAA may be associated with ethanol preference and consumption.

ACKNOWLEDGMENTS: Supported by USPHS Grants DA00254 and DA05773.

ENSEMBLE NEURON CODING IN THE MESOCORTICOLIMBIC SYSTEM OF THE FREELY- MOVING RAT DURING ETHANOL SELF-ADMINISTRATION

P. H. Janak and D. J. Woodward*

Wake Forest University School of Medicine, Winston-Salem, NC and *National Institute on Drug Abuse, Cellular Neurobiology Branch, Baltimore, MD

The mesocorticolimbic circuits of the brain are thought to regulate drug-seeking behavior. Our goal was to determine coding by groups of individual neurons within this circuit during the sequence of sensory and motor events leading to self-administration of drugs. In this study, we tested the hypothesis that phasic activity patterns within this circuit will be correlated with ethanol self-administration behavior. Twelve male Long-Evans rats were trained to nosepoke for 0.1 cc drops of a 10% solution of ethanol in water, using the sucrose-fading technique. Following training, rats were chronically implanted with arrays of 8-16 microwires into the nucleus accumbens (Nac) and/or the amygdala (Am). After recovery, simultaneous recordings of the extracellular spike activity of 6-35 single units per subject were made during ethanol-reinforced operant behavior. Significant changes in spike activity were determined with the Wilcoxin matched-pairs test. Neurons in both regions showed phasic changes in firing related to the operant response, in response to a tone stimulus that signaled ethanol delivery, and during ethanol delivery. In addition, delay period responses, corresponding to anticipation or working memory, occurred in the intervals preceding ethanol delivery. These results demonstrate that spike activity within the Nac and the Am is modulated during ethanol self-administration and support the participation of the mesocorticolimbic circuit in drug-seeking behavior. Our conclusion is that sensory, motor, and putative cognitive events are coded in the mesocorticolimbic "reward" system.

ACKNOWLEGEMENTS: Supported by AA10980 (DJW) and AA07565 (PHJ) and an North Carolina Governor's Institute Young Investigator Award (PHJ).

CUES ASSOCIATED WITH ETHANOL SELF-ADMINISTRATION SUPPORT OPERANT RESPONDING IN RATS

C. J. Heyser and G. F. Koob

The Scripps Research Institute, Dept of Neuropharmacology, La Jolla, CA

Previous research in our laboratory has shown that animals respond for a stimulus previously paired with ethanol (a conditioned reinforcer) in the absence of ethanol reinforcement and renew responding for the conditioned stimulus following extinction. Although responding was directed to the conditioned stimuli, response magnitude was considerably weaker than that observed for the primary reinforcer (ethanol). Given that cues inherently associated with ethanol self-administration (e.g., oral fluids) also prolong or prevent extinction, the present study was conducted to investigate the potential additivity of these cues in modulating operant behavior. Male Wistar rats were trained in a limited access paradigm (30 min/day) to respond for ethanol (10% w/v) in a two-lever free-choice condition using a saccharin fading procedure. Responding to one lever resulted in delivery of ethanol and the presentation of a cue light for 5 sec, while responding to the other lever resulted in delivery of water. The presence of the cue light or water maintained responding during extinction, albeit, at levels lower than that observed for ethanol reinforcement. When presented in combination, the pattern of responding for the cue light and water (in the absence of ethanol) was indistinguishable from that observed during ethanol self-administration. These results confirm the hypothesis that cues associated with ethanol intake may function separately or additively to modulate behavior and provide a model to explore the motivational significance and neurobiological substrates of conditioned reinforcement.

ACKNOWLEDGMENTS: Supported by grants AA08459, AA06420 and AA05403.

GREATER REACTIVITY TO ALCOHOL-RELATED CUES IN WOMEN WITH A FAMILY HISTORY OF ALCOHOLISM

L. H. Lundahl, S. L. Daniels, S. F. Duggan, and S. E. Lukas

Behavioral Psychopharmacology Research Laboratory, McLean Hospital/Harvard Medical School, Belmont, MA

Cue reactivity has been offered as a possible explanation for the early onset of familial alcoholism in men. However, similar studies have not been conducted in women. After providing informed consent, 32 healthy female social drinkers (age 21-25) agreed to participate in this study. Half of the subjects were classified as having a positive family history of alcoholism (FHP) while the other half were family history negative (FHN). Subjects were seated in a recliner chair located inside an isolated chamber and prepared for measurements of heart rate, blood pressure and skin temperature. After a 55 min baseline period subjects were exposed to a series of neutral cues including handling club soda and viewing a videotape depicting scenes from a nature show. The second session occurred 1 hr later and involved alcohol-related cues such as handling and smelling the subject's preferred alcoholic beverage and viewing a videotape of people drinking in a bar. Saliva samples were collected and subjective reports of alcohol craving and mood state were measured via visual analog scales both before and after cue presentation. Significant increases in "Desire to Use Alcohol" and "Urge to Use Alcohol" paralleled increases in salivation and *decreases* in skin temperature only in FHP subjects after exposure to alcohol-related cues. This is the first demonstration of a differential reactivity to alcohol-related cues in FHP and FHN females. These results also suggest that cue desensitization techniques may be more effective in FHP women as FHN women appear to be less reactive to alcohol-related cues.

ACKNOWLEDGMENTS: Supported by grants AA10536 and DA00343 and Livingston Award - Harvard Medical School.

ETHANOL IMPAIRS EYE MOVEMENTS WITHOUT PRODUCING SUBJECTIVE SEDATIVE EFFECTS

L. Holdstock and H. de Wit

The University of Chicago, Department of Psychiatry, Chicago, IL

Eye movement monitoring, including measurements of peak saccadic velocity (PSEV), is a powerful tool to study the central effects of sedative drugs. However, there is controversy about whether drug-induced impairment in PSEV is related simply to the drugs sedative actions. In this regard, ethanol is interesting because it can induce both stimulant-like and sedative-like subjective effects. The aims of the present study were 1.) To quantify and compare the effects of ethanol on PSEV and self-reported mood states, and 2.) To evaluate the correlation between self-reported sedation and impaired PSEV. Twenty healthy social drinkers received ethanol (0.4 or 0.8 g/kg) or placebo on three separate sessions in random order. Eye movements were monitored using an infra-red eyetracker, and PSEV was calculated. Subjective mood effects were measured with standardized self-report questionnaires. Psychomotor performance (DSST) was also assessed. Ethanol dose-dependently decreased PSEV and psychomotor performance, and it increased ratings on prototypical subjective effects measures, such as "Feel drug", "Like drug" and ratings of stimulant effects and "euphoria". Interestingly, in this study, ethanol did not increase subjective ratings of sedation, indicating that the impairment in PSEV was not due to ethanol's sedative-like subjective effects. Moreover, subjects who reported the greatest sedative-like effects did not have greater impairment in PSEV than subjects who reported only stimulant-like effects. To our knowledge, this is the first demonstration that a drug with primarily stimulant-like subjective effects impairs PSEV.

ACKNOWLEDGMENT: Supported by DA02812.

DIFFERENTIAL-DRUG DISCRIMINATION IN ALCOHOL-PREFERRING AND ALCOHOL-NONPREFERRING RATS

M. Li, D. J. Shade, and D. E McMillan

Department of Pharmacology and Toxicology, University of Arkansas for Medical Sciences, Little Rock, AR

Alcohol-preferring (P) and alcohol-nonpreferring (NP) rats were trained to discriminate the presence or absence of the administration of 0.5 g/kg of ethanol by the intraperitoneal route. Both P and NP rats acquired the discrimination, but P rats learned it faster and stimulus control was better in P rats than in NP rats. After ethanol discrimination stabilized, dose-response curves were determined for ethanol, nicotine and *d*-amphetamine. In P rats, there was an increased percentage of responses on the ethanol associated lever with increasing doses of all three of these drugs, but in NP rats, only ethanol produced increased responding on the drug lever with increasing doses. A second group of P rats was trained to discriminate 0.6 mg/kg nicotine from saline and then dose-response curves were determined for nicotine and ethanol. There was increased responding on the nicotine-associated lever with increasing doses of nicotine, but not with ethanol, suggesting that the generalization between ethanol and nicotine was asymmetrical. These data suggest that there are marked genetic differences in the discriminative stimulus properties of ethanol in lines of rats bred to drink ethanol.

ACKNOWLEDGMENT: Supported by NIDA.

A MULTIDIMENSIONAL STUDY OF ENDOCRINE AND PSYCHOLOGICAL FACTORS IN ALCOHOL ABUSE

H. Nyborg and H. Albeck

International Research Center for Psychoneuroendocrinology, Institute of Psychology, University of Aarhus, Denmark

The structure of 17 psychological and 9 endocrine variables was analyzed with respect to their effects on alcohol intake in 2.836 middle-aged white American males. Psychological variables included: Spearman general intelligence g, level of education, Eysenck's personality dimensions (Psychoticism - P. Extraversion- E, Neuroticism N, and Social Desirability - L), and 11 MMPI psychopathology scores (Hypomania, Psychopathy, Ego-strength, Introversion, Depression, Obsession-Compulsion, Schizophrenia, Paranoia, Hypochondria, Hysteria, and Femininity). Endocrine variables included: Plasma Testosterone (t), T4, Dihydro-epi-androsterone sulfate (DHEAS), Cortisol (9 AM), Luteinizing (LH) and Follicle stimulating hormone (FSH), Thyroid stimulating hormone (TSH), T3 uptake and, finally Body Mass Indeks (BMI). Four grouping criteria for alcohol intake were established, with group 1 drinking no alcohol ever. Groups with increasing alcohol consumption were then formed by sorting the alcohol drinking males into 3 groups by K-mean clustering of their log transformed alcohol consumption. A model was formulated with the 17 psychological and 9 endocrine variables as a function alcohol consumption classification, and analyzed by MANOVA to identify the discriminatory power of the variables for alcohol consumption. The model proved highly significant ($p < 0{,}000001$) with a moderate discriminatory power (Wilks' index = 0,77). The following variables - listed in order of discriminative power - demonstrated significant discriminatory power: Psychoticism, Hypomania, T3 uptake, Spearman g, L, P. Education, Ego-strength, Introversion, N. t, BMI, E, Depression, Obsession-Compulsion, Schizophrenia, T4, Paranoia, Hypochondria, and DHEAS. The findings were compared to a previous study of drug abuse (Nyborg, Larsen and Albeck, 1996), suggesting a number of communalities in the physiology, intelligence and personality of substance (ab)users.

ORAL COMMUNICATIONS XXIII

DRUG DEPENDENCE AMONG HOMELESS IN SYDNEY: PREVALENCE, DISABILITY, AND SERVICE USE

M. Teesson, T. Hodder, and N. Buhrich

National Drug and Alcohol Research Centre, University of New South Wales, Sydney

Objective: To study the prevalence, disability, psychiatric comorbidity and service utilization of homeless persons with Drug Dependence living in Sydney, Australia. **Method:** Two hundred and ten homeless men and women randomly selected from Sydney shelters and streets were interviewed using the Australian National Survey of Mental Health and Well-Being (NSMHWB) Interview. Diagnoses were based on a modified version of the Composite International Diagnostic Interview. The NSMHWB is the first survey to administer a structured psychiatric interview to a national probabilistic sample in Australia. This study is the first to apply the same national interview to a randomly selected homeless sample and compare the findings. **Results:** Over 40% of the homeless respondents reported a diagnosis of alcohol dependence or abuse in the past 12 months. Respondents with drug dependence had a high probability of carrying at least one other psychiatric diagnosis. Respondents with drug dependence were less likely to seek services compared to those without. Disability was higher in those respondents with co-occurring drug dependence compared to those without. **Conclusions:** The rates of drug dependence among the homeless is unacceptably high, drug dependence is often associated with other psychiatric disorders, disability and a propensity not to utilize health services. These results argue for the importance of more outreach services for drug dependence among the homeless.

GENDER DIFFERENCES WITHIN THE CRIMINAL JUSTICE SYSTEM: NEEDS VERSUS SERVICES

*S. Ring-Kurtz, J. Merrill, D. Carise, D. McKeon, and A. Harrell**

Treatment Research Institute at University of Pennsylvania, Philadelphia, PA and *Urban Institute, Washington, DC

The number of women entering the criminal justice system has been rising steadily in recent years, thus drawing attention to the difficulties women encounter, the services they need, and how women are different from men. Researchers recently have begun examining the experiences of the different genders in an effort to develop more gender specific methods of treatment that may improve outcomes and decrease recidivism. This paper presents preliminary data from three research projects. These studies include two evaluation projects conducted by the Treatment Research Institute in conjunction with the Urban Institute in Alabama (comparing 31 women and 161 men) and New York (N=96 women) and one descriptive study of a drug court in California (comparing 33 women and 105 men). Participants who were arrested and identified as substance users were administered the Addiction Severity Index (ASI). Initial findings support this study's gender difference hypothesis across several domains. Patterns of substance use differ between gender; typically, women use cocaine, whereas men are more likely to report smoking marijuana. Further, women who use drugs tend to have used them longer than men. Women use more health services and report greater difficulty with psychiatric issues. Finally, the data show that women report substantially more physical and sexual abuse than men. As society struggles with the increase in women entering the criminal justice system, learning more about gender differences could have policy implications and could help to tailor treatment to meet the specific needs of female criminal offenders.

WHO RESPONDS TO DRUG ABUSE TREATMENT? TYPES OF COURT-INVOLVED TEENS

V. Lidz, D. S. Festinger, D. B. Marlowe, E. Merikle, and J. J. Platt

Institute for Addictive Disorders, MCP-Hahnemann School of Medicine, Allegheny University of the Health Sciences, Philadelphia, PA

The present preliminary report examines the responses to substance abuse treatment among 44 adolescents ages 14 to 17, and on probation, who were referred to a 3 month day treatment program by Family Court or their probation officers. The subjects were 16.05 mean years of age; 91% male; 54.55% African American, 20.45% Latino, and 25.0% Caucasian; mean school grade was 9.05 and mean achievement level by Kaufman test was grade 7.18; full scale IQ was 86.84. Lifetime substance use included 100% marijuana, 86.11% tobacco, 69.44% alcohol, 33.33% barbiturates, 27.77% hallucinogens, and 11.11% cocaine. Use in 30 days prior to treatment entry was predominantly marijuana, with a mean of 20.52 days of use. Legal charges include 58.33% drug possession, 30.55% drug dealing, and above 15% for vandalism, robbery, assault, and auto theft, with 13.88% burglary. Forty-one per cent met criteria for conduct disorder. A regression for number of individual counseling sessions on largest number of consecutive clean urines by EMIT® had an R square of. 16 and $p<.05$. Regression of number of group therapy sessions on largest number of consecutive clean urines yielded an R square of .31, $p<.005$. Hierarchical regression of group and individual sessions on consecutive clean urines produced an overall R square of .33, $p<.05$, but showed only group sessions significantly related. Hierarchical regression of severity of drug use at baseline SCID, severity of conduct disorder by SCID, family conflict by Family Environment Scale (FES), and Family Control by FES produced an R square of .3112. Statistical significance was reached by conduct disorder ($p=.030$) and family control ($p=.025$) but, surprisingly, not drug severity and family conflict.

PREDICTORS OF HEALTH SERVICE UTILIZATION OF SUBSTANCE ABUSERS WITH HIV INFECTION

C. Masson, J. L. Sorensen, K. L. Delucchi, C. S. Phibbs* R. L. Okin, J. W. Dilley, and M. Jacoby

University of California, San Francisco and *Palo Alto VA Medical Center

We assessed the contribution of depression and risky injection behaviors on subsequent use of health care services by 86 out-of-treatment substance abusers with HIV infection. Participants were enrolled in the usual care arm of a randomized controlled trial of case management. Health service utilization including emergency and inpatient services were obtained pre-enrollment and during the year of enrollment in the study from a review of computerized records. Beck Depression Inventory scores and risky injection drug use behaviors were used to predict use of health care services during the year of enrollment in the study controlling for age, ethnicity, pre-enrollment health service utilization, health status, and homelessness. Preliminary findings suggest that pre-enrollment health service utilization is a strong predictor of the future use of health care services. Depression and risky injection drug use were not found to be significant predictors of the use of health care services. Together, these findings suggest that a review of health care service records may be helpful in identifying substance abusers with HIV infection who are in need of evaluation and referral to substance abuse treatment systems.

ACKNOWLEDGMENTS: Supported by NIDA R01DA08753 and P50DA09253

DOES CENTRALIZED INTAKE AFFECT CLIENT OUTCOMES?

J. Guydish, M. Chan, C. Ponath, and B. Tajima

Institute for Health Policy Studies, University of California, San Francisco, CA

As part of the national Target Cities Demonstration Project, San Francisco implemented centralized intake in its publicly-funded drug abuse treatment system. Clients who entered 6 treatment programs through the centralized intake unit (CIU group, n=200) were compared to clients who entered the same programs through usual routes (non-CIU group, n=267). Participants were interviewed at the time of admission, and at 1 month and 12 month follow-up. Outcome measures were the 7 composite severity scores derived from the Addiction Severity Index (ASI), the Beck Depression Inventory, the Brief Symptom Index, and a measure of social support. At baseline, the CIU group had greater severity of employment ($t=-2.61$, $p < .01$) legal ($t=-2.01$, $p < .05$) and psychological problems ($t=-2.37$, $p < .05$), more psychiatric symptoms ($t=-2.72$, $p < .01$), and less social support ($t=4.53$, $p < .001$). The CIU was attracting and serving a more severely disordered client population. At 1 month follow-up, both groups showed significant improvement on ASI measures of legal, alcohol, and drug problems, and on measures of depression, psychiatric symptoms, and social support. ANCOVA analyses controlling for baseline differences between groups showed that level of improvement did not differ by group. This effort at systemic change may have resulted in better access to treatment as well as equivalent short-term (one month) outcomes for the more severe client population.

ACKNOWLEDGMENT: Supported by CSAT grant # U95-T100669.

METHODS TO PROMOTE TRANSITION FROM INPATIENT DRUG DETOXIFICATION TO OUTPATIENT AFTERCARE TREATMENT

M. L. Stitzer, M. A. Chutuape, and K. Gruber

Department of Psychiatry, Johns Hopkins University School of Medicine, Baltimore, MD

Outpatient aftercare treatment followingresidential drug detoxification is considered essential to achieve long-term benefits of treatment. However. drug abusers infrequently engage in aftercare treatment (mean transition rate from studies in literature is 35%). Initial contact with the aftercare program represents the first step in the transition process. This ongoing study examines interventions designed to enhance the rate of contact with an outpatient aftercare program following treatment at a 3-day inpatient drug detoxification unit. The referral aftercare program was located approximately 3.5 miles from the detox unit. All study patients were provided with a pass for the shuttle service operating between the two campuses to ensure equivalent access. Prior to discharge. patients were randomly assigned to one of three referral conditions: (1) Staff escort + incentive - patients received a personal escort to the program plus 10 bus tokens after completing intake procedures; (2) Incentive at the program - patients received 10 bus tokens if they showed up at the aftercare clinic on day of discharge and completed the intake process; and (3) Standard referral - patients received information about the aftercare program and shuttle service. The sample (N=116) has a mean age of 38, and is 69% male and 77% African-American. Multiple drug use is the norm; 83% used heroin, 67% used cocaine and 78% used alcohol. Preliminary results show that 77%, 45% and 28% of patients in Staff escort + incentive, Incentive and Standard referral conditions, respectively, completed intake at the aftercare program on day of discharge. At present, only the difference between escort plus incentive versus standard care is statistically significant. These results suggest that transition to outpatient aftercare can be improved. with staff escort plus incentive being one effective method. Results from this and previous studies suggest that the inclusion of staff contact in the intervention may be important for efficacy. Results from this study will provide practical information on methods to enhance treatment program transitions.

ACKNOWLEDGMENT: Supported by NIDA grant R01-DA10192.

MEDICAL VAN OUTREACH TO HOMELESS SUBSTANCE ABUSERS

H. McQuistion, A. Rosenblum, L. Nuttbrock, S. Magura, H. Joseph**, S. Anderson*, and M. Marthol*

***Project Renewal, New York, NY; National Development and Research Institutes, Inc., New York, NY; and **New York State Office of Addiction and Substance Abuse Services, New York, NY**

Objectives: To conduct an evaluation of mobile medical (van) outreach services for homeless substance users with the addition of intensive case management (ICM) as an experimental service enhancement. **Van population:** In 1997, there were 1,709 client visits. This represented 1,048 distinct clients since some persons had multiple visits during this period. The most frequent presenting problems and diagnoses (by client) were for respiratory (42%), skin (33%), substance abuse/psychiatric (30%), and cardiovascular (24%) problems. Mean age was 40; 84% men; 72% African American and 18% Hispanic. **Study subjects:** Seventy-five percent using cocaine (by hair analysis), 16% HIV + and 30% hepatitis C +. Experimental Ss are provided ICM (comprehensive needs assessment, multiple sessions, and incentives for service engagement). Case management services w/o incentives are available to control subjects but controls must make a request to receive **them.** Among the 49 ICM clients, there was a mean of 1.29 referrals arranged and .92 completed referrals; Controls (N=51) had a mean of .58 referrals and .38 completed referrals. **Conclusion:** ICM, which involves immediate availability of on-site case management services in conjunction with the on-going medical van operation, shows promise of successfully referring highly impaired individuals for additional services and treatment. Substance abuse treatment may be the first practical step in accessing more traditional health services for some homeless people. The utility of mobile medical vans as an outreach strategy for homeless substance users warrants additional investigation.

ACKNOWLEDGMENT: Supported by NIDA grant No. RO1 DA10431.

THE DRUG EVALUATION NETWORK STUDY; A NATIONAL ADDICTION TREATMENT INFORMATION SYSTEM

D. Carise, A. T. McLellan, L. S. Gifford, and H. D. Kleber

Treatment Research Institute at University of Pennsylvania, Philadelphia, PA

The Drug Evaluation Network Study (DENS) is an ongoing, nationwide electronic system providing standardized, timely, clinical and administrative information on substance abuse treatment programs and their patients. Four types of treatment modalities are represented: methadone maintenance, inpatient/residential, outpatient and intensive outpatient abstinence oriented. The Addiction Severity Index (ASI) is the primary source of data collection. The system allows for the electronic addition of 35 questions based on issues of contemporary concern. These questions can be added or changed monthly. All data are non-identifying, and the data set is in the public domain. Thirty-four treatment programs, representing the four modalities, in five major metropolitan areas across the country have been piloting the system. Data are collected on lap-top computers during clinical interviews, and transmitted biweekly via modem resulting in "real-time" tracking of trends in the addictions field (data presented at CPDD will reflect approximately 4,000 treatment admissions up to the week prior to the conference). The presentation will include the development and pilot testing of DENS and results from data collected since July 1996. Planned expansion of the DENS system into 100 **randomly selected** treatment programs will also be discuss

CHARACTERISTICS OF ILLEGAL DRUG USERS PRESENTING TO AN EMERGENCY DEPARTMENT

J.-M. Hirshon, W. F. Atha, N. J. Carriero, L. Bowser, C. T. Morrow*, and D. A. Gorelick*

NIH/NIDA Intramural Research Program, Baltimore, MD and * Johns Hopkins Bayview Medical Center, Baltimore, MD

Consequences of illegal drug use are a common reason for presentation to an emergency department (ED). We evaluated the characteristics of such patients by retrospective chart review of all 827 patients coming to the ED of an urban teaching hospital between June, 1992 and December, 1993 (except March, 1993), who met Drug Abuse Warning Network criteria (age $\geq$ 6 years, use of an illegal drug or non-medical use of a legal drug). Only a patient's first visit during the period was included. Illegal drugs were reported used by 573 (69.3%) patients: cocaine by 398 (48.2% of total sample; cocaine only by 211 [25.5%], with heroin by 107 [12.9%]), heroin by 271 (32.8%; heroin only by 122 [14.8%]), phencyclidine (PCP) by 39 (4.7%), marijuana (MJ) by 35 (4.2%), and LSD by 10 (1.2%). Only 22 patients used only MJ, PCP, or LSD. Illegal drug users were more likely to be male, but didn't differ from other patients in age (mean [SD] for all patients = 31.6 [9.7] years). The majority of illegal drug users presented to the ED between noon and midnight (as has been reported in other studies), except for the MJ/PCP/LSD group, which tended to present in the morning. Among illegal drug users, there were significant differences by drug group in age (MJ/PCP/LSD group youngest [27 yrs]), race (MJ/PCP/LSD group 95% white), means of arrival at ED (cocaine only group more likely to have walked in), and duration of visit (heroin only group shorter [4.1 hours]), but no significant differences in sex or marital status. The majority of cocaine and heroin users reported using the drug because of dependence and presenting to the ED seeking detoxification, while psychic effects ("high") was the commonest reason given for use of marijuana and LSD and drug overdose the commonest reason for ED presentation. Only two illegal drug users died (both cocaine users). These findings suggest that the physical dependence liability of illegal drugs is a major influence on why users present to an ED. Limitations of this study include reliance on patient self-report (no toxicology) and only one hospital site.

ACKNOWLEDGMENT: Supported by NIDA intramural funds.

POSTER SESSION I

COST-EFFECTIVENESS OF TUBERCULOSIS SCREENING AND OBSERVED PREVENTIVE THERAPY FOR DRUG INJECTORS AT A SYRINGE EXCHANGE

D. C. Perlman, M. N. Gourevitch,* and N. Salomon

Beth Israel Medical Center, New York, NY and *Montefiore Medical Center, Bronx, NY

Objective: To define whether the costs associated with tuberculosis (TB) screening and directly observed preventive therapy are justified by cases and costs of TB prevented among drug injectors attending a syringe exchange program. **Methods:** We examined program costs and projected savings using actual program rates for voluntary acceptance of TB screening (95%) return rates for skin test interpretation (94%), HIV prevalence (20%), PPD reactivity (14%) and anergy (2%), chest x-ray (CXR) referral adherence (31%), and program costs (staff, supplies. rent, overhead, liver function tests, CXRs, isoniazid (INH), monetary incentives for skin testing) along with conservative literature estimates of INH preventive therapy efficacy. expected rates of INH hepatotoxicity, and incidence and costs of treating active TB (using cost data and not charges). **Results:** For a hypothetical 1000 patients offered screening, the program costs were $14,213 per case of TB prevented, preventing $141,505 in TB treatment costs for a net savings of $84,653. While the real program rates of nonacceptance of screening (5%) and not returning for skin test interpretation (6%) are low and therefore have limited impact on estimated program cost effectiveness, the lower rates of adherence to CXR referral resulting in ineligibility for chemoprophylaxis more significantly affected program outcomes. We modeled the potential impact of a monetary incentive to increase CXR referral adherence. If incentive costs of $35 per person were included for all PPD (+) and anergic subjects, and if CXR referral adherence increased to 50% as a result, the number of TB cases prevented would increase 50% and net cost savings would increase by 64% (from $84,653) to $131,625. If the incentive intervention increased CXR adherence to 80%, estimated net savings would be $199,711. **Conclusion:** TB screening and observed preventive therapy at a syringe exchange is a cost-effective intervention. This cost model is useful in evaluating the potential cost impact of planned program refinements which can then be tested. The use of monetary incentives for those referred for screening CXRs would be justified on a cost basis if it had even a modest beneficial impact on adherence.

BEHAVIORAL RISK FOR HIV IN INJECTION DRUG USERS IN JAPAN

T. M. Sartkary, H. Ohashi, and K. Soda

Department of Epidemiology, University of California, Los Angeles; Medical Care Division, Correction Bureau, Ministry of Justice, Tokyo, Japan; and Dept. of Public Health, Yokohama City University School of Medicine, Yokohama, Japan

In contrast to other countries, the estimated 500,000 IDUs in Japan mostly use methamphetamines and few have been reported as HIV positive. We studied for the first time the HIV risk and reasons for needle sharing among non-hospitalized IDUs using an anonymous survey of the behavior over the past year of all men with a drug history entering two facilities May-Aug. 1996. Of the IDUs (n=157), 95% were Japanese, most aged 20-40 years. Factors promoting HIV transmission: needle-sharing (89%) and having experienced-IDU sharing-partners (89%). Limiting transmission: having only 1-3 partners (89%) and having no foreign partners (91%). Only 61% knew of the HIV risk from needle sharing. Reasons for sharing: 30% “needles hard to get”; 31% “water cleaned”; and others. Only 4.1% always used a condom. Of the 125 (80%) that paid for sex, 80% had unprotected sex. Four of 20 who answered (20%) had male/male sex (3 of the 4 had unprotected sex with (10 partners). Only 40% had an HIV test. Surprisingly, 2% (95% CI = 0.4-4.9%) reported being HIV+. IDUs in Japan have under-recognized HIV risk from sharing needles and from unsafe sex that bridges to the general public and may pose a danger of an expanding epidemic in the future. HIV education targeted to IDUs is greatly needed.

ACKNOWLEDGMENTS: Supported by NIDA training grant #T32 DA 07266 and JSPS-Fogarty International.

SUBTYPING RISKS FOR HIV INFECTION AMONG DRUG USERS: A LATENT CLASS ANALYSIS OF DRUG AND SEX BEHAVIORS

A. B. Abdallah, L. B. Cottler, W. M. Compton, and S. M. Woodson

Department of Psychiatry, Washington University School of Medicine, St. Louis, MO

Most previous research on HIV-related public health programs for drug users emphasized the need for successful intervention prevention strategies to be tailored for specific populations. Therefore, methods for identification of subtypes of HIV risk behaviors are needed. This presentation illustrates the use of Latent Class Analysis (LCA) to classify out-of-treatment drug users into homogenous classes or "case types" based on their self-reported drug use and sexual behaviors. The data for this illustration were derived from the NIDA-funded St. Louis EachOneTeachOne (EOTO) study, one of the multi-site Cooperative Agreement Projects. The sample was randomly divided into halves. The first half was used for the LCA model estimation and to test the sensitivity of the model specification to random variation in the data. The second half of the sample was used in a confirmatory fashion to establish the reliability of the LCA classification system. In this assessment the focus was on behaviors over the past 30 days and only variables measuring frequency of use or practices were used. The selected variables were grouped into twenty scales across five domains, including substance use, drug injection, injection needle practices, general sex activities and other sex practices. Each scale was defined with three levels: lower risk, moderate risk, and higher risk. These scales were used to estimate the parameters of 1- to 12-class models, using methods of unrestricted LCA. The results strongly support the existence of four subgroups of drug users based on their self-reported HIV risk behaviors: 1) Non-injecting drug users with lower risk sex activities, 2) Non-injecting drug users with medium to higher risk sex practices, 3) Drug injectors with medium to higher injection needle practices and lower risk sex activities, and 4) Drug injectors with medium to higher injection needle practices and medium to higher risk sex practices. Sensitivity tests suggested that this 4-class model is very stable. Confirmatory tests were also investigated and showed that the model is reliable. To illustrate the use of the LCA classification, an evaluation of the 3-month change in behaviors among EOTO subjects across the four classes was performed. Suggestions on how to use the results of this classification for planning and evaluating HIV intervention protocols are discussed.

ACKNOWLEDGMENTS: Supported by the NIH, NIDA grant DA08324.

BELIEFS ABOUT CONDOMS AND CONDOM USE AMONG DRUG USERS

S. Tortu, J. McMahon, S. Deren, and M. Beardsley

National Development and Research Institutes, New York, NY

Introduction: This study focused on sexual risk for HIV infection among injection drug users and crack users. We examined demographic and cognitive predictors of condom use with “main” partners (e.g., spouse, “living with”) and casual partners. The sample (n=850) was: 71% male; 57% black, 36% Latino; 40% IDU; 78% unmarried, with drug use verified by urinalysis. After conducting a structured interview (the Risk Behavior Assessment with Condom Beliefs and Behavior Supplement), we offered HIV counseling and testing to all respondents. Independent variables were: demographics; HIV serostatus; nine beliefs about condom use. The dependent variable was “use of condoms in prior 30 days” with main and casual partners. Logistic regression assessed predictors of condom use separately for “main” and “casual” partners. **Results:** 1) With main partners only, HIV seropositivity predicted consistent condom use (OR= 8.67); 2) with both main and casual partners, six beliefs about lack of sexual intimacy and pleasure, decreased partner satisfaction, and inconvenience were associated with reduced condom use (at .05, or better); two beliefs about the threat of AIDS/other diseases were not associated with condom use. **Conclusions:** Interventions focused on sexual risk among drug users must address those aspects of the belief structure which lead to a negative perception of condoms and reduced condom use with both main and casual partners.

LEVEL OF EDUCATION AND INJECTING DRUG USE AMONG AFRICAN AMERICANS

I. S. Obot, S. Hubbard, and J. C. Anthony

Johns Hopkins University, School of Hygiene and Public Health, Baltimore, MD

Drawing upon a nationally representative survey sample of African American (AA) drug injectors and non-injectors, this study tests for a suspected causal association between dropping out of school and the occurrence of injecting drug use (IDU), which remains a major cause of HIV transmission in this population. The data are from public use files of the National Household Surveys on Drug Abuse (NHSDA) conducted between 1991 and 1995. From within the NHSDA's nationally representative sample of adult household residents, a total of 389 African American adults with a history of IDU were matched on neighborhood of residence with 2253 African American adults with no history of IDU. The conditional form of multiple logistic regression was used to estimate the relative risk of having injected a drug for school dropouts relative to a reference category of AA who received the high school diploma but did not go to college. African Americans who dropped out of high school were an estimated 1.9 times more likely to have injected drugs. With statistical adjustment for age, sex, and Hispanic background, the estimated association was 1.8 (95% CI = 1.3, 2.4; $p < 0.001$). Contrary to our advance hypothesis, earning the GED did not seem to affect the magnitude of dropout-associated excess risk for having started IDU (adjusted OR = 2.0, CI = 1.3, 3.2; $p < 0.003$). Hence, school dropout prevention might reduce the risk of IDU per se, in addition to the many other general benefits of educational attainment. The issue of GED-associated reduced risk of IDU remains open for future study.

ACKNOWLEDGMENTS: Supported by NIDA grants T32-DA07292 and DA 09592.

IMPULSIVITY AND NEEDLE USE: DELAY DISCOUNTING METHODS

W. K Bickel and G. J. Madden

Departments of Psychiatry and Psychology, University of Vermont, Burlington, VT

A concern in the spread of HIV/AIDS is needle-sharing among intravenous drug users. These drug users may frequently choose between injecting drugs now with a borrowed needle, versus waiting to use drugs until a clean needle can be found. Our prior research suggests that opioid-dependent individuals make impulsive choices (like needle-sharing) because they discount delayed rewards far more than do nondrug users. In the present study, heroin-dependent outpatients were given four series of choices between hypothetical rewards. In series one, subjects chose between $ 1,000 delivered after seven different delays, and money delivered immediately. At each delay, the amount of the immediate reward was adjusted until subjects were indifferent between the immediate and delayed rewards. This provided a measure of the value of each delayed reward. The same procedures were used in series two through four, with heroin serving as the rewards. In these series, subjects were instructed that if they chose to use heroin now they must inject it either with (a) a clean needle (series 2), (b) a needle borrowed from a friend who they believed did not have AIDS (series 3) or(d) a needle borrowed from a stranger (series 4). Choices were well described by hyperbolic discounting functions and delayed heroin was discounted at a significantly higher rate than delayed monetary rewards. Risk of contracting HIV affected the rate at which delayed heroin was discounted as most subjects preferred delayed heroin when using heroin now required needle sharing. Of those subjects who reported they would needle share, only using a stranger's needle significantly affected discounting. Subjects who would not needle share tended to discount money and heroin at more disparate rates than subjects who would needle share.

ACKNOWLEDGMENTS: Supported by NIDA grants DA06526 and DA07242.

NOVELTY SEEKING AND HIGH RISK BEHAVIOR IN THE TREATMENT OF HEROIN DEPENDENT POLY-DRUG ABUSERS

T. Helmus, K. K. Downey, G. Rhodes, J. A. Hopper, and C. R. Schuster

Wayne State University School of Medicine, Department of Psychiatry and Behavioral Neurosciences, Clinical Research Division on Substance Abuse

This study examined novelty seeking and HIV high risk behavior in relation to early treatment retention and abstinence among heroin dependent poly-drug abusers treated with buprenorphine (BUP). We evaluated the first five weeks of participation in a 29 week BUP trial. Variables assessed included the frequency of route of drug administration (previous six months), the Tridimensional Personality Questionnaire (TPQ), and the HIV Risk Assessment Battery. For all participants (n=41), variables with a significant relationship with retention were entered into a logistical regression analysis. Similarly, for those completing week 5 (n=29), variables related to the number of opiate, cocaine or poly-drug negative urines were entered into a multiple regression analysis. Results showed that high scores on the TPQ Novelty Seeking scale (NS) significantly predicted retention. Of those retained, high risk sexual behaviors and high NS significantly predicted opiate abstinence. High frequency of IV cocaine use significantly predicted cocaine abstinence and high NS significantly predicted poly-drug abstinence. The results suggest that measures of thrill seeking behavior are associated with retention and positive outcome in poly-drug abusers treated with BUP. These results, though counter-intuitive, may be associated with BUP's novelty in the Detroit area, thus attracting and retaining those willing to try an "experimental" medication.

ACKNOWLEDGMENT: Supported by NIDA grant 5 RO1 DA 10816-02.

THE EFFECT OF ACCESSING HEALTH SERVICES ON HIV RISK BEHAVIORS IN A COHORT OF HIV INFECTED DRUG USERS

*R. E. Booth, C. F. Kwiatkowski, and G. Weissman**

University of Colorado School of Medicine, Denver, CO and *Health Resources and Services Administration, Rockville, MD

This study was designed to assess change in health-related service utilization by HIV infected drug users, change in HIV risk-related behaviors, and the relationship between service utilization and risk behaviors. HIV infected injection drug users and crack smokers (N=777) from five US cities were assessed one year before and two years after Ryan White Title I funds, for people infected with HIV, were made available. Respondents were surveyed about use of drug treatment, medical services, housing, mental health, and case management and about their drug and sex risk behaviors. Utilization of medical, housing and case management services increased, while little change was observed in use of drug treatment and mental health services. Sex and drug risk behaviors declined. Overall receipt of services was significantly associated with lower risk behaviors, as was the interaction between time and services received. Risk behaviors did not significantly decrease over time except among those receiving heath-related services. These findings support the protective effect of utilization of health-related services by HIV-infected drug users.

ACKNOWLEDGMENT: Supported by the NIDA grant and Health Resources Services Administration.

CASE MANAGEMENT OF SUBSTANCE ABUSERS WITH HIV/AIDS: PRELIMINARY RESULTS

J. L. Sorensen, J. Dilley, K Delucchi, M. Miller, J. London, C. Masson, C. Phibbs, and R Okin*

University of California, San Francisco, San Francisco, CA, and *Palo Alto Veterans Affairs Medical Center, Menlo Park, CA

Case management is a promising intervention that has not been sufficiently tested with substance abusers. We report preliminary outcomes from a clinical trial of case management with HIV+ substance abusers. One hundred ninety HIV+ substance abusers were recruited from those receiving treatment at a public general hospital. Participants were randomly assigned to case management (n=92) or usual care (brief contact and referral). Case management occurred for 12 months; follow-ups were at 6 and 12 months (presented here), and 18 months after intake. Outcomes are available to date for the 6 and 12-month follow-ups. By the 12-month follow-up, 24 participants had died, and 149 participants (90% of those living) were interviewed. The behavioral measure showed a treatment effect: In urine toxicology screens for opioids, at baseline 66% of the Usual Care and 58% of the Case Management participants tested positive for opioids (p=n.s.). At Month 6, 47% of the Usual Care and 27% of the Case Management participants tested opioid positive (p=.009), and at 12 months 43% of the Usual Care and 31% of the Case Managed participants tested opioid positive (p=.13). On measures based on interviews there was improvement in several areas from baseline to Month 6, but it was equal for the two treatment groups. Results to date are mixed. Continued analysis and extended follow-up in this study will provide more a more definitive view of the efficacy and limitations of this treatment approach with substance abusers who have HIV/AIDS.

ACKNOWLEDGMENTS: Supported by NIDA RO1DA08753 and P50DA09253.

THE PREVALENCE OF PSYCHOLOGICAL DISORDERS IN HEROIN DEPENDENT, HIV INFECTED PATIENTS

M. J. Tucker, A. Umbricht, and K. L. Preston

NIDA Intramural Research Program, Baltimore MD

With declining health status, HIV-infected patients experience severe psychological distress. Heroin dependence is also associated with psychological distress. The psychological status of HIV-infected heroin users with an acute medical illness has not been evaluated. **Purpose:** To assess psychological status of heroin dependent AIDS patients enrolled in a detoxification study, while hospitalized for an acute illness. **Methods:** Fifty-nine patients were screened (questionnaire and urine) for opioid dependence within 24 hours of admission and enrolled in an opioid detoxification study. Psychological measures included the Addiction Severity Index (ASI, N = 45), the Short Beck Depression Inventory (SBDI), and the modified Wisconsin Pain Questionnaire (WPQ part C). **Results:** On ASI: 52% of patients reported a history of serious depression, with 37% reporting past suicidal ideation, and 12% actual suicide attempts; 51 % reported serious tension or anxiety, and 55% concentration difficulties. Within the last 30 days, 32% of patients reported serious anxiety and depression and 43% concentration difficulties. Although 36% were concerned by these psychological problems, only 24% believed that they required treatment. At the time of enrollment, 32% were classified as clinically depressed by SBDI, more than half reported that both, pain and HIV. interfered with their mood (77% and 65%, respectively) (MWPQ C). More than half HIV-infected, opioid dependent drug users report past or current psychological disorders. The prevalence of such disorders does not appear to be higher than the non HIV infected, opioid dependent, illicitdrug-users.

SEX DIFFERENCES IN K OPIOID AGONIST-INDUCED DIURESIS

R. M. Craft and D. J. Raub

Department of Psychology, Washington State University, Pullman, WA

We previously reported that the diuretic effects of the selective κ opioid agonist U69,593 were significantly greater in male than in female rats (Kruzich et al., 1997, CPDD abstracts, p.85). The present study was conducted to determine the generality of this sex difference; thus, diuretic effects of several other κ agonists were compared in male vs. female, adult Sprague-Dawley, normally hydrated rats. Although males weighed approximately 60% more than females did, urine output within the 2-hr sampling period did not differ between males and females treated with vehicle (1 ml/kg). Although the κ agonist butorphanol (0.3-3.0 mg/kg) produced approximately equivalent diuresis in males and females, U69,593 (0.03-3.0 mg/kg), U50,488 (0.3-10 mg/kg), (-)-bremazocine (0.001-0.03 mg/kg) and (-)-pentazocine (1.0-10 mg/kg) all produced significantly greater diuresis in males than in females, as did the non-opioid diuretic furosemide (1-10 mg/kg). However, when data were corrected for sex differences in body weight, 4 of 5 κ agonists produced slightly to significantly greater diuresis/kg in females than in males. The μ agonist morphine produced equivalent anti-diuretic effects in females and males, suggesting that any sex differences in diuretic effects of the κ agonists are not due to μ receptor-mediated effects. Because κ agonists are known to produce diuresis by inhibiting vasopressin release, it is hypothesized that sex differences in diuretic effects of κ opioid agonists may be attributed to the fact that males have significantly higher vasopressin levels than females do. In support of this hypothesis, there was no sex difference in diuresis per kg produced by the non-opioid diuretic, furosemide, which acts via a mechanism that does not involve vasopressin.

ACKNOWLEDGMENT: Supported by NIDA grant DA10284 (RMC).

ANTINOCICEPTIVE EFFECTS OF K OPIOIDS IN MALE VS FEMALE RATS

S. A. Bernal, L. M. Heiderman, and R. M. Craft

Department of Psychology, Washington State University, Pullman, WA

Several investigators have shown that male rodents are more sensitive than females to the antinociceptive effects of mu opioid agonists. The present study was conducted to determine the generality of this sex difference by examining the antinociceptive effects of primarily kappa opioid agonists in female vs. male Sprague-Dawley rats: U69,593 (0.03-0.3 mg/kg), U50,488 (1.0-5.6 mg/kg), (-)-bremazocine (0.003-0.03 mg/kg), (-)-pentazocine (1.0-30 mg/kg), butorphanol (0.1-10 mg/kg), ethylketazocine (0.01-0.1 mg/kg) and nalbuphine (3.0-30 mg/kg). Complete dose- and time-effect curves were obtained for each drug on the 50°C hotplate and warm water tail withdrawal assays. On the hotplate assay, nalbuphine produced significantly greater antinociception in males than in females; additionally, there were sex differences at some doses and/or timepoints for U69,593, U50,488, (-)-bremazocine and (-)-pentazocine. On the tail withdrawal assay, U50,488, (-)-pentazocine and butorphanol produced significantly greater antinociception in males than in females; additionally, there were sex differences at some doses and/or timepoints for U69,593 and nalbuphine. Most agonists produced dose-dependent decreases in spontaneous locomotor activity measured 32-52 min post-injection; however, U50,488 and ethylketazocine produced greater decreases in males than in females, and nalbuphine produced greater decreases in females than in males. Thus, sex differences in antinociception were observed for 6 of 7 opioid agonists on at least one assay at one or more doses and timepoints. Neither sex was consistently more sensitive than the other to antinociceptive or sedative effects of these agonists, and sex differences in antinociceptive effects did not appear to be secondary to sex differences in sedative effects of these agonists.

ACKNOWLEDGMENT: Supported by NIDA grant DA 10284 (RMC).

NO SEX DIFFERENCE IN *KAPPA* OPIOID-INDUCED ANTINOCICEPTION IN MICE

C. A. Patrick, M. C. Ko, J. L. Clemente, and J. H. Woods

Departments of Psychology and Pharmacology, University of Michigan, Ann Arbor, MI

A recent clinical report suggested that *kappa* opioids such as butorphanol and nalbuphinc produce greater analgesia in women than in men. However, both compounds have been characterized as mixed *mu/kappa* opioids in rodent and monkey studies. The aim of this study was to evaluate whether there are sex differences in antinociception caused by butorphanol and nalbuphine as well as more selective *kappa* opioids. Two selective *kappa* opioids (U50,488 and CI-977) and butorphanol as well as nalbuphine were characterized in male and female Swiss-Webster mice by utilizing the acetic acid-induced writhing assay and the warm water (48°C) tail-withdrawal assay. In the writhing assay, all compounds (U50,488: 1-10 mg/kg; (CI-977: 0.01-0.1 mg/kg; butorphanol: 0.032-0.32 mg/kg; nalbuphine: 1-320 mg/kg) dose-dependently inhibited writhing, but there were no sex differences found when comparing ED_{50} values. In the tail-withdrawal assay, U50,488 (10-100 mg/kg) and CI-977 (0.1-3.2 mg/kg) also dose-dependently produced antinociception, although there were no sex differences observed. Nalbuphine (10-320 mg/kg) did not have antinociceptive effects under this condition. On the other hand, butorphanol (0.32-32 mg/kg) produced greater antinociception in male (50% MPE) than female mice (20% MPE). Pretreatment with either the selective mu antagonist β--funaltrexamine or the selective *kappa* antagonist nor-binaltorphimine dose-dependently antagonized butorphanol. Under these conditions, sex differences in response to selective *kappa* opioids in mice were absent.

ACKNOWLEDGMENT: Supported by USPHS grant 00254.

DOPAMINE RELEASE AND UPTAKE ARE GREATER IN STRIATAL SLICES OF FEMALE RATS

Q. D. Walker, M. Bunin, R. M. Wightman,* and C. M. Kuhu*

Department of Pharmacology and Cancer Biology, Duke University Medical Center, Durham, NC and *Department of Chemistry, University of North Carolina, Chapel Hill, NC

We have demonstrated using in vivo cyclic voltammetry that dopamine (DA) release and uptake in the caudate-putamen of female rats are significantly greater than in males. The present studies have tested the hypothesis that release and uptake arc also greater in striatal slices of female rats *in vitro.* This paradigm uses local electrical stimulation of striatum to elicit increases in extracellular DA. A carbon-fiber disk electrode was placed 75 μm below the surface of caudate slices, approximately 200 - 250 μm from the tips of a bipolar stimulating electrode. The maximal DA concentration (DA_{max}) induced by single pulse stimulations (4 msec biphasic, 300 μA) served as an index of release. The maximal rate of DA clearance following 10 pulse at 10 Hz stimulus trains indicated V_{max}. DA release was significantly greater in females than males (3.22 ± 1.08 vs. 1.29 (0.24 μM, $p<0.05$). The V_{max} for DA uptake was 5.48 ± 1.79 and 2.25 ± 0.41 μM/sec in female and male slices, respectively ($p<0.05$). These quantitative relationships are very similar to those determined in intact, anesthetized rats. A qualitative difference in the shape of DA overflow curves was also found. Ten pulse stimulus trains at 10 Hz produced peak [DA] after about 3 to 5 pulses followed by decreasing DA through the end of the train in male slices. However, identical stimulations in the medial caudate of female slices always resulted in increasing [DA] through the end of the stimulus train. To test the possibility that autoreceptors could be mediating this phenomenon, rats were administered 0.5 mg/kg haloperidol *in vivo.* Stimulated DA release following haloperidol was greater in female that male rats. These gender differences in the regulation of extracellular DA may mediate gender differences in cocaine-induced locomotor activity in rats and may have broader implications for substance abuse and neurological disorders such as schizophrenia, Parkinson's disease and depression.

ACKNOWLEDGMENT: Supported by DA 09079.

AN ELECTROPHYSIOLOGIC STUDY OF VENTRAL TEGMENTAL AREA DOPAMINE NEURONS IN MALE VS. FEMALE RATS

D. R. Woolfolk, A. C. McCreary, and K. A. Cunningham

Department of Pharmacology and Toxicology, University of Texas Medical Branch, Galveston, TX

Studies indicate that gender may be a factor in the sensitivity of individuals to some behavioral effects of psychostimulants such as cocaine. This difference could be attributable to gender differences in the activity or responsiveness of dopamine (DA) neurons which provide innervation to limbic nuclei that are critically implicated in mediating the locomotor, discriminative stimulus, and reinforcing effects of cocaine. *In vivo* extracellular recording techniques can be used as tools to measure the electrical events that underlie the cellular, and presumably the behavioral, effects of cocaine. Most electrophysiological studies have utilized male rats, and we have begun to compare the activity of DA neurons in the ventral tegmental area (VTA) of anesthetized male Sprague-Dawley rats to that of intact and ovariectomized (OVX) female rats. VTA DA cells were found 3.0-3.5 mm anterior to the interaural line, 0.5-0.8 mm lateral to the midline, and 6.5-8.5 mm ventral to brain surface. Our data suggest that the basal characteristics of the VTA DA neurons in males, intact females and OVX females are similar. Likewise, somatodendritic autoreceptor tone of VTA DA neurons, as assessed by the inhibitory effects of the D_2/D_3 DA receptor agonist quinpirole (2-64 (g/kg, i.v.), did not differ in male and intact female rats. Cocaine (0.0625-4 mg/kg, i.v.) partially inhibited the firing of VTA DA neurons in male and OVX female rats; however, doses up to 1.0 mg/kg tended to enhance VTA DA cell firing in intact female rats (n=4), but the effect did not reach statistical significance. Although preliminary, the data suggest that the presence of female steroid hormones may contribute to the differential effect of cocaine on VTA DA neurons in intact females vs. males and could plausibly explain the increased sensitivity of intact females to the motor-activating effects of cocaine.

ACKNOWLEDGMENTS: Supported by NIDA DA06511 and DA00260.

THE INFLUENCE OF OVARIAN HORMONES ON THE ACUTE LOCOMOTOR RESPONSE TO COCAINE IN FEMALE RATS

S. L. Sell, J. M. Scalzitti, M. L. Thomas, and K. A. Cunningham

Department of Pharmacology and Toxicology, University of Texas Medical Branch, Galveston, TX

The ovarian hormones estrogen (E) and progesterone (P) may influence the responsiveness of female rats to cocaine. We assessed this hypothesis by measuring the acute locomotor response of intact and ovariectomized (OVX) female rats to doses of cocaine and under different hormonal environments. A cocaine dose-response curve (2.5-10 mg/kg) for locomotor activity was established in intact and OVX female rats (n=6-8/group). Acute cocaine increased activity in a dose-dependent manner in both groups ($p<.001$). A tendency toward a diminished locomotor response was observed in OVX compared to intact females ($F_{1,14}=3.53$, $p=0.081$). Subsequently, 48 female rats were OVX or OVX and implanted with E, P, or E+P. Following 1 hr of habituation to the activity chambers, the rats received saline or 5 mg/kg cocaine. Locomotor activity was monitored for 2 hrs following injection. Upon administration of saline, the OVX group exhibited reduced levels of activity in comparison to all OVX+hormone treatment groups ($F_{3,20}=4.85$, $p=0.0108$). Upon injection of cocaine, OVX rats treated with E or E+P exhibited higher levels of activity than OVX or OVX+P rats ($F_{3.20}=4.90$, $p=0.0103$). These data demonstrate that E potentiates the response to cocaine in OVX rats, and may account in part for the dramatic hyperactivity observed in response to cocaine administration in intact female rats.

ACKNOWLEDGMENTS: Supported by NIDA DA06511 and DA00260.

THE GENDER-SPECIFIC PSYCHOMOTOR STIMULATORY EFFECTS OF COCAINE MAY NOT BE DUE TO HEPATIC MECHANISMS

G. N. Carmona, S. R. Tella, N. H. Greig, Q.-S. Yu, and C. W. Schindler

NIH/NIDA Intramural Research Program, Baltimore, MD; NIH/NIA/GRC Division of Intramural Research, Baltimore, MD; and Department of Pharmacology, Georgetown University, Washington, DC

Previous studies have shown that women and men differ in response to a variety of drugs and that these differences may be involved in the higher incidence of adverse reactions to drugs in women compared to men. Similar gender differences have been found in rodent models. Studies have shown that female rats are acutely more responsive to cocaine than males. It has also been shown that male rats have higher levels of hepatic cytochrome P450 isozymes (CYP2D6) when compared to female rats, which suggests that metabolism may account for some of the observed gender differences. In our first experiment, we used Dark Agouti rats, a rat model of the CYP2D6 poor metabolizer phenotype, and Sprague-Dawley rats (positive controls) to assess the gender/species-specific effects of cocaine using locomotor activity as a measure. In both species, females showed greater locomotor activity following cocaine than did males. To further investigate the role of metabolic mechanisms, different rats were pretreated with SKF525A, an inhibitor of microsomal enzymes or cymserine, an inhibitor of endogenous butyrylcholinesterase (BChE), prior to cocaine. All of the manipulations which would be expected to alter metabolism had similar effects on both genders, indicating that differences in metabolism do not contribute to the observed gender differences. Finally, to investigate whether the observed gender differences may be related to differences in receptor function, a third experiment determined the effects of a variety of dopaminergic compounds on locomotor activity in male and female Sprague-Dawley rats. These studies suggested that differences in receptor function between genders probably accounts for the observed gender differences in response to cocaine.

ACKNOWLEDGMENT: Supported by NIDA Intramural Research Funds,

COCAINE PHARMACOKINETICS IN MEN AND IN WOMEN DURING TWO PHASES OF THE MENSTRUAL CYCLE

J. H. Mendelson, M. B. Sholar, N. K. Mello, A. J. Siegel, and J. H. Halpern*

Alcohol and Drug Abuse Research Center and *Dept. of Medicine, McLean Hospital—Harvard Medical School, Belmont, MA

Numerous reports indicate that gender-related factors may influence cocaine-induced disease and lethality in experimental animals. It has been postulated that differences in cocaine pharmacokinetics may explain, in part, these gender-related differences in cocaine toxicity. Thirty-four healthy adult men and women who fulfilled DSM-IV criteria for cocaine abuse, matched for age and body mass index, provided informed consent for participation in this study. Women were studied during the follicular (cycle days 5-9) and the luteal (cycle days 18-22) phase of the menstrual cycle. Menstrual cycle phase was verified by E_2 and progesterone measures. Cocaine (0.2 mg/kg) or (0.4 mg/kg) was administered intravenously over 1 min to semi supine subjects. Cardiovascular status was continuously monitored. Blood samples were collected from the opposite arm at 2, 4, 8, 12, 16, 20, 30, 40, 60, 80, 120, 180 and 240 minutes after i.v. cocaine injection. No statistically significant gender differences in pharmacokinetic parameters for Tmax, Cmax, T1/2 and AUC were observed following 0.2 mg/kg i.v. cocaine. The only statistically significant gender difference observed was a higher Tmax ($P < 0.05$) following administration of 0.4 mg/kg cocaine during the follicular phase of the menstrual cycle. No statistically significant gender differences or cycle phase differences were observed for cocaine-induced changes in cardiovascular function or cocaine-related changes in mood states including euphoria and cocaine craving.

ACKNOWLEDGMENTS: Supported in part by NIDA grants P50-DA04059, KO5-DA00064, KO5-DA00101 and T32-DA-7252.

GENDER DIFFERENCES IN ACTH AND CORTISOL RESPONSES TO I.V. COCAINE ADMINISTRATION

M. B. Sholar, J. H. Mendelson, N. K. Mello, A. J. Siegel, and J. H. Halpern*

Alcohol and Drug Abuse Research Center and *Dept. of Medicine, McLean Hospital—Harvard Medical School, Belmont, MA

It has been postulated that cocaine-related stimulation of corticotropin releasing factor (CRF) may be one mechanism underlying the reinforcing properties of cocaine. The goal of this study was to compare neuroendocrine responses to cocaine in male and female subjects. Nineteen healthy adult men and women, who met DSM-IV criteria for cocaine abuse participated in a study to assess ACTH and cortisol responses to intravenous cocaine. Cocaine 0.4 mg/kg i.v. was infused over 1 min. and samples for cocaine, cortisol and ACTH analysis were collected at 2, 4, 8, 12, 16, 20, 30, 40, 60, 80, 120, 180, and 240 min. ACTH and plasma cocaine increases were temporally concordant and six women had peak ACTH levels comparable to the men, but their peak plasma cocaine levels were significantly higher than the men ($p<.05$). Seven women had a significantly lower ACTH response ($p<.0001$) to cocaine than the men. The blunted ACTH response in these women may have reflected higher baseline cortisol levels [319 ± 43 vs 191 ± 30 nmol/L ($p=.04$)]. Menstrual cycle phase did not account for the observed differences. The three groups did not differ significantly in their subjective reports of high, euphoria, and cocaine cravings.

ACKNOWLEDGMENTS: Supported in part by NIDA grants P50-DA04059, KO5-DA00064, KO5-DA00101, and T32-DA-7252.

SUBJECTIVE EFFECTS OF COCAINE ARE ALTERED BY GENDER AND MENSTRUAL PHASE IN HUMANS

M. Sofuoglu[1], S. Dudish-Paulsen, D. Nelson, P. R. Pentel[2], and D. K. Hatsukami

Departments of Psychiatry, Pharmacology[1] and Medicine[2], University of Minnesota, Minneapolis, MN

In order to investigate gender and menstrual cycle effects in response to cocaine administration, data from existing studies were analyzed. In the first analysis, gender and menstrual phase differences in response to a single delivery of smoked cocaine were investigated. Twenty-one female and 23 male cocaine-dependent subjects were given a 0.4 mg/kg dose of smoked cocaine. Changes in plasma cocaine levels, heart rate and blood pressure in response to cocaine administration did not show any gender or menstrual phase differences. Gender differences were found on subjective ratings of cocaine effects, with female subjects reporting lower ratings of "Paranoid/Suspicious" and "Heart Racing or Pounding" compared to male subjects. There were also significant effects of menstrual phase on the subjective responses to cocaine. Women in the luteal phase reported diminished ratings of "Feel High," "Feel Stimulated," "Desire Cocaine," and "Heart Racing or Pounding" compared to both women in the follicular phase of the menstrual cycle and men. In the second analysis, gender differences in response to multiple deliveries of smoked cocaine were investigated. Twelve female and 11 male subjects received up to 6 deliveries of 0.4 mg/kg smoked cocaine. The analysis of the change scores for the subjective ratings of cocaine indicated that female subjects, compared to males, had lower ratings on items "Feel High" and "Heart Racing or Pounding." Similarly, the analysis of the post 'delivery and initial baseline scores showed that female subjects rated the items "Feel Stimulated" and "Heart Racing or Pounding" less intensely than males. These results suggest that there are significant gender and menstrual phase differences in the extent of subjective effects of cocaine

ACKNOWLEDGMENTS: Supported by NIH grants P-50 DA09259 and MO1-RR00400.

EFFECTS OF BACLOFEN ON MAINTENANCE AND REINSTATEMENT OF IV COCAINE SELF-ADMINISTRATION IN RATS

U. C. Campbell, S. T. Lac, and M. E. Carroll

Department of Psychiatry, University of Minnesota, Minneapolis, MN

The effects of baclofen pretreatment on maintenance and reinstatement of cocaine-reinforced behavior in rats were investigated. Two groups of rats were trained to self-administer i.v. cocaine (0.2 or 0.4 mg/kg/inf) during daily 7-hr sessions under a fixed-ratio 1 schedule. Rats were pretreated with baclofen (1.25, 2.5 or 5 mg/kg i.p.) or saline before the session for 5 consecutive days. An additional group of rats was trained to self-administer i.v. cocaine (0.4 mg/kg/inf) during the first 2-hr of daily 7-hr sessions. Cocaine was replaced by saline for the remaining 5-hr of the session. Once behavior had stabilized over the 7-hr period, priming injections of saline (i.v.), cocaine (3.2 mg/kg i.v.) or baclofen (1.25 or 2.5 mg/kg i.p.) were administered prior to hour 4. Injections of baclofen (1.25 or 2.5 mg/kg i.p.) or saline were also given before the priming injection of cocaine. Pretreatment with the 2 higher doses of baclofen (2.5 and 5 mg/kg) decreased the number of cocaine infusions in both maintenance groups (0.2 and 0.4 mg/kg/inf) over the 5-day treatment period. Baclofen had a greater suppressant effect on responding maintained by the lower dose of cocaine. Priming injections of baclofen (1.25 and 2.5 mg/kg) or saline did not reinstate responding. However, these same doses of baclofen dose-dependently reduced the reinstatement of responding produced by a priming injection of cocaine. These results suggest that 1) the magnitude of the suppressant effects of baclofen on maintenance of cocaine self-administration depends upon the maintenance dose, 2) baclofen may be useful in preventing reinstatement of cocaine-seeking behavior, and 3) compared to maintenance, reinstatement of responding is more sensitive to the suppressant effects of baclofen.

IMMUNIZATION WITH A COCAINE VACCINE BLOCKS COCAINE SELF-ADMINISTRATION BEHAVIOR IN RATS

*K. M. Kantak, S. L. Collins, E. G. Lipman, and B. S. Fox**

Dept. Psychol., Boston Univ., Boston, MA and *ImmuLogic Pharm. Corp., Waltham, MA

Passive administration of an anti-cocaine monoclonal antibody has been shown to block the reinforcing effects of 1 mg/kg cocaine following its intravenous delivery. Antagonism was dependent on antibody dose and required serum antibody levels above 0.05 mg/ml. The effects of immunization with the cocaine vaccine IPC-14,551 (n=9) and an alum control (n=5) were assessed in rats self-administering cocaine using a similar F15(FR5:S) second-order schedule of drug delivery. IPC-14,55 1 induced average serum antibody levels of 0.08 mg/ml and blocked the reacquisition of behavior by 1 mg/kg cocaine. The vaccine also lengthened the interval of time between infusions and engendered a progressive increase in the latency to the first infusion that correlated with serum antibody level. Antagonism of cocaine self-administration after immunization was evident across a range of doses of cocaine and was only apparent in animals whose serum antibody levels exceeded 0.05 mg/ml. Furthermore, there was no evidence that the antagonism was surmountable within the dose range examined (up to 10 mg/kg). A therapeutic vaccine for cocaine relapse prevention would open a new avenue for the treatment of this serious addiction.

ACKNOWLEDGMENT: Supported by NIH grant DA08979.

REDUCTION IN COCAINE-SEEKING BEHAVIOR AFTER TREATMENT WITH THE NOS INHIBITOR 7-NITROINDAZOLE

S. L. Collins and K. M. Kantak

Department of Psychology, Boston University, Boston, MA

The brain-specific nitric oxide synthase inhibitor, 7-nitroindazole (7-NI), has been previously shown to modulate the discriminative stimulus effects of cocaine. 7-NI produced a 3-fold leftward shift in the cocaine dose-response curve, but alone it did not substitute for cocaine. In order to further understand the influence of 7-NI on the behavioral effects of cocaine, a self-administration study was conducted using a second-order schedule of 1 mg/kg cocaine delivery. 7-NI (5.6-17.8 mg/kg) dose-dependently decreased drug-seeking behavior (AD_{50}=17.46 mglkg) and only modestly influenced drug intake (AD_{50}=47.86 mg/kg) in seven rats. Using a 10 mg/kg pretreatment dose of 7-NI, a downward shift in the cocaine dose-response curve for drug-seeking behavior was observed in four rats tested thus far. However, drug intake was essentially unchanged after 7-NI pretreatment across the range of cocaine doses examined (0.1-3.0 mg/kg). To determine the specificity of these effects, food-maintained responding was examined using a second-order schedule in three rats. Food-seeking behavior was decreased by 7-NI (AD_{50}=14.79), whereas food intake was not affected (AD_{50}>100). These findings suggest that the relatively selective reductions in reward-seeking behaviors, which are behaviors controlled by the CS^+ in a second-order schedule, may be related at least in part to a blockade of an associative cognitive process by 7-NI. Furthermore, these effects may rely on a blockade of glutamatergic neurotransmission in the basolateral amygdala, a brain structure that mediates conditioned stimulus-reward associations.

COCAINE SELF-ADMINISTRATION IN MONKEYS: EFFECTS ON THE ACQUISITION AND PERFORMANCE OF RESPONSE SEQUENCES

K. R. Silvester, J. M. Moerschbaecher, C. P. France, and P. J. Winsauer

Department of Pharmacology, LSU Medical Center, New Orleans, LA

A three-component multiple schedule was used to examine the effects of cocaine self-administration on the acquisition and performance of response sequences in rhesus monkeys. In one component, responding was maintained by i.v. cocaine administration under a fixed-ratio (FR) 30 schedule. In a second component (learning), acquisition of a 5-response sequence was maintained by food presentation under a second-order FR schedule and the response sequence changed each session. In the third component (performance), responding was maintained under the same schedule conditions as in the acquisition component except that the response sequence remained the same each session. All three components alternated with time; 10 min for self-administration and acquisition components, 5 min for performance components. Sessions terminated after 4 cycles of each component. A 0.03 mg/kg/infusion of cocaine maintained reliable self-administration responding and, in general, was not disruptive to either rate or accuracy in the other components. When saline was substituted for cocaine, pausing increased and the number of infusions and response rate decreased in the self-administration component. Saline substitution had no effect on responding in the acquisition and performance components except for small changes in overall response rates. Self administration of a larger cocaine dose (0.1 mg/kg/infusion) also decreased response rate and the number of infusions in the self-administration component, and substantially decreased responding in the acquisition component. In summary, this research indicates that learning is more sensitive than performance to disruption by cocaine self-administration, and suggests that cognitive deficits resulting from cocaine abuse may be more selective for the acquisition of new information.

ACKNOWLEDGMENTS: Supported by DA04775 and K02 DA00211.

PHARMACOKINETIC-PHARMACODYNAMIC MODELING OF THE PSYCHOMOTOR STIMULANT EFFECT OF IV COCAINE: TIMING PERFORMANCE DEFICITS

C. E. Lau, F. Ma, and J. L. Falk

Department of Psychology, Rutgers University, New Brunswick Campus, Piscataway, NJ

We investigated dose-response cocaine pharmacokinetics and metabolite profiles in a within-subject design after IV bolus cocaine administration (1-4 mg/kg) in rats under a food-limited regimen. Cocaine was rapidly distributed ($t_{1/2\alpha}$ < 2.2 min) and eliminated ($t_{1/2\beta}$ < 17.1 min). Norcocaine was not detected. The free fraction of cocaine was 31.3-33.1% for serum cocaine concentrations of 0.5-1 µg/ml. Parallel pharmacodynamics was studied using perfomance on a contingency-controlled timing behavior, a differential reinforcement of low rate schedule (DRL 45-s) in 3-hr sessions. The increases in shorter-response rate and the decreases in reinforcement rate were directly interpretable as functions of cocaine concentrations by using the sigmoidal E_{max} model and the inhibitory E_{max} model, respectively; both models were linked to the central compartment of the pharmacokinetic model. Owing to the rapidity of the IV cocaine dose effect, a hypothetical effect compartment was not included in the PK-PD modeling. Both the shorter-response rate and the reinforcement rate attained their E_{max}s immediately after IV cocaine administration. Because EC_{50}s were greater than IC_{50}s, the shorter-response rate began to return toward baseline sooner than did the reinforcement rate. As cocaine concentration decreased to values smaller than the EC_{50}s, only then did the reinforcement rate begin to return toward baseline. Thereafter, the two measures co-varied. Thus, the reinforcement rate is an index for evaluating the deficit in timing performance. Although cocaine pharmacokinetics and pharmacodynamics exhibiting dose-dependence for some of their parameters, the concentration-effect plots demonstrated that changes in concentration across time accounted for the onset and disappearance of effects of cocaine.

LOCAL ANESTHETIC SELF-ADMINISTRATION AND *IN VITRO* POTENCY AT DOPAMINE TRANSPORTERS IN MONKEYS

K. M. Wilcox, I. A. Paul, and W. L. Woolverton

Department of Psychiatry and Human Behavior, University of Mississippi Medical Center, Jackson, MS

Some local anesthetics have been found to function as positive reinforcers under fixed-ratio schedules of reinforcement in monkeys. The present study examined the relative reinforcing potency and efficacy of cocaine and several local anesthetics under a progressive-ratio schedule. To help establish the pharmacological mechanism of the reinforcing effect, the *in vitro* potencies of these compounds were examined at dopamine transporters and sodium channels in rhesus monkey caudate/putamen and frontal cortex, respectively. Rhesus monkeys (n=5) were trained to respond under a progressive-ratio schedule for injections of cocaine (0.10 mg/kg/inj) or saline available in different sessions. When responding was stable, cocaine (0.017-0.30) and the local anesthetics dimethocaine (0.10-0.56) procaine (0.17-3.0), chloroprocaine (0.30-3.0), and tetracaine (0.100.30) were substituted for the usual daily dose of cocaine. Each dose was available for one session. The relative rank order potency as positive reinforcers and for the displacement of [3H]CFT from DATs for the local anesthetics was identical, cocaine ≥ dimethocaine>tetracaine ≥ procaine≥chloroprocaine. The drugs were also rank ordered based on their relative reinforcing efficacy, cocaine ≥ dimethocaine>procaine≥chloroprocaine. Similarly, the ratio of IC_{50} sodium channel/IC_{50} DAT was cocaine≥dimethocaine>chloroprocaine ≥ procaine. These data suggest that binding at dopamine transporters is involved in the reinforcing effects of local anesthetics. Further, it is possible that relatively low sodium channel binding combined with high dopamine transporter binding determines the relative reinforcing efficacy of local anesthetics.

ACKNOWLEDGMENTS: Supported by NIDA grants DA-10352 (WLW), DA-00161 (WLW), and DA05807 (KMW).

COMPARISON OF THE REINFORCING EFFECTS OF COCAINE, PHENTERMINE, AND GBR 12909 IN RHESUS MONKEYS

M. G. LeSage, D. Stafford, K. Rice, and J. R. Glowa*

Department of Pharmacology and Therapeutics, LSU Medical Center in Shreveport, Shreveport, LA and *Laboratory of Medicinal Chemistry, NIDDK, NIH, Bethesda, MD

Recent experiments have shown that phentermine and GBR 12909 can selectively reduce cocaine-maintained responding in rhesus monkeys at doses that have no effect on food-maintained responding. These findings suggest that GBR 12909 and phentermine may be useful as pharmacotherapies for cocaine abuse. However, these drugs may have abuse potential in their own right. The purpose of the present experiment was to compare the reinforcing effects of GBR 12909, phentermine, and cocaine in four rhesus monkeys using a progressive-ratio (PR) schedule of drug delivery. Under this schedule, the cocaine dose-response curve was an inverted U-shaped function, with 30 ug/kg/inj maintaining a peak of 34.4 ratios completed per session. The dose-response curve for GBR 12909 was also an inverted U-shaped function, with the 30 µg/kg/inj dose maintaining a peak of 13.7 ratios completed per session. Thus, the GBR 12909 curve was significantly more shallow than the curve for cocaine. The phentermine dose-response curve was a shallow ascending function of unit dose, with the 100 µg/kg/inj dose maintaining the highest number of completed ratios (12.5). Given that the number of completed ratios under a PR schedule is considered an index of reinforcing efficacy, the present data suggest the following rank order of reinforcing efficacy: cocaine>GBR 12909>phentermine. However, in two monkeys, the reinforcing efficacy of GBR 12909 approached that of cocaine following self-administration of the highest dose of GBR 12909. Thus, the reinforcing efficacy of GBR 12909 was a malleable consequence of pharmacological history in these monkeys.

ACKNOWLEDGMENT: Supported by NIDA grant RO1 DA09820-01 (JRG).

CARDIOVASCULAR RESPONSES TO COCAINE AND GBR12909 SELF-ADMINISTRATION IN RATS: A COMPARATIVE STUDY

S. R. Tella, D. Chism, C. W. Schindler, and S. R. Goldberg*

Department of Pharmacology*, Georgetown University Medical Center, Washington, DC and Preclinical Pharmacology Laboratory[§], National institute on Drug Abuse Intramural Research Program, NIH, Baltimore, MD

Cardiovascular responses to limited access (2 hr/day) cocaine and GBR12909 self-administration were studied in Sprague-Dawley rats implanted with telemetric devices. The first infusion of cocaine on day 1 of testing produced rapid (< 60 sec) increases in diastolic (DBP), systolic (SBP) and mean blood pressures (MBP) and in heart rate (HR). Subsequent cocaine infusions within the same session produced minimal effects. As the session progressed, there was a gradual elevation in DBP, SBP and MBP and a reduction in HR as compared to pre-session base-line measures. On subsequent days of testing, the first cocaine infusion of session produced a similar rapid increases in BP and HR, but there were no progressive increases in DBP, SBP and MBP as seen on day I. In contrast to cocaine, GBR 12909 self-administration produced rapid, brief and small decreases in DBP, SBP and MBP. Similar to cocaine, there was a gradual increase in DBP, SBP and MBP as the session progressed on day 1, but not on the subsequent days of testing. There was also an overall within session reduction in HR as compared to pre-session base-line measures. These data indicate that dopaminergic mechanisms do not appear to mediate the rapid effects of cocaine, but may mediate the gradual within session elevation in SBP, DBP and MBP induced by cocaine on day 1 of testing.

ACKNOWLEDGMENTS: Supported by NIDA grant DA08830 and the Intramural Research Program of NIDA.

PAVLOVIAN CONDITIONING AND EXTINCTION OF CARDIOVASCULAR RESPONSES TO COCAINE IN SQUIRREL MONKEYS

C. W. Schindler, J. P. Gilman, E. B. Thorndike, and S. R. Goldberg

Behavioral Pharmacology Section, NIH/NIDA Intramural Research Program, Baltimore, MD

When given alone, cocaine produces increases in blood pressure and heart rate in squirrel monkeys up to a dose of 1.0 mg/kg. When paired with external stimuli, the conditioned effects of a drug may be either drug-like or drug-opposite and lead to either a potentiated response (sensitization) or tolerance respectively. The purpose of the current study was to determine whether the cardiovascular effects of cocaine in squirrel monkeys could be conditioned and. if so, whether the conditioned response was drug-like or drug-opposite. Three squirrel monkeys were surgically implanted with arterial and venous catheters. They were then habituated to a 2-min tone-light compound stimulus (with saline given 1 min after stimulus onset) by presenting that stimulus once during a 1-hour daily session. Up to two stimulus presentations were given per week. After 4 stimulus presentations. a 1 mg/kg dose of cocaine was given in place of saline. Ten stimulus-cocaine pairings were given over 6 weeks. with a test presentation of stimulus-saline and of cocaine alone given after the 5th and 7th pairing respectively. Another monkey was given cocaine and the stimulus in an unpaired fashion. Clear increases in both blood pressure and heart rate were observed during the first min of the stimulus for the paired monkeys, which reached a peak after 4-5 pairings. After the 10th stimulus-cocaine pairing, an extinction regimen was instituted. The previously conditioned effects of cocaine were still clearly evident after 15 extinction sessions, and did not return to baseline until after 30 extinction sessions in two monkeys. Thus. the cardiovascular effects of cocaine can be conditioned to external stimuli and the conditioned blood pressure response appears to be drug-like. This conditioned effect is long-lasting and may well potentiate the cardiovascular effects of cocaine.

ACKNOWLEDGMENT: Supported by NIDA Intramural Research Funds.

THE EFFECTS OF 6-OHDA LESIONS OF THE VENTRAL PALLIDUM ON INTRAVENOUS COCAINE SELF-ADMINISTRATION

G. M. Sizemore, C. Co, S. Hemby, T. R. Koves, and J. E. Smith

Department of Physiology and Pharmacology, Wake Forest University School of Medicine, Winston-Salem, NC

The brain mechanisms relevant to cocaine self-administration have been under significant investigation during the last decade. Although much attention has focused on the rote of the nucleus accumbens (NA), recent experiments in our laboratory suggest that the ventral pallidum (VP) may be important in the processes underlying cocaine self-administration in rats. The investigators have previously reported that extracellular fluid levels of dopamine measured in microdialysates of the VP increased in a manner similar to that seen in the NA during cocaine self-administration. This experiment was initiated to determine the overall importance of DA innervations of the VP in self-administration using 6-OHDA induced lesions. Rats were implanted with intravenous catheters and bilateral stainless-steel guide cannulae and allowed to self-administer 3 different doses of cocaine in each daily session. 6-OHDA lesions of the NA and VP were produced by injection of 8.0 mg of 6-OHDA in 2 ml of saline. A sham treated group received infusions of the vehicle. A second lesion or sham treatment occurred 48 hrs after the first. Decrements in drug intake were greater in lesioned rats than in the sham rats in both the VP and NA. This disruption was greater in the VP than in the NA. These data suggest that ventral pallidum dopaminergic innervation may have a significant role in cocaine self-administration.

ACKNOWLEDGMENTS: Supported by USPHS grants DA 03628, DA 06634, and DA 00114.

CHARACTERIZATION OF THE DISCRIMINATIVE STIMULUS EFFECTS OF THE PHENCYCLIDINE ANALOG BTCP

M. S. Klevea, J. Vignon, J.-M. Kamenka**, and W. Koek*

Centre de Recherche Pierre Fabre, Castres, France, *INSERM U336, and **CNRS ER 155, INSERM U249, Montpellier, France

Because the phencyclidine analog, BTCP binds to a site on the dopamine (DA) reuptake complex different from that of cocaine (Maurice *et al., Neuropharmacology,* 30, 591, 1991), it is conceivable that its behavioral effects may differ from those of cocaine. To compare further the behavioral effects of BTCP and cocaine, different groups of rats were trained to discriminate either BTCP (5 mg/kg, i.p.) or cocaine (10 mg/kg, i.p.) from saline in a two-lever, FR10 drug discrimination paradigm. The ability of a variety of selective and nonselective monoamine reuptake blockers to substitute for the discriminative stimulus (DS) effects of each training drug was examined. Compounds were administered i.p., 15 min before the sessions. BTCP engendered dose-related increases in drug-lever (DL) selection in BTCP-trained (ED50=3.3 mg/kg; 95% CL=2.1-5.0) and in cocaine-trained rats (ED50=4.1 mg/kg; 2.9-5.8). Conversely, cocaine engendered dose-related increases in DL-selection in cocaine-trained (ED50=2.0 mg/kg; 1.1-3.9) and in BTCP-trained rats (ED50=1.3 mg/kg; 0.65-2.4). A variety of DA reuptake blockers — mazindol, indatraline, methylphenidate, GBR 12909, and GBR 12935 - occasioned dose-related DL-selection both in cocaine- and in BTCP-trained rats, and did so with similar relative potencies ($r = 0.92$, $P<0.001$). In contrast, relatively selective NE reuptake blockers — nisoxetine, desipramine, and nortriptyline — produced higher levels of DL-selection in BTCP-trained rats than in cocaine-trained rats, a profile previously found by others in rats and monkeys trained to discriminate lower doses of cocaine. Thus, the results suggest that the DS effects of BTCP resemble a relatively low training dose of cocaine.

COMBINING DISCRIMINATIVE STIMULI FOR COCAINE SELF-ADMINISTRATION PRODUCES PERSISTENT INCREASES IN DRUG SEEKING

L. V. Panlilio, S. J. Weiss, and C. W. Schindler*

NIDA Division of Intramural Research, Baltimore, MD and *American University, Washington, DC

In previous experiments, we demonstrated that combining discriminative stimuli that control cocaine self-administration can produce three-fold increases in drug seeking and two-fold increases in drug intake in rats. These effects were observed during a single test session in which two discriminative stimuli (tone and light) were combined for the first time. In the present experiment, we assessed the persistence of this increased drug seeking using a probe technique. Rats (n=3) lever-pressed in tone and in light to receive intravenous infusions of cocaine on a variable-interval schedule. Tone components and light components alternated with the absence of tone and light, where no cocaine was available (extinction) and responding ceased. During each daily session, two probes were presented, consisting of tone and light in compound. The compound significantly increased lever-pressing compared to tone alone and light alone for 15 days, and the total number of responses in the compound was higher than in tone and light alone across the 24 days of testing.

ACKNOWLEDGMENT: Supported by NIDA/DIR.

EVIDENCE FOR COMPOUND STIMULUS DRIVEN CONDITIONED CUED RECOVERY IN AN ANIMAL MODEL OF RELAPSE

J. W. Grimm, P. J. Kruzich, and R. E. See

Department of Psychology, Washington State University, Pullman, WA

Our laboratory has demonstrated conditioned cued recovery of responding on a cocaine paired lever following prolonged extinction (Behav Pharm: 1996:7:754-763). The present study assessed the nature of the conditioned stimulus in this paradigm. Male Sprague Dawley rats were trained to press a lever for food pellets and subsequently were implanted with jugular catheters. Rats then self-administered cocaine (0.33 mg/ 0.05 ml infusion i.v.) via the same lever in daily 3 h sessions. Groups (N=4-9) were divided such that some rats received the presentation of a tone (60 dB, 2 kHz, 2 sec) or the same tone plus the illumination of a light (40 sec) above the operant lever with the delivery of cocaine. After 14 days of self-administration, rats experienced 7 days of extinction wherein lever presses resulted in no consequences. The next day, cued recovery of responding was assessed. Rats trained with a tone+light combination showed a significant increase in responding ($p<0.05$) following non-contingent+contingent presentation of the tone+light combination as compared to the final day of extinction. In contrast, rats trained with the tone alone did not recover responding whether the tone was presented non-contingently, contingently, or a combination of both. Previous results from our laboratory using similar procedures have shown that delivery of a light alone also did not reinstate extinguished responding (Behav Pharm: 1996:7:754-763). These results suggest that a compound stimulus, perhaps one with a long duration component (e.g. light), drives conditioned cued recovery of responding and that conditioning in cocaine reinforced responding may not follow simple contingency principles of classical conditioning.

ACKNOWLEDGMENT: Supported by NIH grant DA10462.

THE DEVELOPMENT OF CRACK COCAINE PICTURE SLIDES FOR CUE REACTIVITY STUDIES: A PRELIMINARY NORMATIVE STUDY

S. F. Coffey, M. E. Saladin, D. J. Drobes, B. S. Dansky, J. Wiesequist, and K. T. Brady

Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina, Charleston, SC

Cue reactivity is a burgeoning area of interest in substance abuse research. Traditional methods of cue presentation have included in Vivo cue presentation, video tape cue presentation, and cue exposure through guided imagery. A relatively new technology for cue presentation is the use of pictures. The advantages of this technology include better time coordination of psychophysiological, self-report, and behavioral responses to the presentation of the cued stimuli, increased range of the stimuli, increased specificity of the stimuli, and the ability to present a large number and a wide variety of cues sequentially. However, current picture slide systems used in substance abuse research do not contain crack cocaine-related pictures. The current study presents a set of 10 pictures that have been developed to fill this void. The slides were selected from a larger set based on ratings of the following dimensions: craving, arousal, valence, interest, approach, avoidance, and dominance. Preliminary normative data are presented on 30 treatment seeking crack cocaine dependent subjects who rated the 10 crack cocaine-related slides on the above mentioned dimensions. The implications and suggested uses for this new technology are discussed.

ACKNOWLEDGMENTS: Supported by NIDA grants RO1 DA10595-01 and T32 07288.

CLASSICAL CONDITIONING OF CUES PAIRED WITH SMOKED COCAINE IN HUMANS

R. W. Foltin, M. Haney, and M. W. Fischman

Columbia University and NYS Psychiatric Institute, New York, NY

The possible role of environmental stimuli paired with cocaine in modulating cocaine use has generated much theoretical and practical interest. The purpose of this study was to examine the emergent stimulus effects of previously "neutral" cues paired with smoked cocaine self-administration. One set of cues was paired with placebo smoked cocaine (inhalation of warm air) and one set was paired with 25 mg smoked cocaine during multiple-dose "binge" self-administration sessions. 1) The conditioned reinforcing effects of the stimuli themselves were evaluated by requiring individuals to select placebo or active cues in a cue self-administration session: participants chose to experience the active cues. 2) The ability of the cues to affect cocaine choice was determined by presenting placebo or active cues and asking participants to purchase, using study earnings, the number of doses associated with those cues they would like to smoke during that session: cue presentation did not alter cocaine choice. 3) Finally, the ability of the placebo cue to attenuate the cardiovascular and subjective effects of active cocaine, as well as the ability of the active cue to increase the effects of placebo cocaine were detemined: active cues alone increased cardiovascular activity, and placebo cues attenuated the effects of cocaine. These results are the first to demonstrate that previously neutral cues paired with cocaine acquire emergent stimulus effects after as few as 12 cue-cocaine pairings, and suggest that emergent effects may be acquired by stimuli in the cocaine-users' natural environment.

ACKNOWLEDGMENTS: Supported by NIDA grant DA-08105 and NIH grant MOI-RR-00645.

URINE AND PLASMA DRUG LEVELS IN MONKEYS TRAINED TO SMOKE COCAINE BASE

S. D. Comer, S. M. Evans, A. S. Ward, and R. W. Foltin

New York State Psychiatric Institute and College of Physicians and Surgeons of Columbia University, New York, NY

Six male rhesus monkeys were trained to smoke cocaine base under a two-component chain schedule of reinforcement. The first component was a fixed interval (FI) 2-min schedule. with a fixed ratio (FR) 5 second order component; after every 5th response, the stimuli associated with drug were presented. Completion of the first FR 5 after 2 min resulted in the lever light extinguishing and the light over the smoking pipe illuminating, signalling the second component of the chain schedule. During the second component, one smoke delivery could be earned under an FR 3 schedule: completion of 3 inhalations within 2 min on the smoking pipe resulted in illumination of two flashing lights over the smoking pipe and volatilization of the cocaine base. Each smoke delivery was followed by a 15 min time-out during which responding had no programmed consequences. Monkeys could receive up to a total of 6 deliveries during each daily session. Urine was collected every 2 hr immediately following a session during which either 1, 2, or 3 mg/kg/delivery cocaine was available. A baseline urine was collected when monkeys had been cocaine-free for at least 24 hr. In separate sessions, monkeys were anesthetized with ketamine and blood samples were collected 5, 10, 15, 30, 45 and 60 min after the last cocaine delivery (2 or 3 mg/kg/delivery). Preliminary analyses indicate that there was a time-related increase in benzoylecgonine levels in urine, which peaked 2-4 hr after the last smoked dose. Plasma cocaine levels peaked 10-15 min after the last smoked dose. However, there were no significant differences in urine or plasma drug levels across doses. These results suggest that urinalysis may be a useful, noninvasive method of confirming smoked drug self-administration in non-human primates.

ACKNOWLEDGMENTS: Supported by NIDA grants DA10975 and DA08464.

DISCRIMINATIVE AND REINFORCING EFFECTS OF ORAL COCAINE IN HUMANS

H. E. Jones[1], B. E. Garrett[2], and R. R. Griffiths[1]

[1]Johns Hopkins University School of Medicine, Baltimore, MD and [2]Yerkes Regional Primate Research Center, Emory University, Atlanta, GA

The present study investigated the subjective, discriminative stimulus, physiological and reinforcing effects of orally administered cocaine. Volunteers with histories of cocaine abuse were trained to discriminate between orally administered placebo and cocaine capsules (100 mg/ 70kg) using a 2-choice discrimination procedure under double-blind conditions. The cocaine discrimination was acquired by all subjects (80 -100% correct guesses). Following acquisition of the discrimination, the reinforcing effects of cocaine were determined in two experiments. In experiment 1 (paired choice), volunteers were exposed to cocaine and placebo once each with a relaxation (sitting in a cushioned chair) activity and a vigilance (performing a computer task) activity. Following exposure to each drug with each activity, volunteers choose which compound they ingested with the vigilance and relaxation activities every other day for 10 days. Volunteers could not choose the same drug with both activities. Volunteers reliably chose cocaine with the vigilance activity and placebo with the relaxation activity. In experiment 2 (unpaired choice), volunteers chose which drug (cocaine or placebo) they ingested with the relaxation activity and, on another occasion (in counterbalanced order), which drug they ingested with the vigilance activity. Volunteers were allowed to select the same drug with both activities. A majority of subjects chose cocaine with the vigilance activity and placebo with the relaxation activity. Results from both experiments show that context can influence cocaine self-administration.

ACKNOWLEDGMENT: Supported by NIDA grant DA-03890.

INDIVIDUAL DIFFERENCES IN THE ACQUISITION OF COCAINE VERSUS PLACEBO DISCRIMINATION IN HUMANS

A. K. Singha, E. McCance-Katz, T. R. Kostew, and A. Oliveto

Yale University and VA Connecticut Healthcare System, West Haven, CT

This report examined individual differences in the acquisition of cocaine versus placebo discrimination in humans. Twenty-six cocaine-abusing volunteers were trained to discriminate cocaine (80 mg/70 kg p. o.) from placebo Based on a discrimination acquisition criterion (i.e $\geq$ 80% drug-appropriate responding for 4 consecutive sessions within 8-10 sessions), 18 subjects were classified as discriminators (Ds) and 8 as nondiscriminatory (NDs). Relative to Ds, NDs showed a trend toward greater frequency and amount of cocaine use. During the training phase, NDs showed significantly lower ratings than Ds on the A subscale of the ARCI, regardless of the training drug condition. During the test-of-acquisition phase cocaine-induced increases in scores on VAS ratings of drug strength anxious/nervous and cocaine high, as well as ARCI ratings on the MBG subscale were significantly greater in Ds than NDs relative to placebo. Thus, drug use history general arousal level, and drug sensitivity may be important variables influencing the acquisition of cocaine versus placebo discrimination in cocaine abusers.

ACKNOWLEDGMENTS: Supported by NIDA grants DA09250, DA08277, and DA00216.

AN EVALUATION OF CAFFEINE-INDUCED MOOD AND STATE-DEPENDENT MEMORY EFFECTS

R. S. Herz and A. Laneader

Monell Chemical Senses Center, Philadelphia, PA

To test whether caffeine induces state-dependent memory (SDM), and explore the role that mood plays in drug-induced dissociative learning, a 5 mg/kg dose of caffeine or placebo was administered during the learning and retrieval sessions of a traditional 2x2 SDM experiment. Forty-eight subjects (24 males, 24 females) were randomly assigned to one of four learning/retrieval treatment conditions. Subjects were low-moderate (50-150 mg/day) users of caffeine, and were caffeine and food deprived for 12 hr before each session. Sixteen words, as to-be-remembered items, were presented during the learning session, and memory was evaluated by the number of words subjects correctly recalled at the retrieval session two days later. Mood was assessed by the Mood Grid, POMS, and a subjective state questionnaire administered multiple times during both sessions. Results revealed that caffeine reliably increased arousal and altered subjective state, but did not affect any emotion dimensions related to feelings of pleasantness-unpleasantness. Moreover, subjects who received caffeine at learning and retrieval were in equivalent mood states at both sessions, in contrast to subjects who received caffeine at only one session. However, caffeine did not induce SDM. In fact, whether or not subjects received caffeine at a session or not at all had no influence on recall performance. These data show that a 5 mg/kg dose of caffeine can dissociate the mood effects of arousal from pleasantness, and suggest that simple mood congruence may not be the key variable in drug-induced dissociations of learning and memory. Further work investigating the singular and interactive effects of arousal and pleasantness in mediating SDM is being pursued.

ACKNOWLEDGMENTS: Sponsored by NIDA B-START grant R03 DA10953-01.

MODELING IMPAIRED JUDGMENT IN COCAINE ABUSERS

J. Corwin, D. Delalot, and J. Rotrosen

NYVA Medical Center; NYU School of Medicine; NYVA/NIDA MDRU

The posited chronic dopaminergic deficit state consequent on cocaine dependence should have a number of behavioral manifestations similar to those seen in Parkinson’s disease, specifically a liberal "yea-saying" guessing strategy. In cocaine users, such a liberal response bias may operationalize an aspect of their impulsiveness. To test this hypothesis, we are investigating aspects of recognition memory and appreciation of changing contingencies in relation to response bias. Bias is a type of judgment or executive function, defined as the decision rule subjects use when uncertain. We evaluated 23 abstinent cocaine users and 10 matched controls on a battery of rating scales and recognition memory tasks. Two-high Threshold Theory, the approach used to mode1 accuracy and judgment for all binary decision tasks used in this study, yields measures in which accuracy of performance and response bias are uncorrelated. Results from 3 recognition memory tasks that manipulate task difficulty and target probability were that: 1. Deficits in accuracy were small, if present at all when the task was easy. 2. Cocaine using subjects forgot more rapidly. 3. Response bias is persistantly more liberal (yea-saying) in cocaine using subjects across manipulations. 4. Manipulation of target probability had a paradoxical effect in cocaine using subjects. Although subjects responded to changes in probability by shifting their response biases in the appropriate direction, the imposition of a conservative probability structure lead to decreased accuracy. In normals, as expected, change in presentation probability had no effect on accuracy. Thus, long term cocaine abuse is associated with persistant alterations in response strategy similiar to Parkinson’s disease. When stressed by increasing processing requirements, the deficits "overflow" into accuracy of performance.

NEUROPSYCHOLOGICAL IMPAIRMENT AMONG COCAINE DEPENDENT TREATMENT CLIENTS AND RESPONSES TO TREATMENT

P. M. Flynn

National Development and Research Institutes, Raleigh, NC

Since the 1980s, cocaine use, particularly in the form of crack, has increased significantly and cocaine has been reported as a primary drug problem in the U.S. The study of treatment effectiveness for cocaine users is in its infancy and questions about responses to treatment by client subgroups with various functional impairments are now being formulated as critical research endeavors. It was hypothesized that cocaine abusers with neuropsychological impairment may respond less well to treatment than those functioning within the normal range. Neuropsychological impairment in cocaine users may be due to single or polydrug abuse, head trauma, learning disabilities, cumulative brain damage, and other causes. Regardless of etiology, neuropsychological impairment can have implications for management and treatment. Almost 6,000 cocaine dependent and/or daily users of cocaine prior to admission to NIDA's Drug Abuse Treatment Outcome Study (DATOS) completed the Trail Making Test (TMT) as a screener for cognitive impairment. Univariate results showed that 21% of the admissions had both parts A and B TMT scores in ranges associated with neuropsychological impairment in other patient populations. Demographic variables known to be related to TMT scores (e.g. age, education, gender) were controlled in multivariate analyses and no significant relationships were found between TMT scores and cocaine use after treatment. Results provide the largest index data set on TMT scores ever collected for a substance abusing and cocaine dependent population. Recommended TMT clinical cut-off scores for general populations may need to be adjusted for screening cocaine dependent populations. Cocaine clients in both the upper quartile (mildly suggestive of impairment) and decile (moderately suggestive of impairment) for most age groups took less time to complete the trails than those in the comparison sample,

ACKNOWLEDGMENT: Supported by NIDA grant U01-DA10377-3 as part of DATOS Cooperative Agreement.

DEVELOPMENT OF A VISUAL ANALOG SCALE TO ASSESS THE SUBJECTIVE EFFECTS OF SMOKED COCAINE

S. A. Dudish-Poulsen and D. K Hatsukami

Medications Development Research Center, Department of Psychiatry, University of Minnesota, Minneapolis, MN

Visual analog scales are frequently used in human laboratory research to assess the subjective effects of drugs of abuse. However, although psychometric data is routinely presented in many areas of psychology, it is often unavailable for the visual analog scales typically used in psychopharmacological research. This study examined the psychometric properties of an 18-item visual analog scale (VAS) designed to measure the subjective and physiological effects of cocaine. Data was culled from studies, conducted over a 5-year period, which examined the effects of smoked cocaine in 59 male and female crack cocaine users aged 21-45. All protocols involved a similar adaptation day in which the VAS was given at baseline and 2.5 min after a 0.4 mg/kg delivery of smoked cocaine. A single change score was computed for each subject by subtracting the baseline value 'from the post-drug value. The results of a principal axis factor analysis with oblique rotation supported a solution comprising three factors: Cocaine High, Positive Affect and Negative Affect. Reliability and validity were strong for the Cocaine High scale and fair for the remaining scales. These results provide initial support for administering only the most salient (Cocaine High) VAS scale in future studies. The use of this single, 4-item scale will allow multiple, rapid and reliable assessments of cocaine effects during experimental protocols.

ACKNOWLEDGMENTS: Supported by NIDA grants P-50 DA09259, DA05844, DA07097, and grant M01 RR00400 from the National Center for Research Resources.

THE DEVELOPMENT OF AN IMPROVED MOOD ADJECTIVE VISUAL ANALOGUE RATING SCALE

K. L. Delucchi[1], W. Lapp[1], and S. P. Berger[2]

[1]UC San Francisco and [2]Cinncinati VA Medical Center

The assessment of moods and emotions is an important aspect of research into drug abuse, both as a potential precursor to relapse and as an outcome measure. In using a cue-exposure paradigm, assessments, including those of moods, are often conducted repeatedly within a short time span. The goal of the work summarized here is to develop a measure of mood using existing data which can be administered repeatedly within a brief timeframe. Data from a set of seven experiments, all using a cocaine cue exposure design as well as the same set of mood adjectives marked on visual analogue scales, were pooled for analysis. In each experiment, 16 100mm. visual analogue scales were marked by each of 125 subjects at six time points across two days. The first item analysis consisted of bootstrapping the eigen-stucture at each assessment time point to estimate the number of components to retain for rotation. Four factors emerged; negative mood, positive mood. fatigue. Two items remained separate; "high" and "hungry." Additional work in underway to replicate the structure using oblique item clustering. Reanalysis of the original data found increases in negative mood and decreases in fatigue as a result of cocaine cue exposure.

ACKNOWLEDGEMENTS: Supported by NIDA grant P50DA09235 and NIDA/VA contract YOIDA 50038-00.

RECREATIONAL COCAINE USERS' EFFECT EXPECTANCIES DO NOT ACCURATELY REFLECT ENTIRE DRUG EXPERIENCE

S. L. Daniels, L. H. Lundahl[1], J. D. Wines, Jr., and S. E. Lukas

Behavioral Psychopharmacology Research Laboratory, McLean Hospital/ Harvard Medical School, Belmont, MA

While many studies have shown that effect expectancies are an important factor in determining drug use patterns and treatment outcomes, few studies have directly compared effect expectancies in subjects who then received a dose of the drug. Healthy male and female volunteers (n=15, ages 21-35, 11 men) who reported using cocaine 1-10 times per month, provided informed consent to participate in this study. Subjects completed the Cocaine Effect Expectancy Questionnaire (Schafer and Brown, 1991) several weeks before receiving a cocaine challenge. Subjects received cocaine (0.9 mg/kg, i.n.) and then completed a series of visual analog scales and the Addiction Research Center Inventory (ARCI) at 15 min. intervals for 1 hr post cocaine administration and at 30 min. intervals for 2 hrs post administration. Responses on the *Relaxation and Tension Reduction Scale* of the CEEQ were positively correlated with several post-cocaine responses during the initial 45 minutes of cocaine intoxication. However, responses to the CEEQ were not correlated with the last 2 hours of cocaine intoxication. These data suggest that the CEEQ is more sensitive to expected positive effects that occur during the first 45 minutes after cocaine administration and less sensitive to the negative effects associated with the dysphoria during the "crash" after acute cocaine intoxication. These data suggest that the success of prevention and treatment efforts may be increased if it is recognized that the *Relaxation and Tension Reduction* expectancies of actual experiences with a highly reinforcing drug such as cocaine may mask the negative effect expectancies.

ACKNOWLEDGMENTS: Supported by grants DA03994 and DA00343.

CHANGES IN BRAIN METABOLISM IN CHRONIC COCAINE USERS AFTER NIMODIPINE ADMINISTRATION

G. Nahas, L. E. Hollister**, N. Mullani**, H. K. Gillespie**, and N. Volkow****

Department of Anesthesiology, New York University School of Medicine*; Departments of Psychiatry and Medicine, University of Texas Houston Medical School; and Brookhaven Natural Laboratory, NY*****

In this study, six male chronic cocaine users were studied before and after nimodipine (a calcium channel antagonist) oral administration. They were given a total dose of 180-450mg nimodipine over two days, while controlled cocaine abstinent subjects were given 450 mg. Imaging of the brain was performed using TOFPET 1 positron emission tomography with $^{15}O_2$ labeled water for blood flow measurement and ^{18}F labeled deoxyglucose (FDG) for glucose uptake estimation. There was no difference between blood flow measurements before or after treatment with nimodipine in either control or cocaine consuming subjects. Before treatment, there was no difference between whole brain metabolism of control and cocaine using subjects. Following nimodipine treatment, there were no changes in brain metabolism in controls, but in cocaine users, there was a significant increase ($p<0.002$). A similar uncoupling of blood flow and metabolism in the brain has been reported in epileptic patients. These changes in brain metabolism might account in part for the improvement in the subjective adverse effects of cocaine reported by cocaine users treated with calcium antagonists.

NEUROCOGNITIVE IMPAIRMENT IN METHADONE-MAINTAINED COCAINE USERS: COMPARISON WITH CONTROLS AND POLYSUBSTANCE USERS

M. P. Vawter[1], K. I. Bolla[2], R. I. Herring[2], A. Umbricht[3], K. Preston[3], and J. L. Cadet[2]

Development and Plasticity[1], Molecular Neuropsychiatry[2], and Clinical Trials Sections[3], Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD

Cocaine induces oxidative stress leading to cell death through apoptosis. Cell death following cocaine abuse ultimately can lead to impairments of neuropsychological performance, increased EEG activity, and decreased blood flow in the brain. In contrast, methadone - maintained opioid dependent outpatients with cocaine use show normal EEG and cerebral blood flow (Tate, Herning, Umbricht, Preston, Cadet, unpublished data). In light of these differences, we tested whether methadone - maintained cocaine users demonstrated neuropsychological impairments as compared to a non-drug using outpatient group, and polysubstance abusers (cocaine, alcohol, and heroin) recently admitted to an inpatient research ward. The neuropsychological scores for an age matched methadone group ($n = 8$) were significantly different from controls ($n = 13$) on tests of executive functioning: Trails B time ($p = 0.031$), the Wisconsin Card Sort Test (WCST) Errors ($p = 0.033$), WCST Perserverative Response ($p = 0.045$), and WCST Trials ($p = 0.026$). Methadone subjects also exhibited lower performance on the Symbol Digit Total ($p = 0.018$), Finger Tapping ($p = 0.001$), Go-No-Go True Positives ($p = 0.043$), Sequential Reaction False Positives ($p = 0.00006$), Block Design ($p = 0.036$), Line Orientation ($p = 0.047$), RAVLT perseverations ($p = 0.0004$), and RAVLT delay memory (p 0.022) compared to controls. A polysubstance control group ($n = 12$) showed less differences compared to controls, with lower performance in Sequential Reaction True Positive ($p < 0.05$). and Symbol Digit Test ($p < 0.05$) and trends for lower performance in Digit Symbol and Trails B. The present results suggest that methadone-maintained cocaine users will exhibit persistently lower neuropsychological performance in multiple cognitive domains. Despite normal EEG and cerebral blood flow findings in methadone-maintained cocaine abuse patients there is a persistently lower neuropsychological performance.

EFFECTS OF COCAINE-RELATED ENVIRONMENTAL STIMULI ON THE SPONTANEOUS EEG AND CRAVING IN POLYDRUG ABUSERS

D. B. Vaupel, X. Liu, S. Grant, and E. D. London

Brain Imaging Center, Intramural Research Program, National Institute on Drug Abuse, Baltimore, MD

Reports on cerebral substrates of cue-elicited cocaine craving in human subjects have been limited to an observation that cocaine-related cues produce a diffuse decrease in the power of the spontaneous electroencephalogram (EEG) (Bauer and Kranzler, 1994) and our finding of specific metabolic activation of cortical and limbic brain regions (Grant *et al.,* 1996). EEG measurements and self-reports of cocaine craving were acquired during the measurement of regional cerebral metabolic rates for glucose (CMRglc) using [F-18]fluorodeoxyglucose and positron emission tomography during two test sessions. A videotape on arts and crafts was presented (neutral stimuli) in the first session, whereas in a later second session, the stimulus complex consisted of cocaine-related scenes or objects (videotape of cocaine-related activity, paraphernalia, and cocaine). The subjects were 17 male cocaine abusers and 5 controls. EEG power in the alpha, and alpha, frequency bands was significantly lower during presentation of the drug-related stimuli when compared to the neutral session for the cocaine users but not for controls. Decreased alpha power was negatively correlated with whole brain CMRglc, but not with either the time course or magnitude of self-reports of craving. Specifically, EEG power decreased while levels of cocaine craving were steady throughout the 30-min session. This disassociation between decreased alpha power and craving implies that cue-elicited self-reports of cocaine craving are not simply due to increases in changes in a generalized state of arousal; craving may be more neuroanatomically localized based on correlations with regional CMRglc.

REFERENCES: Available upon request from senior author.

ACKNOWLEDGMENTS: Supported in part by funding from the Counterdrug Technology Assessment Center, Office of National Drug Control Policy, Executive Office of the President.

NEUROPHYSIOLOGIC PREDICTORS OF SUCCESSFUL COMPLETION OF A COCAINE TREATMENT TRIAL

A. F. Leuchter[1,2], G. Bartzokis[1], S. Venneman[2], M. Beckson[2], J. Wilkins[1,2], M. Schaefer[2], and W. Ling[1]

[1]Medication Development Research Unit, WLA VA Medical Center, West Los Angeles, CA and [2]Department of Psychiatry and Biobehavioral Sciences, UCLA

The objective of this study was to examine possible neurophysiologic predictors of cocaine treatment retention. We studied 24 outpatient subjects meeting DSM-IV criteria for cocaine dependence, who were entering a medication treatment trial. We examined quantitative EEG cordance prior to initiation of treatment. All subjects were examined with serial urine studies for benzolylecognine, as well as rating scales of mood, anxiety, craving, and reported substance use. The level of cordance prior to start of the experimental treatment distinguished between those subjects who were likely to remain or drop-out of the trial. Subjects with high cordance had a 90% retention rate over an 8 week trial, while those with low cordance had only 56% retention. Cordance predicted retention after correction for level of cocaine use, depression, and reported craving. These results suggest that cordance may be used to identify a subgroup of subjects who are most likely to have good outcome from treatment for cocaine dependence.

ACKNOWLEDGMENTS: Supported by the Medication Development Research Unit contract 1YO1 DA50038 from the NIDA to the Department of Veteran Affairs, research grant 1RO1 MH40705 (NIMH), and Research Scientist Development Award 1KO2 MH01165 (NIMH).

PREDICTING COCAINE USE OUTCOMES FROM CRAVING IN SIMULATED HIGH RISK SITUATIONS: PRELIMINARY RESULTS

D. J. Rohsenow, R. Martin, and P. M. Monti

VA Medical Center and Brown University, Providence, RI

Studies of the role of craving (urge to use) in drug seeking behavior are important for refining theories of addiction and improving treatment approaches. The objective of this study is to improve the knowledge base about determinants and consequences of urges to use cocaine. The Cocaine Related Assessment of Coping Skills (CRACS) assesses urges to use within the context of 11 simulated high risk situations for cocaine use. High internal consistency is seen (alphas > .89) for urge to use cocaine and urge to use alcohol across scenes. Assessments were given to 139 cocaine abusers in a partial hospital at admission, discharge and 3-month follow up. Urge to use cocaine is predicted ($p < .05$) by several pretreatment variables, including CPI-So (socialization), $r = -.28$, BDI (depression), $r = .24$, Cocaine Effects Scale Negative Expectancies, $r = .21$, and Cocaine Negative Consequences Checklist, $r = .24$, but is not related to pretreatment quantity or frequency of use, number of years of use, or route. Urge to use cocaine at discharge from partial hospital predicted number of cocaine use days in the first 3 months while covarying pretreatment use (partial corr = .19) but not relapse status. These results suggest some role for urges to use in substance use theories, and indicate that urges are more highly determined by consequences of use than by cocaine use per se. The role of urges in treatment outcome is promising and worth further research.

INTER-CORRELATIONS BETWEEN SEVERAL COCAINE CRAVING SCALES AND THEIR RELATIONSHIP TO RECENT COCAINE USE

J. Mezinskis, E. Somoza, H. Wishnick, C. Kidwell, S. Dyrenforth, T. Winhusen, and F. Kropp.

Cincinnati VA/NIDA MDRU, VA Medical Center, Cincinnati, OH

This study had two objectives: 1) to evaluate the inter-correlations between several measures of cocaine craving, and 2) to evaluate cocaine use as a predictor of craving. Subjects were 39 cocaine dependent patients enrolled in substance abuse treatment at a VA Medical Center. Subjects were asked to describe their craving during the past week, as well as during the past 24 hours. Three measures of craving during the past week were collected: 1) the Brief Substance Craving Scale (BSCS), 2) the Cocaine Craving Questionnaire-General (CCQ-G), 3) the Minnesota Cocaine Craving Scale (MCCS). Inter-correlations between these measures are shown in Table 1. All inter-correlations were significantly greater than zero ($p < .05$). However, none of the craving measures were significantly correlated with: a) cocaine use during the past 30 days, b) days since the last use of cocaine, or c) being in a controlled environment during the past 30 days. Two measures of craving during the past 24 hours were collected: 1) the BSCS, and 2) craving as measured on a 10 cm Visual Analogue Scale. These two measures were significantly correlated ($r = .78$; $p < .05$) However, neither measure was correlated with recent cocaine use, days since last use, or being in a controlled environment during the past 30 days It is concluded that various measures of cocaine craving all tap into the same construct. However, paper and pencil measures of craving are not highly correlated with actual cocaine use.

Table 1 : Inter-correlations -Weekly Measures of Craving

	CCQ-G			MCCS	
	Fct. 1	Fct. 2	Int.	Freq.	Dur.
CCQ-G Factor 2	.72				
MCCS Intensity	.52	.58			
MCCS Frequency	.49	.43	.73		
MCCS Duration	.43	.41	.65	.49	
BSCS	.59	.63	.87	.82	.66

URINE BENZOYLECGONINE (BE) IN ABSTINENT COCAINE-ADDICT PATIENTS: ENDOGENOUS COCAINE SYNTHESIS/ENDOCOCAINE

T. Llosa

International Institute of Investigation on Cocaine, Miami, FL

BE is detected in urine for 2-4 days after the lat use. Negative BE urine is an evidence of abstinence. There are reports of prolonged BE presence in abstinent users - 4 men, volunteers, age avg 32.7 y.o; cocaine (inhalated) - addict patients (DSM-IV criteria), avg use 10.5 years, avg 2.75 binge/week in the last year, avg 2 g per binge, were disintoxicated in inpatient clinic. Positive BE urine (Abbott 30 ng/ml sensitivity), avg 953 13 ng/ml (28430-189457) at entry, became negative in 3.5 (2-5) days, and remained negative at 6, 7 and 14 days after. Patients were submitted to verbal/visual high pressure stimulus, in 30 minute session, only 1 day (day 14th). Urine were collected just before the session (3 p.m.), and then 2, 8, 16, 40 and 64 hours after. Each subject gave 6 urines for BE analysis. In every urine collection, subjects answered a craving-test and had physiological controls. In 7 of the last 20 urine tests appeared BE (patient A: 0; 0; 118; 95; 86; 0; patient C: 0; 70; 106; 180; 210; 0) ng/ml. Craving-test scores vary from 0 to 3, 2.75, 2, 1.25, 1.25 during the six urine collection. Pulse rate increased from avg 76 (baseline) to avg 96 during the 30' session and after session was 84, 78, 78, 76, 72, while the other physiological parameters remained between baseline levels. **Conclusions:** Intense verbal/visual stimulus can release cocaine accumulated in deep body (second) compartments, was postulated as possible explanation. Statistical relationship between urine positive results and craving-score was significative (< 0.001) in 2 patients. Our hypothesis on synthesis of cocaine or related substance by the body of chronic cocaine-addicts (endo-cocaine) was not confirmed. It will be necessary protocols with SPECT and other biochemical methods, for specific analysis of the results.

UNDERREPORTING OF COCAINE USE: IMPROVING VALIDITY

A. Lundy and E. Gottheil

Department of Psychiatry, Jefferson Medical College, Philadelphia, PA

Cocaine abusers often grossly underreport their use of cocaine, distorting program assessments and research. In a NIDA-funded project on improving the validity of self-reports, 146 former cocaine patients were interviewed using the ASI under different, randomly determined conditions, and submitted urine and (for 111) hair samples. We expected that subjects who were warned in advance that their answers would be compared to urine and hair results would report more frequent use of cocaine and show a lower level of underreporting than those who were asked for the samples after the interview. However, the two groups differed little. We suspect that rather than reveal cocaine use, many interviewees adopted other strategies to conceal it. For example, those who were warned may have postponed their interviews to avoid a positive urine report: Despite the fact that the warned group had somewhat more cocaine-positive hair samples, 34% had positive urines vs. 51% of the unwarned group, $p < .05$. Also, among a randomly-assigned half interviewed by telephone, 66% of those warned delayed at least a day before coming to the clinic for payment, vs. 39% of those without a prior warning, $p < .05$. Another strategy may have been adopted by those not warned ahead of time; 16% simply declined to yield one or both samples, compared to 1.5% of the group which, with prior warning, could have postponed or avoided the interview, $p < .005$. While these results are preliminary, it appears that improving the validity of cocaine abusers' self-reports may be more difficult than we had at first expected.

ACKNOWLEDGMENT: Supported by NIDA grant R01 DA 09787.

ANTECEDENTS OF SMOKED COCAINE USE IN MALE COCAINE SMOKERS

D. A. Gorelick, N. J. Carriero, M. S. Simmons, and D. P. Tashkin**

NIH/NIDA IRP, Baltimore, MD and *Department of Medicine, UCLA School of Medicine, Los Angeles, CA

Intranasal (IN) cocaine has been considered to have less abuse liability than smoked (S) or IV cocaine. Therefore, we hypothesized that individuals first using cocaine IN would take longer to progress to regular cocaine use than those first using by smoking, and that few of the latter would switch to regular IN use. These hypotheses were addressed using interview data from a convenience sample of 214 male current heavy cocaine smokers (≥ 1 g/week regularly within past year) with no history of IV or other smoked drug use (except tobacco or marijuana) (mean [SD] age 35.2 [6.5] years, education 13.2 [1.9] years, 83.6% African-American, 82.2% in treatment). The recruiting/screening process tended to exclude those with current physical dependence on alcohol or opiates or a current active medical or psychiatric problem requiring treatment. One hundred sixty-three subjects were current cigarette smokers (12.6 [11.1] pack-years); 166 were current marijuana smokers. Self-reported drug use history was obtained by structured interview by research staff independent of any treatment program. Comparisons among groups were done by ANOVA for continuous variables and chi-square or Fishers exact test for categorical variables. Subjects fell into 4 groups based on cocaine route of administration at first use and first regular use: S→S 37%, S→IN 4%, IN→S 40%, IN→IN 20%. The first two groups had a significantly shorter latency from Eirstcocaine use to first regular use (0.9 [2.1] and 0.4 [1.1] years) than did the latter two groups (7.7 [5.3] and 2.1 [4.1] years). Among the 169 subjects in treatment, the IN→IN group had a significantly longer latency from 1st use to interview than did the S→S and IN→S groups (105.9 [57.1] months vs 52.9 [38.9] and 50.1 [44.8] months). The groups differed significantly in race (fewer African-Americans in IN→IN) and current marijuana use (fewer in IN→S), but not in age, education, marital status, employment status, or treatment status. These findings are consistent with the hypothesis that S cocaine has greater abuse liability than IN cocaine. Limitations of this study include reliance on retrospective self-report data and substantial selection bias.

ACKNOWLEDGMENTS: Supported in part by NIH grants DA03018 and DA04268.

AN ANGER MANAGEMENT TREATMENT FOR COCAINE DEPENDENT PATIENTS

P. M. Reilly, M. S. Shopshire, and H. Westley Clark

San Francisco VA Medical Center, University of California, San Francisco

We report the final results of a Stage I study as defined by NIDA's Behavioral Therapies Development Program. Through an iterative process of trial application, review, and revision, we developed a 12-week cognitive-behavioral anger management treatment (AMT) for cocaine dependent patients. Seven cohorts of men (n = 64) and four cohorts of women (n = 32) received AMT. These participants were compared to a group of 15 men who did not receive AMT. All participants were enrolled in standard substance abuse treatment consisting of group counseling twice a week. Trait-anger and anger-expression were measured at baseline, end of treatment, and at 12-week post-treatment follow-up. Random urine toxicology screens were collected weekly during treatment and at follow-up. Participants who received AMT decreased their trait-anger and anger expression significantly between baseline and end of treatment, while participants in the comparison group did not. Decreased levels of trait-anger and anger-expression were sustained at follow-up, and remained significantly lower than baseline levels ($p < .001$). These findings suggest that an anger management treatment is an important component of substance abuse treatment that warrants further study in controlled clinical trials.

ACKNOWLEDGMENT: Supported by NIDA grant P50DA09253.

A COMPARISON OF SIX MEASURES OF THE THERAPEUTIC ALLIANCE AMONG DRUG DEPENDENT INDIVIDUALS

J. J. Cecero, L. R. Fenton, C. Nich, T. Frankforter, and K. M. Carroll

Department of Psychiatry, Yale University School of Medicine, New Haven, CT

The psychometric properties of six measures of therapeutic alliance (California Psychotherapy Alliance Scales; Penn Helping Alliance Rating Scale; Vanderbilt Therapeutic Alliance Scale; and the Working Alliance Inventory - therapist, client, and rater versions) were compared in a sample of substance dependent individuals participating in a randomized clinical trial of three psychotherapies. Internal consistency, interrater reliability by rater and by instrument, and inter-correlations among the instruments were evaluated. Results supported the construct validity of the alliance and indicated that all six measures had acceptable reliabilities. Correlations between observer and participant measures were comparatively low. Reliabilities did vary, however, by treatment condition, and this important new finding invites future research into matching alliance instruments to specific treatments.

ACKNOWLEDGMENTS: Supported by NIDA grants P50 DA09241, R01 DA10679, and K02 DA00248.

QUANTITATION OF mRNAs FOR KAPPA, MU, AND DELTA OPIOID RECEPTOR IN HUMAN BRAIN BY RNase PROTECTION ASSAY

J. E. Myers[1], R. Spangler[1], C. E. Maggos[1], D. P. Perl[2], S. Morgello[2], E. J. Simon[3], J. Hiller[3], E. M. Unterwald[3], B. L. Kieffer[4], L. Yu[5], V. Yuferov[1], K. S. LaForge[1], and M. J. Kreek[1]

[1]The Rockefeller University, [2]Mount Sinai Medical Center, and [3]N.Y.U. Medical Center, New York City, NY; [4]Ecole Superieure de Biotechnologie, Strasbourg, France; [5]University of Cincinnati College of Medicine, Cincinnati, OH

In this study, we extended our previous pilot investigation of human k, μ, and δ opioid receptor mRNA distribution by quantitating their levels in selected regions of the human brain. Brain specimens were obtained from three post-mortem autopsies from neurologically normal patients. Selected brain regions were dissected between 12 and 23 hours post-mortem. Tissue was obtained from the caudate, putamen, globus pallidus internal and external, and substantia nigra. These regions were homogenized, the mRNA was extracted, and the brain homogenates were assayed for levels of opioid receptor mRNA by a quantitative RNase protection assay. The riboprobes for this assay were generated from subcloned cDNAs coding for the human k, μ, and δ opioid receptors. Levels of mRNA of different opioid receptors in each brain region were quantitated and expressed as attomoles specific mRNA/μg total RNA. Due to limited human postmortem material and low abundance of opioid receptor mRNAs, determinations were made using single samples. Previous experiments using this technique in the animal model showed intra-assay variation to be less than 10%. In this initial study, the individual variation in the levels of opioid receptor mRNA seems to be due to differences between individuals. Our finding that the G3PDH mRNA levels show a trend towards correlation with the total RNA in the samples, but not with the values of k opioid receptor mRNA, suggests that mRNA is not degraded in these human brain specimens. Instead, the differences in absolute values of mRNA may be due to the differences in individual histories or agonal state. The techniques now exist to study the postmortem human brain for opioid receptor mRNAs and to determine whether alterations in mRNA are found in postmortem human brains in well-characterized disease states.

ACKNOWLEDGMENTS: Supported in part by grants DA-P50-05130, DA00049, and DA 10223.

STAGES, PROCESSES OF CHANGE AND TREATMENT OUTCOME AMONG COCAINE-DEPENDENT OUTPATIENTS

J. Rothfleisch, J. Grabowski, R. Elk, and H. Rhoades

Substance Abuse Research Center, University of Texas - Houston

The transtheoretical model of change has been applied extensively to describe, predict and intervene on the process of changing addictive behavior. Constructs from the model, including stages and processes of change have been shown to predict successful quitting of several addictive behaviors. However, to date few studies have examined the predictive validity of transtheoretical measures for cocaine abusers. In the present analyses, 95 individuals completed the University of Rhode Island Change Assessment (URICA) and processes of change questionnaire prior to beginning pharmacological treatments for cocaine dependence. During the treatment phase, patients provided two urine specimens per week which were evaluated for cocaine metabolites. Outcome was defined as cocaine abstinence during treatment, measured by the number of cocaine free urine specimens out of the total number of urine specimens provided. Few demographic and drug history measures were related to outcome, with the exception of marital status, $F(2,88) = 3.5$, $p=0.03$. Results of multiple regression analyses indicated that the transtheoretical measures predicted cocaine abstinence during treatment, $F(2, 83) = 2.9$, $p=0.04$, after covarying for marital status. The processes of change including self-reevaluation, consciousness raising, self-liberation, helping relationships, and counter-conditioning appeared to be the strongest predictors.

ACKNOWLEDGMENTS: Supported by NIDA grants DA-06143 and DA-09262

GOAL SETTING, GOAL COMPLETION AND GOAL TYPE AS PREDICTORS OF ABSTINENCE DURING AND AFTER SUBSTANCE ABUSE TREATMENT

C. McNamara, J. B. Milby, J. Schumacher, S. Usdan, D. Wallace, L. A. Bell, and D. Sanders

University of Alabama at Birmingham, Birmingham, AL and Kansas

This study examines the relationship between abstinence and goal setting and completion in a cohort of 74 participants in an 8 week behavioral day treatment program for cocaine abuse/dependence. Once a week participants were encouraged to formulate social/recreation (SGs) and recovery related goals (RGs) which were reviewed and rated the following week by the client and staff. A positive correlation between number of consecutive weeks abstinent on random weekly urine toxicology testing over a 6 month period (ABSTINENCE), and the average number of goals per week set and rated as completed in social/recreational domains (SGSET and SGCOMP) and recovery domain (RGSET and RGCOMP), was hypothesized. Because SGCOMP were likely to reduce the cocaine withdrawal related dysphoria which has been thought to contribute to relapse by increasing social contacts, we hypothesized SGCOMP would better predict abstinence than would RGCOMP. Mean RGSET was 3.22 (SD=99) and mean SGSET was 4.19 (SD=1.37). The mean RGCOMP was 3.30 (SD=2.26) and mean SGCOMP was 4.61 (SD=2.60). The correlations between RGSET and ABSTINENCE and SGSET and ABSTINENCE, -.28 and -.13 respectively were not significant. In contrast, the correlation between RGCOMP and ABSTINENCE , .35, was significant at the $p=.002$ level, and the correlation between SGCOMP and ABSTINENCE, .50 was significant at the $p>.001$ level. When RGCOMP and SGCOMP together were used to predict abstinence in a multiple regression model, they accounted for 25% of the variance in ABSTINENCE; SGCOMP contributed significantly to the model ($p<.001$) but RGCOMP did contribute significantly to the model, indicating that SGCOMP is a better predictor of abstinence than RGCOMP. Overall these results suggest that goal completion may be a valuable predictor of abstinence.

ACKNOWLEDGMENT: Supported by NIDA RO1 DAO8475.

BEHAVIORAL DAY TREATMENT AND DOSE RESPONSE FOR COCAINE ADDICTION AMONG HOMELESS

S. L. Usdan, J. E. Schumacher, J. B. Milby, C. L. McNamara, *D. Wallace, D. Stange, and M. Michael

University of Alabama at Birmingham School of Medicine and *University of Kansas Medical Center

Research suggests more intensive contact early in treatment results in better long-term outcome with homeless cocaine abusers. Findings from this 2-group randomized controlled study of the effectiveness of treatment for homeless cocaine dependent persons demonstrated attendance during two months of behavioral day treatment (BDT) program was related to abstinence. Treatment groups were BDT vs. BDT plus abstinent contingent housing and work therapy. BDT consisted of psychosocial groups, individualized goal-setting, and a voucher system for social-recreational goal achievement. Subjects (N=141) were 78% male, 86% African-American, 38.2 years of age, crack cocaine dependent, homeless persons. Participation in BDT was measured by attendance at any of 24 different therapeutic activities (range=0, 242, median=149). Cocaine abstinence was measured by urine toxicology. Logistic regression was used to model cocaine abstinence as a function of BDT attendance. This model resulted in an odds ratio of 1.28 (95% CI=1.19, 1.39, $\underline{p} < 0.0001$) for every 10 activities. A Hosmer- Lemeshow Goodness of Fit test yielded a p-value of 0.66, indicating an excellent fit. When adjusting for the model by adding type of treatment group, there is no evidence of a difference in effect of attendance across the two treatment groups. Results demonstrate the importance of treatment engagement and suggest higher attendance independent of treatment group results in better abstinence outcomes.

ACKNOWLEDGMENT: Supported by NIDA grant R01 DA 08475.

INITIAL FOLLOW-UP, RESULTS OF RESIDENTIAL TREATMENT AND COMMUNITY SUPPORT FOR HOMELESS CRACK-USING WOMEN

G. J. Stahler*, T. E. Shipley, Jr.*, I. Shandler**, J. DuCette*, L. Simons**, K Godboldte, L. Joy***, G. Grannum*, and E. Weiss****

***Temple University, **Diagnostic and Rehabilitation Center, ***Bridges to the Community, Philadelphia, PA**

This paper presents initial follow-up results on a CSAT-funded demonstration project designed to provide residential treatment and community support for homeless women and their preschool children. The intervention involves six months of residential treatment in a comprehensive community-based program designed specifically to accommodate women and up to two children per client. In addition to traditional psychosocial treatment services, the program utilizes a coalition of local African-American churches (Bridges to the Community) to provide social support to prevent relapse and help clients become re-integrated into prosocial communities. The Bridges program provides mentors and culturally-relevant educational, spiritual, and cultural programming. Volunteers are trained to be "community anchor persons" (CAP), providing clients with daily individual and group fellowship and companionship, sponsorship and mentoring, as well as assistance with housing, child care, and other concerns. Based on initial ASI follow-up data on 57 clients (a follow-up rate of 71%) assessed approximately one year after program entry, 90% of the women reported no cocaine use during the prior 30 days, and 85 % reported no alcohol use. In addition, other treatment outcomes including days paid for working, sexual risk behaviors, social support, self-esteem, depression, and residential stability significantly improved between baseline and follow-up. It is concluded that residential treatment enhanced with culturally-relevant, spiritually-based community support may represent a promising approach to maintaining long-term sobriety in the community. However, the project should be viewed as a pilot study meriting further investigation since it did not include a control group, and outcome assessments were based solely on self-report. This approach merits further systematic investigation employing a randomized clinical trial with urinalysis verification to more rigorously assess its effectiveness.

AGONIST-INDUCED SEQUESTRATION OF HUMAN κ OPIOID RECEPTORS: INVOLVEMENT OF β-ARRESTIN AND DYNAMIN

J.-G. Li, L.-Y. Luo, J. L. Benovic, and L.-Y. Liu-Chen*

Department of Pharmacology, Temple University School of Medicine, and *Kimmel Cancer Institute, Thomas Jefferson University, Philadelphia, PA

Agonist-induced sequestration of G protein-coupled receptors has been proposed to play a role in receptor desensitization, resensitization, and down-regulation. Here we investigated potential mechanisms involved in agonist-induced sequestration of the human κ opioid receptor stably expressed in Chinese hamster ovary (CHO-hkor) cells. Sequestered receptors were quantitated by radioligand binding on intact cells. Under basal conditions, 10-15 % of κ receptors were intracellular. Exposure to the selective κ agonist U50,488H promoted a time- and concentration-dependent increase in intracellular receptors, with 35-40 % of the receptors sequestered following a 30-min exposure to 1 μM U50.488H. After removal of the agonist, sequestered receptors gradually returned to the cell surface over a 60-min period. The antagonist naloxone blocked U50,488H-induced sequestration without affecting sequestration itself. Pretreatment with pertussis toxin had no direct effect on basal or U50,488H-induced sequestration. In contrast, incubation in sucrose (0.4-0.8 M) significantly reduced U50,488H-induced sequestration. In addition, CHO-hkor cells transfected with a dominant negative mutant of G protein-couple receptor kinase 2 (GRK2). β-arrestin, or dynamin also significantly inhibited U50,488H-induced receptor sequestration. while co expression of wild type GRK2 had no effect. These results indicate that agonist-induced sequestration of the human κ opioid receptor in CHO cells is mediated by β-arrestin- and dynamin-dependent process that likely involves clathrin-coated pits.

ACKNOWLEDGMENTS: Supported by NIH grants DA 04745, DA10702, GM44944, GM47417, and Adolor Corp.

DETERMINING THE OPIOID RECEPTOR SELECTIVITY OF AGONISTS AND ANTAGONISTS WITH THE [^{35}S]-GTP-γ-S BINDING ASSAY

J. S. Partilla, Q. Ni*, K. C. Rice†, and R. B. Rothman**

***CPS, IRP, NIDA, NIH, Baltimore, MD and †LMC, NIDDK, NIH, Bethesda, MD**

The [^{35}S]-GTP-γ-S binding assay has gained wide acceptance as a tool to measure the functional effects of agonists and antagonists which act at G-protein linked receptors. We sought to apply this method to determine the subtype selectivity of novel opioid agonists and antagonists using guinea pig caudate membranes rather than cell lines expressing the cloned opioid receptors. Stimulation of [^{35}S]-GTP-γ-S binding by the subtype-selective agonists DAMGO (μ), SNC80 (delta), and U69,593 (kappal) was saturable (Kd values = 515, 309, and 433 nM. respectively). The subtype-selectivity of selected opioid antagonists was assessed by determining their Ki values for inhibition of DAMGO-, SNC80- and U69,593-stimulated [^{35}S]-GTP-γ-S binding. Results are nM (mean±SD, n=3).

	Ki vs DAMGO	Ki vs SNC80	Ki vs U69,593
CTAP	65.7±6.0	>5000	5147±840
TIPP	>5000	4.56±0.52	>5000
nor-BNI	16.8±1.5	10.1±1.0	0.04±0.01
naltrindole	3.21±0.20	0.06±0.01	8.85±0.82
naloxone	1.39±0.14	24.9±2.2	11.4±1.2

Using selective antagonists of mu (CTAP), delta (TIPP) and kappal (nor-BNI) receptors, conditions were developed to determine the subtype-selectivity of agonist compounds. These data, which will be presented, demonstrate that the [^{35}S]-GTP-γ-S binding assay can be used to profile the opioid receptor subtype-selectivity of opioid agonists and antagonists using brain membranes.

BUPRENORPHINE IS A POTENT AND SELECTIVE μ/κ RECEPTOR ANTAGONIST IN THE [^{35}S]-GTP-γ-S FUNCTIONAL BINDING ASSAY

D. Romero, J. S. Partilla, S. O. Heyliger, K. C. Rice, and R. B. Rothman

***CPS, IRP, NIDA, NIH, Baltimore, MD**

We utilized the [^{35}S]J-GTP-γ-S functional binding assay to determine the selectivity of opioid receptor agonists in guinea pig caudate membranes. The study focused on two opioid agonists used for treating opioid dependent patients: methadone and buprenorphine. The following blocking agents were used: to measure mu receptors (TIPP, norBNI), to measure delta receptors (CTAP, norBNI), to measure kappa receptors (TIPP, CTAP). The assay was first validated with opioid agonists of known subtype specificity (DAMGO for mu, SNC80 for delta and U69,593 for kappa receptors). Methadone-stimulated [^{35}S]-GTP-γ-S binding was mu specific and less potent than DAMGO (Kd=2012 nM vs Kd=396 nM), but just as efficacious. Buprenorphine failed to stimulate [^{35}S]-GTP-γ-S binding, but inhibited agonist-stimulated [^{35}S]-GTP-γ-S binding. The antagonist-Ki values (nM) of BUP and naloxone are summarized below.

	Ki vs DAMGO	Ki vs SNC80	Ki vs U69,593
BUP	0.088	1.15	0.072
Naloxone	1.39	24.9	1.14

Autoradiographic studies showed that BUP failed to stimulate [^{35}S]-GTP-γ-S binding in caudate-level rat brain sections but blocked DAMGO-stimulated [^{35}S]-GTP-γ-S binding. Viewed collectively, these data indicate, that in this assay system, BUP is a potent mu and kappa receptor antagonist. The clinical implications of these findings remain to be elucidated.

PHARMACOLOGICAL CHARACTERIZATION OF TWO ENANTIOMERS OF THE MIXED OPIOID AGONIST/ANTAGONIST CYCLAZOCINE

J. P. McLaughlin and J. M. Bidlack

Department of Pharmacology and Physiology, University of Rochester, Rochester, NY

Cyclazocine has been proposed as a low-liability analgesic and potential therapeutic for the treatment of drug abuse. Seeking improvements in opioid activity, the affinity, selectivity and antinociceptive properties of the (+) and (-) enantiomers of cyclazocine for the multiple opioid receptors were characterized and compared to the racemate. In competition binding assays, racemic cyclazocine showed little opioid selectivity but high affinity in binding to the μ, δ and κ receptors, having a K_i value of 1 nM or less. In contrast, (+)cyclazocine demonstrated a five-fold or greater selectivity for the κ receptor over the μ and δ receptors, but bound with low affinity, binding to the κ receptor with a K_i value greater than 70 nM. Conversely, (-)cyclazocine bound with little selectivity but high affinity, binding to all three receptor types with K_i values of 0.5 nM or less. In behavioral analgesic assays, racemic cyclazocine administered i.c.v. produced a 50% antinociceptive response with a dose (and 95% C.L.) of 4.2 (2.1-8.1) nmol in the mouse writhing assay. The (-) enantiomer proved more potent, producing a 50% antinociceptive response with an i.c.v. dose of 2.9 (1.4-6.1) nmol, whereas the (+) stereoisomer required a 15-fold higher dose to duplicate the effect. Likewise, a 0.3-nmol i.c.v. dose of either racemic or (-)cyclazocine antagonized the antinociceptive effect of 3 nmol morphine in the tail-flick test, whereas (+)cyclazocine required a 30-fold higher dose to produce a similar antagonistic response. Co-administration of opioid-selective antagonists demonstrated both (+) and (-)cyclazocine produce antinociception through the μ and κ receptors, but unlike racemic cyclazocine, neither enantiomer had any effect at the δ receptor. Taken together, these data promote findings associating the opioid activity of cyclazocine and its racemic analogues to their (-) enantiomers.

ACKNOWLEDGMENTS: Supported by NIDA grants DA01674, DA03742, and DA07232.

EFFECTS OF THE STABLE DYNORPHIN A(1-8) ANALOG, E-2078, ON SEDATION AND SERUM PROLACTIN LEVELS IN RHESUS MONKEYS

E. R. Butelman, M. Gamstedt, and M. J. Kreek

Laboratory on the Biology of Addictive Diseases, The Rockefeller University, New York, NY

These studies focused on the effects of the stable dynorphin A(1-8) analog, E-2078, in comparison with the selective k-opioid agonist spiradoline and the peripherally-selective k-agonist ICI204,448 on sedation / muscle relaxation and serum prolactin levels in rhesus monkeys. E-2078 (0.1-3.2 mg/kg, s.c., n=5) produced a dose-dependent increase in sedation and muscle relaxation observational rating scores, but these scores reached an apparent plateau below the maximum possible effect. Spiradoline (0.0032-0.1 mg/kg) was more potent than E-2078 in this procedure, and appeared to cause higher maximum sedation and muscle relaxation scores than E-2078. ICI204,448 (0.1-3.2 mg/kg) was approximately equipotent and equieffective to E-2078 on sedation and muscle relaxation scores. Spiradoline (0.001-0.1 mg/kg, n=4) dose-dependently increased serum prolactin levels in females during their follicular phase (ED_{50}=0.006 mg/kg). E-2078 was equieffective and approximately equipotent to spiradoline in this procedure (ED_{50}=0.003 mg/kg), whereas ICI204,448 was slightly less potent (ED50=0.03 mg/kg) but slightly more effective than either E-2078 or spiradoline. The cumulative dose-effect curve for E-2078 on serum prolactin levels was shifted in a parallel, surmountable manner by pretreatment with the opioid antagonist naltrexone (0.1 mg/kg, s.c.). The present studies show that a subcutaneously administered dynorphin analog E-2078, can produce clear k-opioid effects in rhesus monkeys, and that in contrast with the non-peptidic k-agonist, spiradoline, E-2078 is substantially more potent in increasing serum prolactin levels (thought to be under tonic inhibitory control by the tuberoinfundibular dopaminergic system) than in causing sedative or muscle relaxant effects.

ACKNOWLEDGMENTS: Supported by NIDA grants DA 11113, DA05130, and DA00049.

DELTA-OPIOID RECEPTOR MEDIATED HYPOTHERMIA IN MICE

L. K. Chambers, R. Murphy, and R. S. Mansbach

Department of Neuroscience, Pfizer Central Research, Groton, CT

Opioid receptors are thought to play a role in thermoregulation. Some agonists produce increases in body temperatures and some produce decreases, the effect being dependent on receptor selectivity, ambient temperature, species and other factors. Thermic responses to delta opioid receptor agonist administration have not been extensively studied, and the available results with peptide agonists are mixed. In the present study, effects of the small-molecule, delta-selective agonist SNC80 were studied on body temperature in male ICR mice housed at an ambient temperature of ~20°C. SNC80 produced a significant and dose-dependent hypothermia 30 min post-injection, with a maximal temperature decrease of approximately 4°C. This effect was reversed by the delta-selective antagonist naltrindole, with significant blockade at doses as low as .032 mg/kg s.c. In contrast, naltrindole (0.1-10 mg/kg) did not significantly reverse the hypothermic effects of morphine (10 mg/kg), and the kappa-selective antagonist nor-BNI (10 mg/kg) did not block the hypothermic effect of SNC80. SNC80 produced a modest (0.8°C) hypothermia in rats, consistent with effects previously reported with peptide agonists. Taken together, these data support a role for delta opioid receptors in thermoregulation, and suggest that the magnitude of thermic responses to delta agonists may be species-dependent.

POSSIBLE MECHANISM OF HYPOTHERMIA INDUCED BY INTRACEREBROVENTRICULAR INJECTION OF ORPHANIN FQ

X. H. Chen, D. B. McClatchy, L. Y. Liu-Chen, E. B. Geller, and M. W. Adler

Department of Pharmacology, Temple University School of Medicine, Philadelphia, PA

Orphanin FQ (OFQ)/nociceptin, a 17-amino-acid peptide, is an endogenous peptide whose receptor is similar in sequence to μ, δ and κ opioid receptors (~75% homology). It is well known that the μ opioid receptor is involved in hyperthermia in rats and the κ opioid receptor in hypothermia. Studies have reported that OFQ can block the antinociception induced by μ, δ and κ opioid agonists in the rat and in the mouse, and that OFQ (1.8 μg, icv) can decrease morphine-induced hyperthermia, indicating that there is a functional interaction between opioid receptors and OFQ receptors in the brain. However, icv injection of a high dose of OFQ (9-18 μg) was found to produce hypothermia in rats. The present studies were designed to explore the mechanism of OFQ hypothermia. Adult male SD rats were used. The antisense (AS) oligodeoxynucleotides (oligos) to the OFQ receptor were dissolved in sterile saline. The sequences are as follows: OFQ receptor-AS-oligo, 5'-TCCATGCTG-TCACCCTGC-3' (complementary to nucleotide number 40-57 of the coding region) and OFQ receptor-missense (MS)-oligo, 5'-ACCATCCTCTGT-CGCTGC-3'. These results showed that (1) the opioid receptor antagonist, naloxone (10 mg/kg, sc) and κ opioid receptor antagonist nor-BNI (1 μg/5μl) did not reduce the hypothermia induced by icv injection of OFQ at dose of 20 μg ($p>0.05$); (2) a 20 μg/5μl AS oligo treatment (icv, days 1, 3 and 5) against OFQ receptors reduced, but not significantly, the hypothermia induced by icv injection of 18 μg OFQ. Because of a very high concentration of OFQ receptors in the brain, longer or higher doses of OFQ receptor AS oligo treatment may be needed to decrease the OFQ receptors in the brain sufficiently to antagonize the OFQ-induced hypothermia. After 60 μg/5μl AS oligo (icv treatment on days 1, 3 and 5) against OFQ receptors, the hypothermia induced by icv injection of 9 μg OFQ was significantly reduced ($p<0.01$). These results suggest that the hypothermia induced by icv injection of a high dose of OFQ (9 or 18 μg) is mediated, at least partially, by its own receptor, not by an opioid receptor in rat brain.

ACKNOWLEDGMENT: Supported by NIDA grant DA 00376.

EFFECTS OF PERTUSSIS TOXIN AND CYCLIC AMP ON HYPERTHERMIA CAUSED BY THE μ-OPIOID RECEPTOR AGONIST PL017 AND MORPHINE

L. Xin, E. B. Geller, R. B. Raffa, and M. W. Adler

Department of Pharmacology, Temple University School of Medicine, Philadelphia, PA

It has been reported that μ-opioid receptor agonists exert their analgesic effect through coupling with the Ci / Go proteins. In order to find out if similar mechanisms exist in hyperthermic effects by the agonists, pertussis toxin (PTX), a Gi / Go protein inactivator, cholera toxin (CTX), a Gs protein activator, or saline was given i.c.v. to male S-D rats, before i.c.v. injection of PL017 or morphine (M). In the rats pretreated with saline, PL017 (1 μg) and M (10 μg) increased body temperature (Tb) up to 1.6 ± 0.4 °C and 1.8 ± 0.3 °C, respectively, at 60 min. Pretreatment with a single injection of PTX (0.5 μg) 6 days earlier reduced the hyperthermia induced by PL017 and M to 0.7 ± 0.4 and 0.6 ± 0.3 °C, respectively. Pretreatment with a single injection of CTX (0.5 μg) did not affect the hyperthermia caused by either opioid drug. Two groups of rats without any pretreatment were injected with 8-bromo-cAMP (40 μg), an analog of cyclic AMP that can penetrate the cell membranes, 20 min before injection of PL017 or M. This pretreatment decreased the hyperthermia caused by PL017 and M to 0.6 ± 0.3 and 0.3 ± 0.3 °C, respectively. I.c.v. injection of 8-bromo-cAMP 20 min before saline also decreased Tb to -0.6 ± 0.3 °C. PTX (0.5 μg) attenuated the analgesic effect of PL017 (1 μg) and M (10 μg) by reducing the percent maximum possible analgesia (% MPA) to 60 % and 55 %, respectively, in the cold water tail-flick test, while CTX (0.5 μg) did not affect the analgesia induced by either opioid drug. These results suggest that the Gi / Go proteins and the cAMP level may be involved in the intracellular signal transduction mechanisms of the hyperthermia, as well as analgesia, caused by μ-opioid receptor agonists

ACKNOWLEDGMENT: Supported by NIDA grant DA 00376.

PHOSPHORYLATION OF THE L-TYPE CALCIUM CHANNEL BY PKA IN THE BRAINSTEM OF MORPHINE-TOLERANT MICE

M. A. Bernstein, V. L. Haller, and S. P. Welch

Department of Pharmacology and Toxicology, Medical College of Virginia of Virginia Commonwealth University, Richmond, VA

Cross-tolerance develops between the antinociceptive effect of morphine and that of drugs acting at the "L-type" or dihydropyridine (DHP)-sensitive class of voltage-gated calcium channels. Previous studies conducted in this laboratory indicate that the number of L-type channels is unaltered following acute or chronic morphine treatment. However, tolerance to morphine-induced antinociception can be reversed by administration of an inhibitor of protein kinase A (PKA). This study examines whether changes in channel phosphorylation occur with chronic opioid treatment, contributing to the expression of cross-tolerance between morphine and DHPs. Binding studies were conducted by displacing [^{3}H]nitrendipine with (S)-Bay K 8644, an activator of the channel that has been shown to be sensitive to the channel's phosphorylation state. Brainstem tissue from chronically morphine-treated or control mice was prepared in the presence of phosphatase inhibitors. EBDA analysis revealed a curvilinear Hofstee plot for morphine-tolerant mice but not acutely morphine-treated or control mice, suggesting that a second (S)-Bay K 8644 binding site is present following chronic morphine treatment. Pre-incubation of the tissue with a cAMP analog or purified PKA catalytic subunit also produced a curvilinear plot for (S)-Bay K 8644, implicating phosphorylation of the channel as the source of this second site. Using an anti-peptide antibody specific for the α_{1c} subtype of the L-type channel, immunoprecipitation followed by back-phosphorylation reaction with PKA was conducted to assess subunit phosphorylation state induced by in vivo morphine treatment. Our results indicate that the phosphorylation state of the α_{1c} subunit is unaltered by morphine.

ACKNOWLEDGMENTS: Supported by NIDA grants R01DA01647, T32DA07027, and K02DA00186.

THE ROLE OF NITRIC OXIDE PRODUCTION IN SPINAL CORD DURING MORPHINE WITHDRAWAL IN RATS

W. Zhou, B. Zhu, X. Xie, Y. Zhang, and G. Yang

Ningbo Microcirculation and Henbane, Ningbo, China

Recent evidence has shown that nitric oxide (NO) mediates many physiological processes through the NO-cGMP system in spinal cord. The decrease or increase of cGMP level in spinal cord during morphine dependence or withdrawal has been observed in this lab. In addition, intrathecal injection with inhibitor of NO synthase (NOs) could control the morphine withdrawal. These evidences suggested that NO production system may be regulated by chronic morphine treatment. The present results showed that the activities of NOs in morphine dependent rats were 1.3+0.37 nmol/mg, which were lower than that the activities of NOs (2.97±051 nmol/mg, n=5, $p<0.05$) in control animals, while the activities of NOs in morphine withdrawal rats precipitated by naloxone were 3.85±1.42 nmol/mg which increased significantly compared with morphine dependent rats (n=5, $p<0.05$). The NO_2/NO_3 (the end products of NO) level in spinal cord was 0.58±0.13 nmol/mg in morphine dependent rats, which was decreased compared with the control animals (1.3±0.2 nmol/mg, n=5, $p<0.01$), and during morphine withdrawal, the NO level was increased over that of morphine dependent rats (1.09±0.23 nmol/mg, n=5, $p<0.01$). L-N-nitroarginine methyl ester (L-NAME), a competitive inhibitor of NOs, was administered as a single injection (10 mg/kg, ip) 1 h before the injection of naloxone in morphine dependent rats, it was revealed that L-NAME reduced the total ratings of withdrawal signs, and also decreased the NO production in spinal cord. The results indicated that the NO production and release at spinal level may play an important role in the morphine dependence or withdrawal.

EFFECTS OF MUSCARINIC RECEPTOR ANTAGONISTS ANISODAMINE AND ANISODINE ON MORPHINE DEPENDENCE IN RATS

G. Yang, W. Zhou, and Y. Zhang

Ningbo Drug Withdrawal Research Center, Ningbo, China

Muscarinic systems appear to play an important role in the processes of morphine dependence and muscarinic receptor selective antagonist can block the morphine withdrawal. Anisodamine and anisodine, both muscarinic receptor antagonists, have been used in a clinic in China, moreover, their side-effects were less than those of scopolamine and atropine in clinical practice. The present study was to observe the effects of anisodamine and anisodine on the morphine withdrawal. The male Sprague Dawley rats were made dependent on morphine and ratings of opioid withdrawal signs were made every 15 minutes for one hour. Pretreatment with anisodine hydrobromid (0.25, 0.75, 2.25, 4.5 mg/kg, i.p., n=5 in each group), the ratings of naloxone precipitated morphine withdrawal signs across the session were 21.8±2.9, 18.5±2.1, 12.5±1.7 and 8.0±2.3, respectively, which were different significantly from that of placebo (25.8±3.2), while pretreatment with ansodamine at dose of 1.0, 4.0, and 16 mg/kg, the ratings of morphine withdrawal signs were 15.0±3.2, 12.5±2.6 and 12.0±1.9, respectively, which were lower than those of control animals. The present observation showed that anisodine could inhibit the morphine withdrawal signs such as irritating, diarrhea, wet dog shakes and weight loss in dose-dependent manner, however, anisodamine only partially inhibit the withdrawal, suggesting that both anisodine and anisodamine may be useful for management of opioid withdrawal syndrome.

EFFECTS OF HEROIN ON HIPPOCAMPAL THETA AND VTA FACILITATION OF DENTATE RESPONSES

J. R. Criado, S. C. Steffensen, R. A. Gallegos, and S. J. Henriksen

Department of Neuropharmacology, The Scripps Research Institute, La Jolla, CA

Conditioning and learning processes are known to play a key role in drug addiction. Dopamine (DA) neurons in the ventral tegmental area (VTA) are a fundamental component in the neural system underlying drug reward and play a role in the regulation of septohippocampal cholinergic transmission and in cognitive processes. Opiates and opioid peptides have been shown to enhance transmission of auditory sensory information from the entorhinal cortex to the dentate gyrus and to modulate hippocampal theta rhythm. Therefore, we sought to pharmacologically characterize the effect of heroin on VTA facilitation of dentate responses and its relationship to hippocampal theta rhythm. Conditioning stimulation of the VTA produces a robust facilitation of perforant path to hippocampal dentate population spikes, termed VTA facilitation. Our data from this study show that generation of hippocampal theta induced by tail-pinch markedly reduced VTA facilitation of dentate responses. Consistent with these findings, high doses of heroin (0.6 mg/kg, s.c.), which significantly enhanced VTA facilitation, completely blocked the generation of hippocampal theta. On the other hand, low doses of heroin (0.1 mg/kg, s.c.), which suppressed VTA facilitation, had little effect on the generation of hippocampal theta. Systemic administration of naloxone (1.0 mg/kg, i.p.) also had little effect on VTA facilitation, but blocked the inhibitory and the excitatory effects of heroin on VTA facilitation. Naloxone also blocked the suppressive effects of heroin on hippocampal theta. Evidence from these studies suggests that hippocampal theta is an important index of opioid effects on mesolimbic modulation of hippocampal function. Further studies will determine the neuroanatomical sites and neurotransmitter systems mediating this dose-dependent effect of heroin and the functional relationship between VTA facilitation and hippocampal theta.

ACKNOWLEDGMENTS: Supported by grants DA-08301, AA-10075 and AA-06420.

CHRONIC HEROIN ABUSE ALTERS THE DOPAMINE SYNAPSE IN HUMAN BRAIN

S. Izenwasser[1], B. J. Ciliax[2], A. I. Levey[2], and D. C. Mash[1]

'Department of Neurology, University of Miami School of Medicine, Miami, FL and [2]Department of Neurology, Emory University, Atlanta, GA

Chronic abuse of heroin produces alterations in brain neurochemistry that underlie the tolerance and addiction of this drug. Since opioid agonists such as heroin regulate dopamine release in terminal regions of the brain, it is likely that continued use of heroin will produce alterations in dopaminergic markers. In order to determine what effects chronic heroin abuse has in human brain, immunoautoradiographic techniques were used to measure levels of dopamine D_1 and D_2 receptors in the striatum and nucleus accumbens of human brain from heroin overdose and control cases. A monoclonal antibody against the carboxy terminus of the dopamine D_1 receptor, or a polyclonal antibody against the third intracellular loop of the dopamine D_2 receptor was used to visualize receptor distribution. This methodology allows the opportunity of selectively measuring these subtypes of dopamine receptors, in the absence of selective ligands for subtypes within each family of receptors. In addition, tyrosine hydroxylase immunoreactivity was measured, as a marker of presynaptic integrity. Chronic heroin abuse and subsequent overdose produces a significant decrease in dopamine D_1 receptors in the anterior caudate and putamen, and in nucleus accumbens of human brain. In contrast, there is no significant alteration in dopamine D_2 receptors in these brain regions. Tyrosine hydroxylase immunoreactivity was also greatly reduced in these regions in heroin overdose as compared to control cases. Thus, chronic heroin use selectively alters D_1 but not D_2 receptors, and also interferes with the dopamine synthesis pathway.

ACKNOWLEDGMENT: Supported by NIDA grant DA-09484.

DOPAMINE D1/D2 RECEPTOR INTERACTIONS IN COCAINE'S DISCRIMINATIVE STIMULUS EFFECTS IN RHESUS MONKEYS

R. S. Sinnott, R. H. Mach, and M. A. Nader

Department of Physiology/Pharmacology, Wake Forest University School of Medicine, Winston-Salem, NC

Both dopamine D_1 and D_2 receptors have been shown to play a role in the behavioral effects of cocaine. The present studies were designed to investigate the hypothesis that D_1- and D_2-like receptors interact to modulate cocaine's discriminative stimulus effects. For these experiments, rhesus monkeys (n=3) were trained to discriminate cocaine (0.2 or 0.3 mg/kg, i.m., 10-min pretreatment) from saline under a fixed-ratio schedule of food reinforcement. First, the cocaine-like discriminative stimulus effects of the D_2/D_3 agonist (±)-7-OH-DPAT and the high efficacy D_1 agonist SKF 8 1297 were evaluated alone. Pretreatment times were varied from 10 min to 2 hr. (±)-7-OH-DPAT (0.003-0.3 mg/kg) did not substitute at 10 min but fully substituted for cocaine when given 60 min prior to a test session. SKF 81297 (0.1-5.6 mg/kg) did not substitute at 10 min but completely substituted for cocaine in one animal at 30 min, and in a second animal at 2 hr. Next, the cocaine-like discriminative stimulus effects of combinations of SKF 81297 and (±)-7-OH-DPAT were evaluated. Preliminary data suggested that doses of each compound that alone occasioned only saline-appropriate responding, resulted in 100% cocaine-appropriate responding when given in combination. Together, these data suggest that 1) agonists that stimulate only D_1 or D_2-like receptors can substitute for cocaine and 2) the combination of a high efficacy D_1 agonist and a D_2-like agonist may summate to produce cocaine-like discriminative stimulus effects.

ACKNOWLEDGMENTS: Supported by NIDA grants DA 09142, DA 06634, and DA 05782.

COCAINE-ANTAGONIST PROPERTIES OF THE D1 PARTIAL AGONIST SKF 83959 IN SQUIRREL MONKEYS

D. M. Platt, R. D. Spealman, and J. K. Rowlett

Harvard Medical School, New England Regional Primate Research Center, Southborough, MA

Preclinical studies suggest that dopamine partial agonists warrant consideration as candidate medications for cocaine abuse. The benzazepine derivative SKF 83959 is a D1 partial agonist with a distinctive profile of agonist-like and antagonist-like properties. The present study assessed the potential antagonism of the behavioral effects of cocaine by SKF 83959. Squirrel monkeys were trained either to respond on a fixed-interval (FI) schedule in which cocaine produces consistent increases in response rate or to discriminate cocaine from saline using a two-lever drug discrimination procedure. When combined with cocaine (0.030-10 mg/kg), SKF 83959 (0.10-3.0 mg/kg) attenuated both the rate-increasing effects of cocaine on FI responding and the discriminative stimulus (DS) effects of cocaine, resulting in dose-dependent rightward shifts in the dose-response functions. These cocaine-antagonist effects are similar to those observed for the Dl antagonist ecopipam (SCH 39166, 0.030-0.18 mg/kg). In the absence of cocaine, SKF 83959 neither mimicked the DS effects of cocaine nor increased FI response rate. In quantitative observational studies, SKF 83959 (0.10-17.8 mg/kg) and ecopipam (0.010-0.30 mg/kg) produced decreases in locomotion and environmental manipulation, along with increases in the frequency of species-typical resting postures. The highest doses of SKF 83959 and ecopipam also induced cataleptic-like postures in at least half of the monkeys tested. These doses. however, were 10-33 times higher than doses that antagonized the behavioral effects of cocaine. The results suggest that SKF 83959 has properties of a functional cocaine antagonist with primarily sedative-like side effects.

ACKNOWLEDGMENTS: Supported by NIDA grants DA00499, DA11054 and RR00168.

IDENTIFICATION OF C-TERMINAL PEPTIDES FROM COCAINE- AND AMPHETAMINE-REGULATED TRANSCRIPT (CART) IN SPRAGUE-DAWLEY RATS AND EVIDENCE FOR PEPTIDE PROCESSING

P. R. Couceyro and M. J. Kuhar

Yerkes Regional Primate Research Center and Emory University, Atlanta, GA

CART is a brain enriched transcript that encodes for a putative novel neuropeptide(s). Previous work has implicated in drug reward and reinforcement. Exogenous and endogenous CART peptides mediate food intake and these effects can be produced by different CART peptide fragments. We now demonstrate the presence of CART peptides in the rat brain and periphery for the first time. Tissue extracts from male Sprague-Dawley rats were run on Tricine SDS-PAGE gels and transferred to PVDF membranes. Western blot analysis with an antiserum to CART 106-129 identified specific bands of 11.0, 9.8, 7.6, 5.4 and 5.0 kD in the longitudinal muscle-myenteric plexus (LM-MP), bands of 9.8, 5.4 and 5.0 kD in the pituitary and bands of 11.0, 9.8, 7.6 and 5.4 kD in the nucleus accumbens/olfactory tubercle, hypothalamus, olfactory bulb (except the 9.8 kD), and hippocampus (except the 11.0 and 9.8 kD). Under these conditions, the described bands were undetectable in the dorso-caudal striatum, motor cortex, vermis of the cerebellum, thalamus, midbrain, hindbrain, and smooth muscle-submucosal plexus of the ileum. This distribution pattern of CART peptides by Western blot analysis is consistent with our previous immunohistochemical and in/situ hybridization studies. Tissue-specific differential processing of the CART pro-peptide is inferred from the different bands seen in the LM-MP, pituitary and several brain areas, but further work is needed for definitive proof. These data also support our previous work demonstrating that C-terminal CART peptides are behaviorally and functionally relevant. In summary, we demonstrate for the first time the presence of several CART peptides in the rat. These data will assist in the sequencing and structural characterization of endogenous CART peptides as well as help elucidate the role CART peptides in reward, reinforcement, and drug addiction.

ACKNOWLEDGMENTS: Supported by NIH grant DA 10732.

CART PEPTIDE IMUNOREACTIVITY IN THE HYPOTHALAMIC PVN IN MONKEYS: DISTRIBUTION AND INTERACTIONS WITH NPY

S. E. Dall Vechia, J-F. Pare, P. Lambert, P. Couceyro, M. Kuhar, and Y. Smith

Yerkes Primate Research Center, Emory University, Atlanta, GA

Cocaine and amphetamine related transcript (CART) mRNA levels have been reported to increase in the striatum after acute injection of cocaine or amphetamine. CART has been identified to be one of the most abundant mRNA transcripts in the hypothalamus. In addition, intraventricular injections of CART peptides decrease food intake in the rat. In contrast, Neuropeptide Y (NPY), a major neuropeptide involved in the control of feeding increases food intake mostly via interactions with PVN neurons. To better understand the potential role of CART peptides in neuroendocrine functions, such as feeding, the goals of our study were, first, to characterize the distribution. ultrastructural features and synaptic connectivity of CART peptide- immunoreactive (CARTir) neurons in the monkey PVN and. second, study their synaptic interactions with NPY- immunoreactive (NPYir) terminals. Although CARTir cell bodies, dendrites and terminals are distributed throughout both the parvicellular and magnocellular regions of the PVN, the parvicellular region contains more immunoreactive elements. Electron microscopic analysis revealed that CARTir dendrites in the PVN rerceived mostly asymmetric synapses from immunoreactive and nonimmunoreactive terminals. Immunoreactive neurosecretory dendrites were found throughout the nucleus. Most CARTir terminals, which are densely packed with both small. round electron lucent vesicles and intensely stained dense core vesicles, form asymmetric synapses with dendrites. In double immunolabeling studies, NPYir varicositics are found in apposition to CARTir perikarya. However, direct synaptic links between NPYir terminals and CARTir neurons were not found in the electron microscope. In conclusion, our findings suggest that CARTir neurons may play a role in feeding via interaction with NPY in the PVN.

ACKNOWLEDGMENTS: Supported by DA10732 and R00165.

BEHAVIORAL AND HPA RESPONSES TO CHRONIC "BINGE" PATTERN COCAINE IN MICE DEFICIENT IN THE PROTEIN PHOSPHATASE INHIBITOR DARPP-32

A. Ho, S. D. Schlussman, Y. Zhou, A. A. Fienberg, P. Greengard, and M. J. Kreek

The Rockefeller University, New York, NY

As part of a systematic investigation of the role of protein phosphatase inhibitors in mediating the actions of psychostimulant drugs, mice with a targeted disruption of the gene coding for DARPP-32, a dopamine- and cyclic AMP-regulated protein found in rodent brain in regions involved in behavioral responses to cocaine, were studied (Fienberg *et al,* in press; Ouimet *et al,* 1984). **Method:** Nine individually caged adult males deficient in DARPP-32 and 9 wild-type mice received 3 daily injections of cocaine (15/mg/kg ip) at hourly intervals starting half an hour into the light portion of the 12-12 hr light-dark cycle, while 8 of each genetic group received saline on the same schedule for 14 days. The spontaneous locomotor activity of each mouse was recorded on a 24-hour basis, and ratings of behavioral stereotypy were made after each injection in the home cage. **Results:** In the baseline period, there were no significant differences between mice with different genotypes in circadian rhythm of activity. Cocaine-treated mice showed significantly higher levels of locomotor activity following each injection than did saline controls, in agreement with our earlier studies in Fischer rats (Unterwald *et al,* 1994), and in C57BL/6J mice (Ho *et al,* 1998). Cocaine also produced significant stereotypy as seen in the Fischer rat (Spangler *et al.,* 1997), and in both C57BL and 129 mice (Schlussman *et al,* 1998). No differences between mice with and without the gene coding for DARPP-32 were found in either unstimulated circadian locomotor activity or in behavioral responses to cocaine. However, mice with the DARPP-32 gene disruption failed to show the significantly elevated levels of plasma corticosterone found in wildtype controls after 14 days of chronic binge pattern cocaine administration.
References avai table on request.

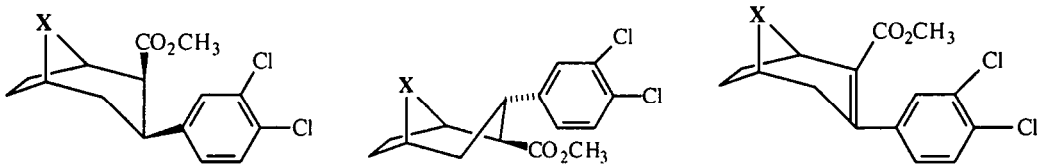
ACKNOWLEDGMENTS: Supported by NIDA grants P50-DA05130, DA00049 (MJK) and DA10044 (PG)

MOLECULAR INTERACTIONS AT THE DOPAMINE TRANSPORTER: THE BICYCLO[3.2.1]OCTANE SYSTEM

P. C. Meltzer, P. Blundell, Z. Chen, Y. F. Yong, and B. K. Madras

Organix Inc, Woburn, MA and Harvard Medical School

Cocaine is a potent stimulant of the mammalian central nervous system and its reinforcing and stimulant properties have been associated with its propensity to bind to the dopamine transporter (DAT). The binding interaction between the tropanes and their biological target at the molecular level is still uncertain. An 8-amino nitrogen has been assumed to be a prerequisite for binding between the DAT and its ligands. We reported that substitution of the 8-amino nitrogen by an 8-oxygen atom can result in potent ligands for the DAT and showed that a hydrogen bonding interaction may mediate binding to the DAT. We have now prepared 8-carbatropanes and the potency of these compounds has demonstrated that the function of the 8-atom is not an active binding one but rather a topological one. Could it be that the 8-atom holds the molecule in its three dimensional conformation and stereospecifically provides a molecular volume for recognition by a putative cylindrical transporter? This leads to the speculation that a multitude of molecules should interact with the DAT as long as they occupy homologous three dimensional space.



X = CH_3N; O; CH_2

ACKNOWLEDGMENTS: Supported by NIDA DA4-8309, DA7-8081, DA09462, DA06303, and RR 00168.

PIPERIDINE ANALOGS OF COCAINE: POTENT INHIBITORS OF THE DOPAMINE TRANSPORTER WHICH LACK THE TROPANE SKELETON

J. W. Boja, G. L. Araldi, W. M. Meil, K. M. Johnson,[†] C. George,[#] and A. P. Kozikowski**

Dept. of Pharmacol., NEOUCOM; Drug Discovery Program, Georgetown University Medical Center; and [†] University of Texas Medical Branch; [#] Naval research Laboratories

The piperidine-3-carboxylic esters were first reported by R. L. Clarke (*J. Med. Chem.* **1973,** 16, 1260), these compounds differ from the familiar WIN series of compounds in that they lack the two-carbon bridge in the tropane ring. Unlike the WIN series of compounds the racemic piperidine-3-carboxylic esters were shown to lack locomotor stimulant activity when tested in mice. These compounds were synthesized and tested for their ability to inhibit the binding of the cocaine analog [^{3}H]WIN 35,428 and the uptake of [^{3}H]dopamine. The (-)-3*b*-*n*-propyl piperidine analog was the most potent of all the compounds tested. The binding affinity of this compound was 33-fold greater than cocaine, and 29-fold more potent than cocaine in the inhibition of [^{3}H]dopamine uptake. Surprisingly, the binding affinity of the the (+)-3*a*-*n*-propyl analog was only 5-fold less potent than the 3*b* analog. This is in contrast to the tropane series of compounds which demonstrate a greater lowering of activity. The smaller shift in binding affinity may reflect the smaller size of the piperidines relative to the tropanes rather than a different binding domain since these compounds recognize the high- and low-affinity [^{3}H]WIN 35,428 binding sites. The significant effects for the dopamine transporter and reported lack of motor stimulating effects of the 3*a*-piperidine derivatives suggest these compounds deserve attention as potential agents for the treatment of cocaine addiction.

ACKNOWLEDGMENT: Supported by NIDA grant DA 11546.

SYNTHESIS AND BIOLOGICAL EVALUATION OF A SERIES OF N-SUBSTITUTED 3'-CHLORO ANALOGS OF BENZTROPINE

A. H. Newman, M. Robarge, G. E. Agoston, R. H. Kline, S. Izenwasser, and J. L. Katz

Psychobiology Section, NIDA-IRP, NIH, Baltimore, MD

Although 4'-chlorobenztropine (4'Cl-BZT) and many of the analogs we have prepared, bind with high affinity to the dopamine transporter and inhibit dopamine reuptake, they do not demonstrate cocaine-like behavioral profiles in animal models of drug abuse. However, we recently reported that 3'-chlorobenztropine (3'CI-BZT), despite its similar structural and neurochemical profile to other phenyl ring substituted analogs, demonstrated efficacious locomotor stimulant activity in mice and generalized to cocaine in drug discrimination. The reason for these results is not clear and further study seemed warranted. The 3',4"-dichlorobenztropine analog (3',4"-diCI-BZT) was prepared and evaluated. This compound was equipotent at dopamine transporters (K_i=33 nM) but ~17-fold less potent (K_i=17 nM) at muscarinic sites as compared to the parent 3'- and 4'CI-BZT analogs. Interestingly, this compound did not show a cocaine-like behavioral profile, as did 3'CI-BZT, but was behaviorally more like 4'CI-BZT. In a series of N-substituted analogs of 4',4"-difluoro-benztropine (4',4"-diF-BZT), muscarinic receptor binding of these compounds was significantly reduced with certain N-substituents and this further altered the behavioral profile of these compounds. Subsequently, selected N-substituted (H, butyl, Bz, propylPh, butylPh) 3'CI-BZTs were prepared and evaluated. Preliminary binding results suggest that the sterically bulky N-substituents in the 3'CI-BZT series may not be as well tolerated at the dopamine transporter as observed for the 4'4"-diF-BZT series of compounds. Ongoing molecular modeling studies and additional biological data will be used to propose structure-activity relationships in this novel series of benztropine analogs.

ACKNOWLEDGMENT: Supported by NIDA Intramural Research Program.

A COMPARISON OF THE NEUROBIOLOGICAL AND NEUROBEHAVIORAL EFFECTS OF PTT AND COCAINE IN RAT

C. S. Freedland, H. R. Smith, J. B. Daunais, S. L. Hart, H. M. L. Davies, and L. J. Porrino*

Department of Physiology and Pharmacology, Wake Forest University School of Medicine, Winston-Salem *Department of Chemistry, SUNY Buffalo, Buffalo, NY

PTT (2-propanoyl-3(4-toluyl)-tropane) is a novel cocaine analog that acutely induces cocaine-like increases in locomotor activity. These increases are much longer lasting than those induced by cocaine. The purpose of the present study was to compare the neurobiological and behavioral consequences of chronic PTT administration with the established effects of chronic cocaine administration. In this study, PTT (1.0 and 3.0 mg/kg. i.p.) and cocaine (30 mg/kg) were administered to rats daily for ten days. Locomotor activity was measures each day following drug treatment for four hours. Both PTT and cocaine induced increases in horizontal activity. Locomotor activity was augmented in all three groups from Day 1 to Day 10 suggesting behavioral sensitization. The neurobiological effects of PTT and cocaine were assessed using in vitro receptor autoradiography and in situ hybridization histochemistry. Autoradiographic experiments utilized [3H]CFT, a dopamine transporter (DAT) selective ligand. PTT produced dose-dependent increases in DAT binding sites consistent with the increases seen with chronic cocaine administration. Chronic PTT also produced dose-dependent decreases in DAT message consistent with the decreases seen following chronic cocaine administration. These data suggest that the substrates underlying the neurobiological and behavioral effects of PTT parallel those underlying cocaine's actions.

ACKNOWLEDGMENTS: Supported by DA06634, DA07522, and DA06301.

STRUCTURE-ACTIVITY RELATIONSHIPS FOR METHYLPHENIDATE ANALOGS AND COMPARISONS TO COCAINE AND TROPANES

H. M. Deutsch, M. M. Schweri, S. Holtztman^, X. Ye, and B. Ojo*

Georgia Institute of Technology, School of Chemistry and Biochemistry, Atlanta, GA; *Mercer University and School of Medicine, Macon, GA and ^Emory University School of Medicine, Atlanta, GA

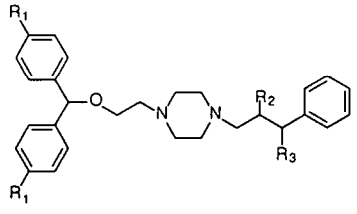
Because of its increased legal use and its similar mechanism of action to cocaine, there has been a renewed interest in methylphenidate (Ritalin®). Over the last several years we have synthesized a series of (±)-methylphenidate derivatives and evaluated these compounds for inhibition of [^{3}H]WIN 35,428 binding, inhibition of [^{3}H]dopamine uptake and drug discrimination in rats. *Threo* methylphenidate derivatives with halo-substituents on the aromatic ring had the increased binding potency, while electron donating substituents caused little change, or a small loss of binding potency. N-substituents generally caused a marked loss of potency, except for benzyl which was somewhat more potent. For the unsubstitued amine, reduction of the methyl ester to hydroxyl sharply reduced potency; conversion of the hydroxyl to methyl ether restored affinity. For N-benzyl (tertiary amine) derivatives, these same transformations both increased affinity. Although the potency of the methylphenidate derivatives in the two assays was highly correlated, a number of compounds were 4 to 8-fold more potent at inhibiting [^{3}H]WIN 35,428 binding than [^{3}H]dopamine uptake (cocaine has a ratio of 2.3). For most aromatic ring substituted compounds there was a clear correlation between its binding potency and its ability to substitute for cocaine in drug discrimination studies. However, this correlation did not hold for N-substituted analogs which generally were much less potent in the drug discrimination test than predicted by their binding affinity.

HYDROXYLATED ANALOGS OF GBR 12909. THE DEVELOPMENT OF LONG-ACTING COCAINE ABUSE THERAPEUTIC AGENTS

L.-W. Hsin, D. Lewis, C. M. Dersch,[§] R. Horel,[§] J. S. Partilla,[§] R. B. Rothman,[§] and K. C. Rice

LMC, NIDDK,NIH, Bethesda, MD and Clinical Psychopharmacology Sect., IRP, NIDA, NIH, Baltimore, MD

Recently in a behavioral study, we found that a single dose of the depot preparation of the decanoate ester 1 of a racemic benzylic hydroxylated analog 2 of GBR 12909 effectively decreased cocaine-maintained behavior in the rhesus monkey for nearly a month without affecting food-maintained performance. With the intent to eliminate the hazards of performing pharmacological studies on racemic compounds and further study the structure-activity relationships of hydroxyl-containing analogs of GBR 12909, we designed and synthesized a series of optically pure hydroxylated derivatives of GBR 12909 (3-8). In the dopamine transporter (DAT) binding and DA reuptake inhibition, the ***S*** hydroxyl analogs, **5** and **7,** are more potent and much more selective than the corresponding ***R*** isomers, **6** and **8.** But interestingly, there is no significant difference between the ***S*** and ***R*** isomers of benzylic hydroxyl derivatives, 3 and 4. In this novel series of GBR 12909 analogs, compound **5** displayed the highest affinity (IC_{50} = 0.745 nM) in DAT binding. Compound **7** is one of the most selective ligands yet known for the DAT relative to the serotonin transporter (SERT) and in the DA reuptake inhibition versus the 5-HT reuptake inhibition (937 and 792 fold, respectively).



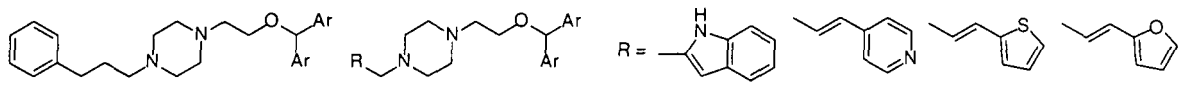
	R_1	R_2	R_3
GBR 12909	F	H	H
1	F	H	~OCO(C_9H_{19})
2	F	H	~OH
3	F	H	—OH
4	F	H	····OH
5	F	—OH	H
6	F	····OH	H
7	H	—OH	H
8	H	····OH	H

HETEROAROMATIC ANALOGS OF BRIDGED PIPERAZINE GBR 12909 AS HIGH AFFINITY DOPAMINE REUPTAKE INHIBITORS

Y. Zhang, L. Hsin, R. B. Rothman[§], C. M. Dersch[§], J. S. Partilla[§] R. Horel[§], and K. C. Rice

LMC, NIDDK, NIH, Bethesda, MD and [§]Clinical Psychopharmacology Sect., IRP, NIDA, NIH, Baltimore, MD

One of the current approaches to the treatment of cocaine abuse is to develop high affinity and selective dopamine transporter (DAT) ligands as dopamine (DA) reuptake inhibitors. Among various ligands identified, the disubstituted piperazine GBR 12909 demonstrated high affinity and selectivity for the DAT and in dopamine reuptake inhibition. In our previous SAR study, we replaced the piperazine moiety of GBR analogs with a bridged piperazine resulting in a series of novel high affinity GBR analogs that resemble the tropane skeleton of cocaine. An earlier SAR study by Matecka *et al.* showed that some *N*-heteroaromatic analogs of GBR 12909 possessed higher affinity in the DAT binding as well as higher selectivity at the DAT relative to the serotonin transporter (SERT). As a continuation of the SAR study, we incorporated heteroaromatic rings into the bridged piperazine GBR derivatives. The preliminary data showed that the indole, thiophene, and furan-containing analogs displayed higher affinity in the DAT binding than the corresponding phenylpropyl GBR 12909 derivative. In this series, the indole-containing compound showed the highest affinity (IC_{50} = 1.4 nM) in DAT binding and the highest selectivity (74-fold) for the DAT relative to the SERT, exhibiting a six-fold increase in binding affinity for the DAT over the corresponding phenylpropyl derivative. Interestingly, this compound displayed a relatively lower activity (IC_{50} = 40 nM) in DA reuptake inhibition, exhibiting a high ratio (29-fold) of IC_{50} for the inhibition of DA reuptake versus binding to the DAT.



TURNOVER OF DOPAMINE TRANSPORTERS IN RAT BRAIN

H. L. Kimmel, A. Vicentic, P. D. Lambert, M. J. Kahar, and F. I. Carroll

Neuroscience Division, Yerkes Regional Primate Research Center, Emory University, Atlanta, GA and Research Triangle Institute, Research Triangle Park, NC

The dopamine transporter protein (DAT) is a substrate for many drugs of abuse, including amphetamine and cocaine. Cocaine administration and withdrawal after repeated cocaine exposure have both been found to alter DAT levels. Changes in DAT levels may play a role in the craving and other effects following cocaine withdrawal. The compound RTI-76 {3β-(3*p*-chlorophenyl)tropan-2 β-carboxylic acid *p*-isothiocyanatophenylethyl ester hydrochloride} has been used to irreversibly inhibit DAT binding in brain and to calculate DAT turnover in the rat striatum (JPET 279:200-206, 1996). In this study, we administered RTI-6 intraventricularly (ICV) in order to study more brain regions. By using this route of administration, presumably, less local damage was caused than would be by direct tissue injection. Dose-response studies were carried out in order to determine the dose of RTI-76 that gave significant inhibition of DAT binding in several brain regions. After ICV injection, DAT binding was inhibited in striatum, nucleus accumbens, and ventral midbrain. The DAT binding slowly returned to basal levels over a period of several days. Assuming a model of protein synthesis and degredation, the synthesis rate and degredation rate constant were determined in several brain regions. The turnover parameters and effects of various drugs on those parameters were determined.

ACKNOWLEDGMENT: Supported by DA 10732.

SEROTONIN TRANSPORTER PRODUCTION AND DEGRADATION: STUDIES WITH RTI-76

A. Vicenti[*1], *F. I. Carroll*[2], *G. Bbattaglia*[1], *and M. J. Kuhar*[3]

Departement of Pharmacology, Loyola University, Chicago, IL, [2]Research Triangle East, NC, and [3]Neuroscience Division Yerkes Research Primate Center-Emory University, Atlanta GA

RTI-76, {3b-(3-p-chlorophenyl) tropan-2b-carboxylic acid *p*-isothiocyanato-phenylethyl ester hydrochloride} is a cocaine analogue that irreversibly binds to and inhibits dopamine transporter (DAT) density and function (JPET 279:200-206, 1996). DAT binding recovered with time allowing for the estimate of synthesis and degradation of DAT. Since RTI-76 also has nanomolar affinity for serotonin transporter (SERT), our objective was to determine the utility of RTI-76 to study the turnover kinetics of SERT and its regulation by psychostimulant drugs. Male, Sprague-Dawley rats were injected unilaterally with either vehicle or RTI-76 (20 ,50, 100 and 400 nmol, I.C.V) and sacrificed 24 hr post-injection. At 24 hr., SERT binding was inhibited and Bmax values expressed as % of control in both contra and ipsilateral hippocampus were 89% at 20 nmol; 74% at 50 nmol ,and 45% at 100 or 400 nmol. Dose-dependent decrease in SERT binding after RTI-76 was also observed in both contra and ipsilateral striatum and hypothalamus. Furthermore, at 96 hr post-treatment (100 nmol, I.C.V), hippocampal and striatal SERT Bmax recovered to 70%, suggesting that half life (t1/2) of SERT repopulation is approximately 3 days. The results indicate that RTI-76 can be a valuable tool to study production and degradation of SERT. Current detailed studies on SERT turnover will bring better understanding of how physiological and pharmacological factors influence SERT levels.

ACKNOWLEDGMENT: Supported by NIDA DA 10732.

THE ROLE OF SEROTONIN IN COCAINE DEPENDENCE AND ITS TREATMENT

A. S. Wikler

New York VA Medical Center/VA New York NIDA MDRU; New York University School of Medicine

Several independent but converging lines of evidence suggest that serotonergic systems play important roles in cocaine dependence and potential pharmacological interventions. This includes neuronal binding and displacement studies, autoradiographic studies, effects on serotonin biosynthesis and metabolism, animal self-administration studies, human probes with serotonin agonists, and clinical trials with selective serotonin re-uptake inhibitors (SSRIs). Cocaine binds strongly to the serotonin transporter, perhaps with greater affinity than to either the dopamine or norepinephrine transporters. SSRIs have been shown to displace cocaine completely from serotonergic binding sites in the hippocampus and partially displace it in the basal ganglia and cortex. The functional relevance of such serotonergic cocaine binding sites is suggested by animal behavior studies, in which the incentive value of cocaine is raised or lowered by respectively depleting or increasing serotonin. To date, some but not all SSRIs have been investigated in clinical trials. A open trial of sertraline demonstrated reduced cocaine usage in 1992. Some studies found that fluoxetine reduces cocaine craving and usage in depressed cocaine users as well as non-depressed cocaine addicts. However, a large-scale study in 1995 found no significant improvement in cocaine usage with fluoxetine, reducing enthusiasm for further trials with SSRIs. A recent study demonstrating that mice genetically altered to eliminate the 5-HT_{1B} serotonin receptor are more motivated to self-administer cocaine has renewed interest in serotonergic approaches to understanding and treating cocaine dependence.

EFFECTS OF ANTIHISTAMINES ON FENFLURAMINE-INDUCED DEPLETION OF BRAIN SEROTONIN IN RATS

S. Y. Yeh

Molecular Neuropsychiatry Section, NIH, NIDA, IRP, Baltimore, MD

Effects of chlorpheniramine (CPA), diphenhydramine (DIPH), tripelennamine (TRIP) and pyrilamine (PYRI) on fenfluramine (FEN)-induced depletion of serotonin in the brain of rats were investigated in the present study. Rats were injected i.p. with FEN (10 mg/kg), or CPA (5, 10, 20 mg/kg), DIPH (20 mg/kg), TRIP (20 mg/kg), PYRI (20 mg/kg) and saline or FEN plus one of the antihistamines concurrently, once or twice daily for 4 days, and sacrificed 7 days later. In addition, CPA (10 mg/kg) was administered 3 and 6 hr after FEN. Rectal temperature was measured prior to and hourly for 5 hr following drug administration. Levels of 5-HT and 5-HIAA in the frontal cortex, hippocampus and striatum of rats treated with FEN decreased significantly to about 30% of those of controls with no significant changes after CPA, DIPH, TRIP and PYRI. Treatment with FEN plus CPA and FEN plus DIPH, but not FEN plus TRIP and FEN plus PYRI, increased brain serotonin levels 2- to 3-fold of those treated with FEN plus saline group. Treatment with FEN plus CPA and FEN plus DIPH, but not FEN plus TRIP and FEN plus PYRI, decreased rectal temperature with no significant change after of FEN. The effects of FEN plus antihistamines on FEN-induced depletion of indoles correlated better with the data on body temperature alteration by FEN plus antihistamines rather than with other biochemical parameters. The antihistamines decreased temperature at 1 hr period and enhanced FEN-induced reduction in body weight.

THE DISCRIMINATIVE STIMULUS EFFECTS OF HISTAMINE H1 ANTAGONISTS IN RATS

M. Mallaret, C. Barjhoux*, F. Le Doze***, M. Dematteis, and G. Baragatti***

***CEIP, ** Laboratoire de Pharmacologic, Cedex, France and ***CHU Pharmacologic, Cedex, France**

The abuse of combinations of some histamine H1 antagonists like tripelennamine with pentazocine (an agonist at kappa 1- opioid receptors) is well established. The abuse of some H1 antagonists like dimenhydrinate has been described in the literature. Ten Sprague-Dawley rats were trained to discriminate cocaine (10 mg/kg i.p.) from saline. The discriminative stimulus effects of tripelennamine (3; 4.5; 6 mg/kg i.p.), chlorpheniramine (3; 6; 10; 15; 20 mg/kg i.p) and hydroxyzine (1; 10; 15; 20 mg/kg i.p.) were studies after administration. **Results and Discussion:** Rats required approximately 19 sessions to acquire the cocaine-saline discrimination. Once rats attained the criterion, drug-saline discrimination stabilized and was maintained with a high degree of accuracy. During the dose-response tests, cocaine (2.5-15 mg/kg) produced a dose related increase in drug appropriate responses and the training dose of cocaine engendered more than 90% drug-appropriate responses in all of the rats. In the generalization tests, tripelennamine and chlorpheniramine produced cocaine like discriminative stimulus effects. On the other hand, hydroxyzine did not generalize to the discriminative stimulus effects of cocaine. In the present study, we found that some-H1 antagonists like tripelennamine and chlorpheniramine induce rewarding effects like cocaine. The psychostimulant-like discriminant stimulus effects of tripelennamine and chlorpheniramine seem to be, at least in part, mediated by the dopaminergic system. Investigators have found that tripelennamine and chlorpheniramine substituted for amphetamine in amphetamine trained pigeons and that some H1 antagonists increase the response rate under fixed-interval schedules of either food presentation or shock avoidance in squirrel monkeys. Hydrozyzine did not. Our results corroborate previous results that some H1 antagonists have psychostimulant-like discriminative stimulus effects in animals. The cocaine saline discrimination study in rats seems to be an interesting method to characterize the different H1 antagonists and to differentiate those without psychostimulant effect (hydroxyzine) and those with psychostimulant-like abuse potential (tripelennamine, chlorpheniramine).

REGULATION OF INTRAVENOUSLY SELF-ADMINISTERED NICOTINE IN RATS

W. J. Lynch and M. E. Carroll

Department of Psychiatry, University of Minnesota, Minneapolis, MN

A 2-lever self-administration procedure was developed to investigate the extent to which rats regulate their intake of nicotine when both dose size and interdose interval were under the subjects' control. Fifteen male Wistar rats were trained to i.v. self-administer 9 unit doses of nicotine (0.01 to 0.1 mg/kg) during daily 5-hr sessions. Operant chambers were equipped with 2 levers and associated stimulus lights. A response on the lever with stimulus lights signaling an increase in dose size increased the infusion duration by 1/8 of a log unit, and a response on the lever with stimulus lights signaling a decrease in dose size decreased the infusion duration by 1/8 of a log unit. Once responding for nicotine stabilized, nicotine infusions were replaced with either cocaine infusions (available under a modified 2-lever procedure) or saline infusions. Saline substitution results indicated that nicotine functioned as a reinforcer. Pharmacological regulation of nicotine was compared with that of cocaine regulation by correlating dose size with the following interdose intervals. Results revealed that although this correlation was significant for both nicotine and cocaine self-administration, nicotine self-administration was less precisely regulated. This paradigm is useful for comparing dose regulation of self-administered drugs.

ACKNOWLEDGMENT: Supported by NIDA grant R37 DA03240.

PREFRONTAL CORTICAL NEURONAL RESPONSE TO NICOTINE IN THE ANESTHETIZED AND UNANESTHETIZED RAT

J. L. Giacchino, R.-S. Lee, and S. J. Henriksen

Department of Neuropharmacology, The Scripps Research Institute, La Jolla, CA

Studies of nicotinic effects on brain areas within the mesocorticolimbic system have emphasized the roles of the ventral tegmentum and nucleus accumbens in this network. However, recent work suggests that the prefrontal cortex (PFC) may provide a major contribution to the etiology of nicotine addiction (Nisell et al., 1997; Pagliusi *et al.,* 1996; Nisell *et al.,* 1995). The PFC is in a key position to contribute to the development and maintenance of nicotine addiction. It receives major convergent inputs from mesencephalic and diencephalic brain areas and functions in cognitive processes essential to the formation of organized and motivated behaviors. The PFC has been demonstrated in our laboratory to undergo electrophysiological and neuropharmacological alterations associated with drugs of abuse such as opiates. In the present study, the effects of nicotine on PFC neuronal responsivity have been investigated in both anesthetized and unanesthetized animals. Extracellular recordings were made from medial PFC neurons in halothane-anesthetized and in unanesthetized, freely-moving young adult male Sprague-Dawley rats. Systemic nicotine (0.5-1.5 mg/kg, i.p.) increased firing rate in the majority of cells studied. Evoked cellular responses were also increased by systemic nicotine. Mecamylamine (5.0 mg/kg, i.p.) reversed these effects. Electrophoresed nicotine (50 or 100 mM) increased firing rates in 22% of spontaneously firing cells; firing patterns were also modified.

ACKNOWLEDGMENTS: Supported by NIDA grants DA00201 and DA08301.

ALTERED COGNITIVE TASK-INDUCED BRAIN ACTIVATION IN CHRONIC CIGARETTE SMOKERS: A HUMAN FMRI STUDY

A. S. Bloom, J. Wright, B. Hegarty, S. Tadros, S. M. Rao[†], L. L. Sperry, T. Ross* and E. A. Stein*

Departments of Pharmacology, *Psychiatry, [‡]Biophysics and [†]Neurology, Medical College of Wisconsin, Milwaukee, WI

Nicotine produces alterations in mood and may increase attention and cognitive performance. Chronic use of nicotine products produces physiological and/or psychological dependence. However the effects on cognitive processing are not well understood. We therefore compared brain activation patterns induced by two cognitive tasks in smokers and age matched control subjects using functional magnetic resonance imaging (FMRI). Chronic smokers (mean duration of smoking - 14.5 ± 7.0 years) performed two cognitive tasks (visuospatial working memory and concept formation) while undergoing whole brain FMRI scanning. Scanning was performed one to two hours after each subject's last smoking episode. There was a decrease in task performance on the concept formation but not the visuospatial working memory task in the smokers when compared to control subjects. Both tasks produced activation in frontal cortex including dorsolateral prefontal cortex and strong activation in parietal and visual cortical areas. The extent of activation was significantly greater in controls than in smokers in most activated regions. Studies are currently being conducted to determine the mechanism underlying differences in task activation, specifically, whether chronic cigarette smoking alters neuronal activity or vascular responsivity.

ACKNOWLEDGMENT: Supported by DA-09465.

EFFECTS OF STANDARD AND PLACEBO CIGARETTES AFTER 3 AND 12 HOURS OF TOBACCO DEPRIVATION

W. B. Pickworth, R. V. Fant, R. A. Nelson, J. Nichels, M. Chenoweth, and J. E. Henningfield

NIDA, IRP, Addiction Research Center, Baltimore, MD

The purpose of the present study was to provide a preliminary evaluation of a new placebo cigarette to be used in tobacco research. Under a contract from NIDA, placebo cigarettes designed to have similar taste, mouth feel and draw characteristics as commercial cigarettes, but to deliver virtually no nicotine, were developed. The effects of smoking standard cigarettes that delivered (FTC methods) typical amounts of nicotine (0.6 and 1.1 mg) and tar (11 and 16 mg) with placebo cigarettes that delivered equivalent amounts of tar but minimal amounts of nicotine (<0.06 mg) were compared. Subjects (n=20; 10 men) participated in four experimental sessions in which they smoked either a standard cigarette or a denicotinized cigarette under each of two tobacco deprivation conditions, 3 and 12 hr. Before, and for 1 hr after, *ad lib* smoking of a single cigarette, measures of heart rate, blood pressure, eye tracking and EEG were recorded. Preliminary analyses indicated that the placebo cigarettes did not increase heart rate. Measures of smoking satisfaction indicated that the subjects preferred the cigarettes that delivered nicotine more than the placebo cigarettes. However, both types of cigarettes reduced subjective measures of tobacco craving and withdrawal. There were no apparent differences in the effects of the cigarettes after either 3 or 12 hr of tobacco abstinence. These data extend the results of other research that suggested the process of smoking and components of tobacco smoke other than nicotine may mediate some effects of cigarette smoking. These placebo cigarettes may prove useful in evaluating other effects of smoking independent of the delivery of nicotine.

ACUTE EFFECTS OF NICOTINE TRANSDERMAL PATCH IN PATCH-NAIVE AND PATCH EXPERIENCED SUBJECTS

S. F. Duggan, S. L. Daniels, L. H. Lundahl, and S. E. Lukas

Behavioral Psychopharmacology Research Laboratory McLean Hospital/Harvard Medical School, Belmont, MA

While transdermal nicotine patches have been used successfully for many years to treat tobacco dependence, not all patients continue to use it as the dose and route of administration is quite different than smoking. We hypothesized that first-time users of the patch may have more difficulty adjusting to the treatment. Healthy male and female tobacco smokers (10 cigarettes/day) provided informed consent and volunteered for this study. Each subject served as his/her own control and was tested on separate days during which they had either a placebo or 14 mg nicotine transdermal patch (NicodermCQ®)applied to their upper arm approximately 2.5 hours after their last cigarette. Subjective effects were evident at 60 minutes, paralleling the rapid rise in plasma nicotine levels with this brand of patch. Heart rate, skin temperature, blood pressure and mood states were continuously monitored for 6 hours at 30 minute intervals for the first 4 hours, and 1 hour intervals thereafter. Compared to patch-experienced subjects, who reported few negative side effects, patch-naive subjects reported elevated levels of anxiety. confusion, fatigue, nausea and feeling "high". These results suggest that the acute effects of nicotine transdermal patches differ between patch-naive and patch-experienced subjects. Future efforts to use the patch for treating tobacco dependence may need to consider the increased sensitivity of patch-naive subjects.

ACKNOWLEDGMENTS: Supported by grants DA03994 and DA00343.

COTININE REPLACEMENT AS AN OUTCOME PREDICTOR OF NICOTINE PATCH TREATMENT FOR SMOKING CESSATION

P. Gariti, A. I. Alterman, N. Bedi, G. Luck, A. Cnaan, and E. Lala

Philadelphia VAMC and University of Pennsylvania Center for the Study of Addictions, Philadelphia, PA

This study examined plasma cotinine replacement levels (%CR) of 56 outpatient smokers administered a 21 mg/day nicodermal patch (Nicoderm CQ). Predictors of %CR (post patch initiation/pre-patch cotinine level) and the relationships between %CR and several during-treatment and post-treatment smoking cessation variables were also examined. %CR ranged from 35% to 232% (M= 107%; Md= 90.5%). Four subject variables were found to be significantly correlated with %CR - baseline cotinine level, prior quit attempts, gender, and the Fagerström Tolerance Questionnaire score. An all subsets logistic regression approach was utilized to determine the optimal predictor combination for %CR. A two-variable model consisting of baseline cotinine level and gender provided the most powerful predictor combination. Thus, having a lower baseline cotinine level and being a woman were predictive of higher %CR. Replacement level was not associated with baseline number of cigarettes smoked per day (CPD), during-treatment withdrawal scores, patch treatment completion rates, and post-treatment abstinence rates. The relatively high levels of cotinine replacement obtained using a 21 mg/d patch suggest cautious use of higher dose treatment with this particular patch. There was only one clinically significant adverse event.

ACKNOWLEDGMENT: Supported by NIDA grant DA 10070.

SMOKING CESSATION VIA SELF-TALK AND CUE EXPOSURE

U. Malkerneker, B. Poddig, J. Lisiecki, and W. Belanger

Edward Hines, Jr. VA Hospital, Hines, IL

Cigarette smoking is a major health risk behavior with poor responses to traditional treatment. This study is designed to measure the effectiveness of a specific intervention for smoking cessation compared to traditional quit smoking technique. Patients were randomized to one of two groups, experimental (E) or traditional (T) treatment. Patient assigned to the T-group attended the smoking cessation program offered at the hospital. This program consisted of attendance at weekly groups that offered traditional skills training. Patients assigned to the E group were limited to 12 sessions and the focus of treatment was to assist the smoker to cope with the urges, thoughts, feelings and images to smoke via self-talk. Participants in the E group were exposed to a person smoking a cigarette during the treatment session. These interventions were chosen since literature revealed that traditionally smokers are exposed to a wide menu of techniques that they gradually forget and that successful ex-smokers simply talked themselves out of the urge to smoke. Being in the presence of a smoker is a powerful smoking cue but traditional programs do not deal with this issue as directly. Patients in both the E and T-group had access to nicotine replacement patches and were monitored for abstinence via a Breathalyzer that determined carbon monoxide levels. At baseline, both T and E groups were well-matched with regard to age, years smoking, daily tobacco use, and previous attempts at smoking cessation. T-group attendance was 25% of compared to 67% for E-group. Use of Rx aids was similar with 43% of the T-group and 69% of the E-group receiving Nicotine Supplement Therapy. Follow-up data indicated that a larger percentage of the E-group was abstinent at three months (40% vs. 25%), six months (39 % vs. 13%) and nine months (28 % vs. 13%). Overall patients enrolled in the E-group demonstrated a better outcome compared to those in T-group.

A LABORATORY ANALOG OF CONTINGENCY-MANAGEMENT: EXCHANGE DELAYS AND REINFORCER MAGNITUDE

J. M. Roll, M. P. Reilly, and C. E. Johanson

Department of Psychiatry and Behavioral Neurosciences, Wayne State University, Detroit, MI

Contingency-management interventions which provide vouchers exchangeable for retail goods and services contingent on drug abstinence are one of the most effective treatment strategies available. Factors known to contribute to the efficacy of these interventions are voucher magnitude and the schedule with which vouchers are made available. Another factor which may be important is the delay between earning a voucher and exchanging it for a desired good or service. Because reinforcement is most effective when reinforcers are delivered immediately, the exchange delay inherent in voucher programs may ultimately decrease intervention effectiveness. We have recently adapted a laboratory analog of a voucher program in order to examine the effects of exchange delay and reinforcer magnitude on voucher efficacy. Use of analog procedures has been particularly fruitful in refining contingency management interventions. In the present procedure abstinent cigarette smokers make repeated choices between puffs on a cigarette (which are the drug analog) and points worth a variety of monetary values (which are the voucher analog). The time at which these points can be exchanged for money varies from immediately to one or three weeks. Preliminary results from this ongoing study suggest that participant behavior is sensitive to the manipulations with delayed reinforcers being less effective than immediate reinforcers and high magnitude reinforcers being discounted less severely than low magnitude reinforcers.

ACKNOWLEDGMENTS: Supported by NIDA grant 5 T32 DA 07267-04 and Departmental Funds.

INTERACTING EFFECTS OF SOCIAL CONTEXT AND NICOTINE ABSTINENCE AND REPLACEMENT ON HUMAN COOPERATIVE AND AGGRESSIVE BEHAVIOR

R. Spiga, J. D. Day II, J. Roache, and J. Schmitz

Department of Psychiatry and Behavioral Sciences, University of Texas-Houston Health Science Center, Houston, TX

The effects of nicotine abstinence and replacement on the cooperative and aggressive behavior of nicotine dependent participants were examined. Participants were divided into two groups. Participants assigned to the first, *high cooperative,* group were ostensibly paired with a computer-simulated fictitious "other" person who was highly cooperative and rarely aggressive. Those assigned to the second, *high aggressive,* group were paired with an "other" person who was rarely cooperative but highly aggressive. During three daily trials, participants were provided the opportunity to either initiate cooperative episodes with, respond aggressively toward, or work independently of a computer-simulated other person. Participants could also respond cooperatively or independently when the "other" initiated a cooperative episode. Doses were administered prior to each trial. Dose conditions were nicotine abstinence, 0, 2, and 4 mg nicotine gum, and *ad libitum* smoking. For females, doses were administered during the luteal phase. Participants in the *high cooperative* experimental group were more cooperative and less aggressive than those in the *high aggressive* group. The differences in cooperative behavior between non-nicotine and nicotine conditions were greatest in the *high aggressive* group. Nicotine replacement mitigated aggressive behavior in both groups. Results demonstrated that social context mediates the effects of nicotine abstinence and replacement therapy. Nicotine replacement therapy had its clearest effect under aversive social conditions.

ACKNOWLEDGMENTS: Supported by NIDA grant DA-06633 and DA-07452

RELATIONSHIPS AMONG THREE COMMON MEASURES OF NICOTINE DEPENDENCE

R. L. Riggs and J. R. Hughes

HBPL, Department of Psychiatry, University of Vermont, Burlington, VT

Three measures of nicotine dependence, the American Psychiatric Association's Diagnostic and Statistical Manual IV (DSM-IV), the Fagerstrom Test for Nicotine Dependence (FTND), and cigarettes per day (cigs/day), are frequently used interchangeably in the smoking literature. The current study utilized a diverse sample of smokers (10 smokers for each of the following groups: 1-10, 11-20, 21-30, 31-40, 41+ cigs/day) to examine the relationship among the three measures. Twenty-three men and 28 women, with a mean age of 44 years, participated in the study. Participants underwent a 30-minute interview concerning their smoking. The interview generated DSM-IV nicotine dependence diagnoses, as well as FTND scores. Participants had a mean FTND score of 5.6, and endorsed an average of 4.2 DSM-IV dependence criteria. Gigs/day correlated poorly with DSM-IV (r=0.23), but was highly correlated with FTND scores (r=0.71). DSM-IV and FTND scores were also poorly correlated (r=0.13). These results indicate that DSM-IV dependence, FTND scores, and cigs/day are measuring different constructs and thus should not be used interchangeably as measures of nicotine dependence. Future studies comparing the predictive validity of the three measures are needed to help decide the relative utility of each.

ACKNOWLEDGMENTS: Funded by Pinney Associates (Pittsburgh, PA) and RSDA DA-00109 (JRH).

PERSONALITY AND BEHAVIORAL MEASURES SHOW THAT CIGARETTE SMOKERS ARE MORE IMPULSIVE THAN NEVER SMOKERS

S. H. Mitchell

University of New Hampshire, Durham, NH

Drug users are thought to be more "impulsive" than nonusers. To examine this idea, smokers ((15 cigarettes/day) and never smokers were recruited. Participants completed 5 personality questionnaires to assess impulsivity: the Adjective Checklist. Barrett's impulsivity scale, Cloninger's tridimensional personality questionnaire, Eysenck's personality questionnaire, and Zuckerman's sensation-seeking scale. Participants also performed 3 behavioral tasks. In the delay task, it was assumed that increasing impulsivity would be shown as a preference for small monetary rewards available immediately rather than larger delayed rewards. In the probability task, it was assumed that increasing impulsivity would be shown as a preference for small monetary rewards that were available for sure rather than larger uncertain rewards. In the work task, it was assumed that increasing impulsivity would be shown as a preference for small monetary rewards that were available for a minimal amount of work rather than larger rewards following hard work. Data from 20 smokers and 20 never smokers indicated that smokers have higher scores for numerous scales on the personality questionnaires that index impulsivity than never smokers. On the behavioral tasks, smokers chose immediate money (immediate gratification) over delayed money more than never smokers and smokers selected which alternatives they preferred on the behavioral tasks more rapidly than never smokers. These results indicate that cigarette smokers are more impulsive than never smokers.

ACKNOWLEDGMENT: Supported by NHLBI grant 058225.

DIFFERENCES IN COPING PERFORMANCE BETWEEN MEN AND WOMEN WHO SMOKE

B. Navarro, J. M. Schmitz, and R. Spiga

Substance Abuse Research Center, University of Texas - Houston

Coping is a factor that appears to play a major role in smoking cessation and relapse prevention. Gender differences in coping abilities have been offered to explain findings that women have greater difficulty than men in quitting smoking. We used a modified version of the Situational Competency Test (SCT) to elicit descriptions of how men versus women cope in situations that place them at high risk for smoking. The SCT generates verbal responses to audiotaped scenarios in which the possibility of drug use exists. It was hypothesized that male and female smokers would show dissimilar patterns of responding across a range of high-risk situations, and that such differences may contribute to our understanding of gender differences in smoking outcome. Transcribed SCT responses from 39 adult smokers (19W, 20M) were scored on multiple dimensions, including latency, duration, compliance, specification of new behavior, coping method used, and number of coping alternatives generated. Analysis of coping responses produced findings that support the notion of situational specificity, in that each coping response was used differentially across situations. Scores on objective measures of coping, such as latency, duration, specification, also were found to be dependent on type of high-risk situation. Our findings do not support the hypothesis that women respond less favorably in certain situations, e.g., negative emotional states, than men. There was a tendency for women to give shorter responses (duration) and to use less Active Cognitive Coping methods compared to men. It is unlikely that poorer smoking outcomes in women, if they exist, can be explained on the basis of differences in coping alone. It remains to be seen whether coping abilities may interact with other factors, such as social support, depression, weight concerns, or nicotine reinforcement, in a way that adversely affects women.

ACKNOWLEDGMENT: Supported by NIDA grant DA-08888-01.

CHANGES IN PSYCHOLOGICAL AND PROCESS VARIABLES AS A FUNCTION OF GENDER, TREATMENT, AND DEPRESSION DIAGNOSIS

G. Humfleet, S. Hall, V. Reus, and R. Muñoz

Department of Psychiatry, University of California, San Francisco

In a series of studies examining the efficacy of a cognitive-behavioral (CB) mood management group intervention for smokers with a history of depression (MDD), we have found that the CB treatment appears to be differentially effective for MDD history-positive smokers when compared to a standard health education (HE) intervention. This effect is particularly strong for history-positive male subjects. The purpose of the present study is to examine changes in psychological and process variables potentially contributing to the differences in outcome. Findings are based on 400 subjects from two clinical trials. Subjects were 54% female and 27% reported a history of MDD. Mean age = 40.2. Mean daily cigarettes = 23.2. Mean years smoking = 21.6. In both studies, subjects were randomly assigned to the CB intervention or HE intervention. CB process variables assessed included number of pleasant activities, frequency of positive and negative thoughts. Mood was assessed using the Beck Depression Inventory (BDI) and the Profile of Mood States (POMS). Assessments were conducted at baseline, end of treatment, and l-year follow-up for all measures. Analyses of the CB process variables found no significant changes over time as a function of the interaction of gender, diagnosis, and treatment condition. Subjects (both male and female) with a history of depression assigned to the CB interventions reported greater increases in pleasant activities than the three other groups but this difference did not reach significance ($p < .15$). Analyses of mood changes indicate that history-positive male subjects in CB intervention had a reduction in total POMS scores and were more likely to maintain those reductions at l-year follow-up ($p < .05$). Specific process factors contributing to the differential success of history-positive males in the CB treatment are still unknown. Further evaluation will be conducted.

ACKNOWLEDGMENTS: Supported by NIDA grants DA02538 and DA09253.

INCREASED CONCENTRATIONS OF PLASMA COTININE IN SCHIZOPHRENIC SMOKERS COMPARED TO NORMAL SMOKERS

*P. A. Crooks, O. Ghosheh, L. P. Dwoskin, T. Rogers, and J. de Leon**

College of Pharmacy and *Dept. of Psychiatry, Univ. of Kentucky, Lexington, KY

Smoking is more prevelant and more intense in schizophrenic patients compared to the general population (Hughes *et al.,* 1986; de Leon *et al.,* 1995). Recently, cotinine, a major metabolite of nicotine, was reported to be 1.6-fold higher in the urine of schizophrenic smokers compared to normal smokers, suggesting that nicotine intake is higher in schizophrenic smokers (Olincy *et al.,* 1997). In the present study, blood was drawn from schizophrenic smokers (n = 12) and normal smokers (n = 12) from 1 - 4 pm and immediately centrifuged at 1,000 g at 4°C for 15 min. Plasma samples were frozen at -70°C until analysis. Plasma (0.5 ml containing 1 mg of isonicotinamide as internal standard) was added to 0.5 ml of 0.5 M NaOH, and the mixture extracted once with dichloromethane (10 ml). The organic layer (8 ml) was rapidly evaporated to dryness in air, and 300 ml of water added. Plasma extracts (200 ml) were analyzed by HPLC on a Partisil SCX column (25 x 0.46 cm) connected to a Phenosphere SCX guard column (5 x 0.46 cm) using a 90% $NaHPO_4$ (0.1 M, pH 5.0)/10% methanol buffer (flow rate, 1.5 ml/min). Retention times were: isonicotinamide, 3.9 min; caffeine, 4.7 min; 3-hydroxycotinine, 6.3 min; and cotinine, 10.4 min. Plasma cotinine concentrations in schizophrenic smokers were greater ($P= 0.03$) than in normal smokers (353 ± 54.0 and 211 ± 26.0 ng/ml, respectively). Plasma 3-hydroxycotinine concentrations was not different between schizophrenic smokers (87.0 ± 18.0 ng/ml) and normal smokers (58.4 ± 17.0 ng/ml). Plasma caffeine concentrations were not different between schizophrenics (902 ± 310 ng/ml) and normals (1007 ± 335 ng/ml). The plasma concentrations of the nicotine metabolites found in schizophrenics in this study are consistent with the urinary concentrations of cotinine in schizophrenics in the recent study by Olincy *et al.* (1997). The higher intake of nicotine by schizophrenics may result from their need to target specific nicotinic receptors in the brain to alleviate their pathophysiology.

ACKNOWLEDGMENTS: Supported by NARSAD Young Investigator Award and THRI, Lexington, KY.

CIGARETTE SMOKING IN HEROIN ADDICTS IN METHADONE TREATMENT

K. L. Sees, H. W. Clark, C. Masson, K. Delucchi, and S. Hall

Department of Psychiatry, University of California, San Francisco, CA

Despite years of cigarette smoking research, information on smoking and smoking cessation in adult heroin addicts is limited. This study describes the smoking behaviors of 139 patients during their first six months of treatment in a long-term (180-day) methadone detoxification versus methadone maintenance study. Assessments were taken at intake then monthly. Sixty percent of the patients were males, 52% Caucasian, 49% unemployed, 74% not married with an average age of 40 years and 12 years of education. Only five had never smoked and four were former smokers. For the 130 smokers, the following means were found: age started smoking 15.5 years (StD=4.91), Fagerstrom Tolerance Scale 5.9 (StD=2.19), and cigarettes per day 20.8 (StD=10.19). The majority smoked a pack or more per day (67.7%), non-mentholated (73.1%) and filtered (88.5%) cigarettes. At intake, the reported plans for quitting smoking were: 20.3% no plans, 26.6% in more than one year, 37.5% within a year, and 15.6% starting now; the quit plan was not related to the amount smoked or ethnicity. Beck Depression Inventory Scores were significantly related to the Fagerstrom Scores, but not to the type or amount of cigarettes smoked. As in the general adult population, Caucasians had significantly higher Fagerstrom Scores (6.5) than either African Americans (5.2) or Hispanics (5.0), and African Americans smoked fewer cigarettes per day (17.2) than Caucasians (22.0) and were more likely to smoke mentholated cigarettes (57%) than either Hispanics (18%) or Caucasians (11%). Contrary to predictions, there was no significant increase in the rate of smoking during methadone tapering.

ACKNOWLEDGMENT: Supported by NIDA grant P50-DA09253.

DESCRIPTION AND EVALUATION OF A SOFTWARE PACKAGE FOR MANAGING MULTI-SITE CLINICAL TRIALS DATA USING COMPUTER-READABLE AND FAXABLE CRFS

T. Winhusen, J. Mezinskis, T. Sun, M. Stookey, and E. Sornoza

Cincinnati VA/UC/ NIDA MDRU: VA Medical Center, Cincinnati OH

The Cincinnati Teledata Manager (CTM) is a Visual Basic (application which orchestrates the data tracking, verification, and documentation process completed by a data management center. CTM facilitates data tracking by automatically generating a list of overdue Case Report Forms (CRFs) for each study site and a report about the completeness of the final database. The particular strength of CTM lies in its management of the data entry and verification process. CTM provides data personnel with user-friendly interfaces for entering errors identified during a three-stage error checking process and automatically generates site-specific reports detailing any errors found. Moreover, CTM automatically completes several checks for CRF and data entry errors. Finally, CTM creates monitoring reports detailing study sites' performance in data collection and participant enrollment. Overall, CTM has proven to be a useful program but, due to some of its limitations, a second version of this program will be released in September of 1998.

ACKNOWLEDGMENTS: Financial Support for the Development of the CTM software package was provided by NIDA under agreement #Y01 DA 50038-00.

EFFECTS OF COVARIANCE MODEL MISPECIFICATION AND MISSING DATA ON TYPE I ERROR IN ANALYSIS OF LONGITUDINAL DATA

H. M. Rhoades, S. R. Doyle, and J. Grabowski

Substance Abuse-Medication Development Research Center, Department of Psychiatry and Behavioral Sciences, University of Texas Medical School at Houston

Longitudinal studies evaluating the effectiveness of proposed treatments for substance abuse often result in two major analysis problems: missing data and violations of the sphericity (or compound symmetry) assumption. Maximum likelihood procedures for analyzing longitudinal designs with missing data are increasingly being used in place of traditional ANOVA methods, which have often necessitated deleting subjects or imputing data. These maximum likelihood programs (e.g., BMDP 5V, SAS Proc Mixed) use all observed data and do not impute data. However, they require the user to specify the covariance matrix structure to be modeled. The choice of an incorrect covariance model may result in p-values being overly conservative (i.e., H_o not being rejected often enough) or overly non-conservative. Unless the researcher has prior knowledge, the data must be analyzed using several covariance models and the best fitting model chosen. In either case, an incorrect covariance model can lead to invalid p-values and erroneous conclusions. As part of an ongoing series of Monte Carlo analyses, data from three observed covariance patterns (symmetry, temporal decay, and empirical) are analyzed under three covariance models (compound symmetry, autoregressive, and unstructured) for Type I (alpha) error in a two-group, five repeated measures design. Type I error, estimated from 10,000 data sets, indicated that p-values from maximum likelihood analyses are sensitive to mismatches between the observed and modeled covariance structures. These results will help researchers evaluate the validity of computer generated p-values for the described analysis strategies under several combinations of missing data, and sample size, when various covariance model assumptions are used.

ACKNOWLEDGMENTS: Supported in part by USPHS grant DA09262 from NIDA.

META-ANALYSIS OF CONTINGENCY MANAGEMENT (CM) IN DRUG ABUSE TREATMENT SETTINGS

J. Griffith, G. A. Rowan-Szal, R. Roark, and D. D. Simpson

Institute of Behavioral Research, Texas Christian University, Fort Worth, TX

Contingency management (CM) involves a system of rewarding or punishing behaviors in order to promote change. Several individual studies have demonstrated that CM is an effective behavioral treatment for drug use (Higgins, 1993; Stitzer, 1992; Silverman, 1996). This meta-analysis evaluated the effectiveness of CM interventions as used in drug abuse treatment settings. Over 50 CM studies that met specified eligibility criteria were coded and analyzed. The principal focus was on urinalysis-based outcomes in drug abuse treatment settings, and the independent variables examined included treatment setting, type of reinforcement (incentives, vouchers, methadone manipulations), primary drug addiction, and duration of contingency periods. Moderating variables also were examined to determine conditions under which CM strategies function optimally. The results show that CM interventions are effective, based on the average estimated effect sizes across studies. Findings from this study should help identify the optimal conditions for implementing CM interventions in drug treatment settings.

ACKNOWLEDGEMENT: Supported by NIDA grant No. R01 DA06162.

DRUG ABUSE TREATMENT EFFECTIVENESS: A META-ANALYSIS OF TREATMENT-CONTROL GROUP DESIGNS

M. L. Prendergast, D. Podus, and E. Chang

UCLA Drug Abuse Research Center, Los Angeles, CA

The effectiveness of drug abuse treatment is central to policy and programmatic decisions about demand-side strategies for dealing with drug abuse. The current study uses meta-analysis to quantitatively analyze findings of treatment outcome studies conducted in the United States and Canada since 1965 that meet specified eligibility criteria. The full dataset consists of 297 studies that have been coded on 260 items covering study context, methodology, subject characteristics, treatment characteristics, dependent variable characteristics, and effect size calculation. The current analysis focused on studies that used treatment-control group designs (N=69). The analysis was limited to outcome variables related to substance abuse. The estimated average weighted effect size across studies was 0.27, which is equivalent to a 56% success rate for treated subjects compared with a 44% success rate for control subjects. In a weighted regression analysis (R-square=.59), larger effect sizes were associated with the following variables: use of a passive control group and use of drug tests. Smaller effect sizes were associated with the following variables: larger sample sizes, high attrition rates, high treatment integrity, and studies with federal funding.

ACKNOWLEDGMENT: Supported by NIDA grant RO1DA9151.

ASSESSING THE RELATIONSHIP BETWEEN METHODOLOGICAL QUALITY AND EFFECT SIZE IN STUDIES ON THE EFFECTIVENESS OF DRUG ABUSE TREATMENT

D. Podus, M. L. Prettdergast, and E. Chang

UCLA Drug Abuse Research Center, Los Angeles, CA

This study uses data from a meta-analysis or “study of studies” on the effectiveness of drug abuse treatment to examine the relationship between the methodological quality of a study and outcome effect sizes. The meta-analysis is conducted on approximately 200 studies, published and unpublished, evaluating the effectiveness of methadone maintenance, therapeutic communities, outpatient drug-free programs and variety of specific treatment techniques. The analysis will look at various aspects of study quality--among them, study design, sample selection, attrition, statistical power, integrity of treatment implementation, and reliability--and focus on their impact on the average effect size estimates of a broad range of outcome variables among them: substance use, crime, employment/education and others. The analysis will contribute to a better understanding of the design of drug abuse treatment evaluation research and its implications for the interpretation of study findings.

ACKNOWLEDGMENT: Supported by NIDA grant RO1DA9151.

PROSPECTIVE STUDY ON SIGNIFICANT FACTORS OF HCV TRANSMISSION AMONG IVDUs

L. Okruhlica

CPLDZ, Institut drogovych zavislosit, Bratislava, Slovak Republic

A short history of illicit drug use followed by intense health demand reduction measures is providing a good opportunity to study the problems of HCV transmission in the drug using population of Slovakia. We have registered more than 2,500 opiate abusing clients in our multi modal treatment center and 1,442 participants in Needle Exchange Program (NEP) in Bratislava. We have conducted an HCV survey among drug users, who come to our outpatient clinical center. The results show that 43.1% (138 out of 321) were HCV+. Secondly, we did a limited case-control study among our participants in NEP, which was targeted more on the possible modes of HCV transmission. Out of 150 surveyed NEP participants, 72 were tested for HCV and out of them 31 (43.1%) were HCV+. All of them were asked by the same interviewer about their habits in relation with needle-sharing and condom usage. Two groups were formed: (1) one group exposed to needle-sharing, and (2) the other, the control group, comprised of those who were not. The null hypothesis was not confirmed (OR=3.5). The results show that the IVDUs who share their needles with others are at a significantly higher risk of contracting the HCV infection. However, it does not seem to be the sole risk factor, which could explain the HCV transmission among drug users. The research in the future is going to be oriented in the following directions: (1) more detailed investigation of the risk factors of HCV transmission in the group of those who were HCV+ and have not reported needle-sharing; (2) follow-up study of those who were exposed to needle-sharing, but still tested as HCV-; (3) the follow-up preventive trial with those who were tested as HCV-.

HIV INFECTION PREVENTION AMONG IDUs IN RIO DE JANEIRO, BRAZIL

P. R. Telles

State University of Rio de Janeiro (NEPAD/UERJ), PEB/UFRJ, RJ, Brazil; FAPERJ, Brazilian Ministry of Health

Introduction: Injecting drug use is an important risk category for AIDS-HIV infection in Brazil. Approximately 25% of the 120,399 reported AIDS cases in Brazil are among injecting drug users (IDUs). The three main studies done among IDUs were the WHO multicentric study, the PROVIVA study (part of the NIDA multicentric collaborative study) and Projeto Brazil. **Methods:** The Harm Reduction Program (HRP) in Rio de Janeiro was launched at the end of 1996. The project operates with a fixed place (close to a drug treatment facility) and a mobile unit (a van). Counseling, distribution of informative folders and other preventive materials, HIV testing, needle exchange, and referral to other clinical or drug treatment places, are among the activities offered by the HRP. **Results:** In the past 12 months, the project reached a growing number of IDUs. The HRP distributed/exchanged 6,810 informative folders, 9,944 condoms, 6,371 needles/syringes and 331 kits (containing the above material plus bleach and distilled water). Many non-injecting drug users and more than 450 sex workers, considered as potential bridges to IDUs, were also contacted. In the effort to enroll to the project the "hard to find" IDUs, several parallel activities were developed, like drug treatment visits, group meetings with ex-IDUs and drug treatment professionals, night visits with the van to prostitution places and low-priced hostels (used by IDUs to inject in privacy), etc. As slums are traditional places of drug dealing, community leaders of important slums were also invited to cooperate with the program. At the moment distribution of preventive material to IDUs is taking place at eight important slums of Rio de Janeiro. **Discussion:** The results of the program seem to be satisfactory, to the extent that we are dealing with an extremely segregated population (marginalized even by non-injecting drug users), scattered in small networks all over the state, very difficult to find and enroll in preventive activities. Specially noteworthy is the work of ex-IDUs in the project (as outreach workers), which has shown to be a very effective way of reaching IDUs.

WITHDRAWAL FROM LONGTERM COCAINE SELF-ADMINISTRATION ALTERS PROOPIOMELANOCORTIN, PROENKEPHALIN AND CORTICOTROPIN RELEASING FACTOR mRNA CONTENT IN SEVERAL RAT BRAIN REGIONS

J. M. Oliva*, J. A. Crespo*, J. Corchero#, S. Martin*, C. Garcia-Lecutnberri, R. Ferrado*, J. Manzawares# and E. Ambrosio*

***Dept. Psicobiología. UNED, Madrid, Spain and Dept. Psicología Biológica y Salud, UAM, Madrid, Spain and #Unidad de Cartografía Cerebral, Inst. Pluridisciplinar, UCM, Madrid, Spain**

The neurochemical mechanisms involved in the cocaine withdrawal are not well understood Previous works have reported that cocaine administration and its withdrawl affects gene expression regulation of different brain genes. The aim of the present work has been to study the effect of the cocaine withdrawal on proopiomelan ocotin(POMC), proenkephalin (PENK) and CRF mRNA content in several cerebral regions using the yokedbox prodedure and cocaine self-administration behavior. Fifteen littemate male Lewis rats were randomly assigned in triads to one of three conditions: a) contigent intravenous self-administration of 1 mg/kg/injections of cocaine (CONT) and b) non-contingent injections of either 1 mg/kg/injection of cocaine (NONCONT) or c) saline yoked (SALINE) to the intake of the self-administering subject. The self-administering rats were trained to self-administer cocaine under a FR5 schedle of reinforcement during daily 2 hr sessions for a long period (between 4 and 6 weeks). After stable baseline levels of drug intake had reached, saline was substituted for drug during at least. Flollowing this first extinction period cocaine sof-administration was reinstated for an additional minimun period of 2 weeks and until stable baseline of cocaine self-administration behavior was again obtained On the 10th day after cessation of cocaine self-administration, animal brains in each triad were removed to be processed for in situhybridzation. Frozen serial coronal brain sections (20μm) made at the level of the dorsal striatum and nucleus accumbens (NACC), paraventricular nucleus (PVN) of the hypothalamus, arcuatus uncleus and substantianigra(SN) were processed for in situ hybridzation histochemistry. The brain sections were hybridzed with oligodeoxyribonucleotide probes complementary to POMC, PENK and CRF genes. Autoradiograms were analyzed with a Macintosh computer using the public domain NIH Image program. Optical densities were calculated from the uncalibrated grey scale values. POMC mRNA levels were significantly lower in the CONT group when compare with NOCONT and SALINE groups in the araraus nucleus, but not staistical differences were found between NOCONT and SALINE groups. PENK mRNA levels were significantly higher in the NOCONT group when compare with CONT and SALINE groups in the NACC, but there were not statistically significant differences between CONT and SALINE groups. In the SN, PENK mRNA levels were significantly lower in the CONT group when compare to NOCONT and SALINE groups. In addition, no statistical differences were found betweeen NOCONT and SALINE groups. CRF mRNA levels were significantly higher in the CONT group when compare with SALINE group in the PVN CRF mRNA content was also higher in the NOCONT group, but not statistical difference were found when compared with SALINE or CONT groups. These results suggest that changes in the gene expression of POMC, PENK and CRF might be implicated in the neurobiological processes involved in cocaine withdrawal.

ACKNOWLEDGMENT: Supported by DGICYTPB93-0290.

SCHIZOPHRENIA, COCAINE DEPENDENCE, AND NEGATIVE SYMPTOMS

I. Maany[1], A. Macfadden[1], P. Fudala[1], G. Gamble[1], J. Cornish[2], S. A. Poole[2] and C. R. Boardman[3]

Philadelphia Veterans Affairs Medical Center[1], The University of Pennsylvania[2], and The Children's Hospital of Philadelphia[3]

The mechanisms underlying the observed comorbidity between schizophrenia and substance abuse have not been identified. It is estimated that between 15% to 60% of schizophrenic patients abuse psychoactive drugs, with cocaine as the most frequently used substance. At the Philadelphia VAMC outpatient clinic, the point prevalence of cocaine use has been estimated to be 24% based on single urine drug screenings. We examined a group of veterans (N=40) with a diagnosis of schizophrenia and cocaine dependence to assess the possible correlation between negative disease symptoms and cocaine use. Participants for this 12-week study were outpatients attending the depo-neuroleptic clinic. Data were obtained at 2-week intervals for a total of 12 weeks (6 visits). At each visit, individuals provided a urine specimen for drug screening and were rated by a clinician (blinded to their substance abuse diagnosis) with the following scales: Scale for the Assessment of Negative Symptoms (SANS), Brief Psychiatric Rating (BPRS), Modified Simpson/Angus Extrapyramidal Symptom (SAPS), and the Hamilton Depression (HAM-D). Vital signs and patient-reported cocaine craving for the past 24 hours were also assessed at each visit. Statistical analysis of the data from the six time points will involve longitudinal mixed effects models/random regression for the continuous psychometric variables (SANS, SAPS, BPRS, HAM-D), cocaine craving, and vital signs. Cocaine use will be described using a four level ordinal variable at each time point. The ordinal data will be analyzed using an extension of generalized estimation equations. Important time-stationary and time-varying covariates will also be included in both analyses. Data analysis is currently ongoing.

POSTER SESION II

STRONG ETHNIC IDENTITY SERVES AS A PROTECTIVE BUFFER AGAINST FIRST TIME DRUG USE

S. Orozco[1] and S. E. Lukas[1]

[1]Behavioral Psychopharmacology Research Laboratory, McLean Hospital/Harvard Medical School, Belmont, MA

Many studies have found that high acculturation into mainstream society may signal increased risk of drug use among different ethnic groups. However, few studies have been able to measure different ethnic groups using one acculturation scale due to the ethnic specificity of the available scales. We developed a new multi-ethnic acculturation scale using key components of presently established scales. Drug use histories were collected from 18 African-Americans (8 males, 10 females) and 10 Hispanics (5 males, 5 females) using a standardized questionnaire and were compared with the degree of acculturation. Males were significantly more acculturated and reported having used more drugs than females although they did not differ in their age of first drink. Ethnic Identification, gender, and scores on the Social Scale and Personal Relationship subscales of the acculturation questionnaire were most predicative of increased drug use. In addition, for males only, ethnic pride also was predicative of increased drug use. Thus, this study suggests that low levels of acculturation can be a protective buffer against the onset polydrug use (or abuse) among different ethnic groups. Also, acculturation and drug studies must consider the importance of gender within and across ethnic sub-populations.

ACKNOWLEDGMENTS: Supported by grants DA00343 and DA09657.

PERSONAL CHARACTERISTICS ASSOCIATED WITH INJECTING-DRUG USE AMONG LATINAS IN THE U.S.

J. Delva, C. D. M. Furr, and J. C. Anthony

Department of Mental Hygiene, Johns Hopkins University, Baltimore, MD

This study examines injecting-drug use among Latinas in a nationally representative sample of 12 year and older household residents in the United States. Injecting-drug use has become a serious public health problem for Latinas in the United States. Data from the 1990-1995 National Household Surveys on Drug Abuse were analyzed using the conditional form of multiple logistic regression, with matching of injecting Latinas (n =154) and non-injecting Latinas (n = 602) on neighborhood of residence. The odds of injecting-drug use are 4.6 to 6.5 times greater for young-adult Latinas(18-44 years old) when compared to Latinas aged 12 through 17 years old ($p<0.05$). Latinas with past or current histories of using marijuana or inhalants also are more likely to have a history of injecting-drug use. The odds of injecting-drug use are an estimated 7.1 times greater for Latinas who report marijuana use and 5.4 times greater for Latinas who report inhalant use when compared to Latinas not using these drugs ($p<0.01$). The observed associations of injecting-drug use with age and history of drug use represent first steps in an effort to understand Latina sub-groups most affected by injecting-drug use, and the underlying risk factors or causes.

ACKNOWLEDGMENT: Supported by NIDA Training grant DA07292.

CLUSTERS OF MARIJUANA USE IN THE UNITED STATES

G. V. Bobashev and J. C. Anthony

Department of Mental Hygiene, Johns Hopkins University, Baltimore, MD

In this study, we test for and estimate the clustering of marijuana use within United States neighborhoods, making use of data from annual nationally representative household sample surveys conducted during the period 1990-1995 (n=88,902). A recently developed statistical method, alternating logistic regression, was used to quantify the clustering of marijuana users in neighborhoods. The resulting estimates of Pair-Wise Odds Ratios (PWOR) ranged from 1.3 (95% confidence interval, CI, 1.22-1.42) for the lifetime history of marijuana use to 2.0 (95% CI, 1.6-2.6) for recent sharing of marijuana from one person to another. The order of magnitude of these estimates is comparable to the clustering of annual family income in the U.S. and to the clustering of diarrheal disease in villages in the Third World countries. Exploratory analysis showed a slight decrease of clustering effects after adjustment for individual-level covariates: age, sex, race, education, annual family income, and history of tobacco use. Nevertheless, the main factors that account for clustering remain to be determined. Alternating logistic regression provided useful estimates of marijuana use clustering, and can be used to estimate clustering of the other drug-related behavior, including sharing of needle injection equipment and other HIV risk behaviors. As a form of multi-level analysis, the alternating logistic regression can accommodate shared community-level characteristics that might influence drug-taking (e.g., 'collective efficacy'), as well as individual-level covariates such as age and sex.

ACKNOWLEDGMENT: Supported by NIH grant DA09592 (to JCA).

CLUSTERS OF COCAINE USE & PERCEIVED RISK OF COCAINE USE: 1991-93

K. R. Petronis and J. C. Anthony

Johns Hopkins University, Baltimore MD

Epidemiologists have studied clusters and ‘hot-spots’ of infectious and chronic diseases for more than 150 years. But epidemiological research on clusters of drug-taking has been virtually non-existent until recent studies of drug users’ social networks. Here, we use the alternating logistic regression (ALR) to test for and to estimate the magnitude of clustering of cocaine use within neighborhoods, with adjustment for age, sex, race, social class, and residential mobility; we also estimate neighborhood clustering of perceived harmfulness of cocaine use. METHODS: Data ate from self-report assessments completed for the National Household Surveys on Drug Abuse from 1991 (n=32,594) through 1993 (n=26,489), with nationally representative samples drawn from within census block groups (‘neighborhoods’). The ALR yields a pair-wise odds ratio (PWOR); its null value is 1.0 when no clustering exists. RESULTS: As hypothesized, cocaine use clustering varies with recency and frequency of cocaine use: in general, PWOR estimates for neighborhood clustering of recent weekly cocaine use tend to exceed PWOR estimates for clustering of less recent and frequent cocaine use. To illustrate, for recent weekly use, PWOR tend to be greater than 2.0. In contrast, estimates for lifetime cocaine use are closer to 1.5. Evidence also supports neighborhood clustering of perceived harmfulness, as indicated by answers to questions on whether regular cocaine use is risky, with PWOR greater than 2.0. COMMENT: This study presents the first epidemiological estimates on clustering of cocaine use and perceived risk of cocaine use, with evidence of clustering within neighborhoods. We will extend this work to understand how neighborhood-level sharing of perceptions of risk about cocaine use and other features of social context might influence the occurrence of clusters of cocaine-sharing and pockets of active frequent cocaine use.

ACKNOWLEDGMENTS: Supported by NIDA R01DA09592 and NIDA training program award T32DA07292.

DRUG AND ALCOHOL USE AMONG PANHANDLERS

S. E. Lankenau

Medical and Health Research Assocation of New York City, Inc. (MNRA), New York, NY

What are the effects of drug and alcohol use and abuse on the life-course of homeless panhandlers? Conversely, what are the effects of being a homeless panhandler on drug and alcohol use? To address these questions, I examined the life histories of a sample of male and female panhandlers (N=37) in three phases - pre-panhandler, panhandler, and ex-panhandler. Drug use is often associated with prison history in the pre-panhandler stage: two-thirds of panhandlers who indicated a drug or alcohol problem in the pre-panhandler stage served prison sentences. During the panhandler stage, drug use typically escalates: four out of five panhandlers reported current mild to heavy drug or alcohol use. This finding may be partially explained by the following observations: drugs are readily available on the streets and the hardships of a homeless panhandling existence may promote drug use. Few panhandlers in this study exited their panhandling careers. Drug and alcohol use is likely to discourage career exits for the several reasons. First, chronic alcohol or drug use affects daily functioning and the ability to plan long-term. For instance, panhandlers who support a drug habit with panhandling earnings are less likely to temporarily give up this income to seek more gainful employment. Second, outreach services often require persons they serve to undergo drug or alcohol treatment. Chronic users who are unwilling to undergo such treatment forfeit outreach services that offer housing and employment opportunities. Third, prospective employers may require job applicants to be drug tested. Panhandlers who regularly use drugs are likely to fail a drug test. In sum, drug and alcohol use is associated with prison and the beginning of a panhandling career, drug and alcohol use typically increases during the panhandling career, and drug and alcohol use reduces the likelihood of exiting a panhandling career. This research is based upon a street ethnography of homeless panhandlers living in Washington, DC.

DRUG USE AMONG MIDDLE-AGED AND ELDERLY PERSONS

M. M. Wang,[1,2] and M. D. Anglin[1]

[1]UCLA Drug Abuse Research Center and [2]WestEd

Researchers who investigate drug use in middle-aged and elderly populations often examine drug use from a medical model perspective, focusing on the biological underpinnings of drug use and abuse. For prevention purposes, it will also be crucial to understand the social and psychological antecedents of drug use in this little-studied user population. Because alcohol and other drug use tapers off dramatically by age 50, it is sometimes assumed that older persons have no need or demand for prevention (or treatment) services. Indeed, while the overall prevalence of heavy use or misuse in the total middle-age and elderly population may be "low," suggesting a rosy picture, the "small" proportion of older persons who do use may have a lengthy drug use career and have incurred significant health, societal, and financial consequences. To reduce personal and societal harm from drug involvement in older populations, it is important to investigate the social and psychological factors that may trigger use or escalate use. To assess the need for prevention services for older users, we will use data from Californians age 50 and over from several databases. Our preliminary analyses will examine the relationship between household size (proxy social support measure) and health status and involvement in alcohol, tobacco (smoking), and other drug use. For some middle-aged and elderly persons, a lack of social support may be associated with greater alcohol and other drug involvement and poorer physical or mental health; that is, "drug involvement as coping." Additionally, a lack of social support may have quite a different effect upon drug use in different age groups, for example, those in early middle age versus seniors (age 65 and over).

ACKNOWLEDGMENTS: Supported by grant 95-00223-A2 from the California Department of Alcohol and Drug Programs and Grant No. 277-95-1032 from the Center for Substance Abuse Prevention.

EFFECTS OF LOSS OF BENEFITS ON FORMER SSI RECIPIENTS

C. Ponath, B. Tajima, A. Coutts, and J. Guydish

Institute for Health Policy Studies, University of California, San Francisco, CA

As of January 1, 1997, substance abuse is no longer recognized as a disability qualifying individuals for SSI benefits. A convenience sample of 63 individuals who had previously been in drug treatment programs in San Francisco and were receiving SSI benefits on the basis of their addiction were interviewed in December 96 and again in June 97. Respondents had a mean age of 44; 56% were African American, 33% Caucasian: 70% were male; 55% had a least a 12 grade education. We predicted that the loss of benefits would have a destabilizing impact on former recipients with possible loss of housing and health insurance as well as increases in substance use and criminal activity. At 6 month follow up, 60 recipients were re-interviewed. Half (30) reported receiving SSI benefits for a different disability. The most notable difference between SSI-recipients and non-recipients was a decrease in mean monthly income ($880 vs $544, t= -2.07; p<.05). Most of the non-SSI recipients (74%) were receiving General Assistance. The main difference for the group as whole over time was the loss of representative payees (89% had payees at baseline vs. 37% at follow up, c2=39.7; p<.001), and less treatment exposure (at baseline, over 70% of respondents reported having been in drug treatment in the last 6 months vs 18% at follow up, c2=35.7; p<.001). Other outcome measures were the seven Addiction Severity Index (ASI) severity scores. There was no significant difference between ASI scores either over time for the group as a whole or between SSI-recipients and non-recipients at 6 month follow up. These findings indicate a shift in financial burden from federal to state and local levels. The anticipated destabilization is noticeable, though not as pronounced as expected. Longer term follow up or data from larger samples are needed.

PATTERNS AND CORRELATES OF ANABOLIC-ANDROGENIC STEROID USE

J. Copeland, R. Peters, and P. Dillon

National Drug and Alcohol Research Centre, University of New South Wales, Australia

Abuse of anabolic-androgenic steroids (AAS) for athletic and aesthetic purposes is an increasing concern for clinicians, researchers and policy makers. There has been, however, a paucity of epidemiological and behavioural research into the patterns and correlates of AAS and related drug use. This paper will report on the experiences of a sample of 100 current AAS users interviewed in New South Wales, Australia. This sample of predominantly injecting drug users had a very different demographic profile to other illicit drug users in Australia. The subjects were generally employed and only 27% earned less than $30,000 per annum. Only 32% of AAS users in the sample smoked cigarettes and only 1% reported drinking alcohol daily. The average age of first use of AAS was 25 years and the majority of the sample (83%) injected from their first use. Two thirds of the sample were using a combination of human and veterinary preparations. The most important benefit of AAS use for 41% of the sample was "increased size" and for 38% it was “improved appearance”. Body image was the primary motivation for AAS use for the majority of the sample. Two thirds of the sample were concerned about the side-effects of AAS use and there was evidence of AAS abuse/dependence and the phenomenon known as "roid rage". The resulting primary and secondary intervention materials developed for AAS use will be presented.

ACKNOWLEDGMENT: Supported by a grant from the New South Wales Department of Health

ADOLESCENT SUBSTANCE USE: A PILOT TREATMENT PROJECT

C. Thomas, A. Huber, J. Obert, and R. A. Rawson

Friends Research Institute, Inc., Matrix Institute, Los Angeles Addiction Treatment Research CenterLos Angeles, CA

Twenty-two students at a Los Angeles area school for children with special needs (educational, psychiatric, and/or abuse/neglect) participated in a pilot drug and alcohol treatment project. The program consisted of daily group and individual counseling sessions, with education, risk reduction, abstinence support, and relapse prevention components. This report presents participants' reports on substance use and psychosocial functioning using the Problem Oriented Screening Instrument for Teenagers (POSIT), the drug and alcohol sections of the Adolescent Problem Severity Index (APSI), and the students' perceptions of the dangerousness and accessibility of drugs/alcohol. At baseline, 83.2% of the teens admitted using alcohol, 89.4% marijuana, 42.1% hallucinogens, 26.3% speed, 21.1% cocaine and 10.5% inhalants in the past year. Nearly all reported having a parent or family member with a substance use problem. Despite reports of regular use and significant problems related to substance use (42.1% have injured themselves or others while under the influence, 26.3% feel that drugs make them do things they would not otherwise do), only 36.8% perceived themselves as addicted. Project results indicated that the program was attractive to participants with 20.5 weeks being average retention in treatment. Urine results showed that by the end of the project, 77% of the teens either reduced drug use or used no more than before they began treatment. Contingencies also improved results as measured by urinalysis in the last 4 weeks of the study. For this sample of adolescents with multiple problems, successful treatment requires innovative intervention strategies.

ACKNOWLEDGMENT: Matrix Center and NIDA grant 1 DA R01 10923.

RISK FACTORS ASSOCIATED WITH CHILEAN ADOLESCENT SUBSTANCE USE

P. T. McWhirter

UCLA Neuropsychiatric Institute Drug Abuse Research Center, Los Angeles, CA

Chilean adolescents (n=628) of diverse demographic characteristics were surveyed to assess the relationship between salient psychosocial risk factors (peer substance use, attitudes about peer users, parental and sibling use, family structure, refusal skills, empathy, impulsiveness, venturesomeness, trait anxiety, self concept, SES, age, and sex) and substance use. For each of the step-wise multiple regression models performed, a combination of the psychosocial variables predicted a significant amount of variance for alcohol (53%), cigarette (32%), marijuana (41%), solvent inhalant (50%), and cocaine use (53%). Findings suggest the importance of role models (peer, sibling and parental) in predicting adolescent substance use among Chilean youth.

ACKNOWLEDGMENT: NIDA Research Training grant DA0727-06.

THE RELATIONSHIP BETWEEN ADOLESCENT SMOKING AND DRINKING AND LIKELIHOOD ESTIMATES OF ILLICIT DRUG USE

P. B. Johnson, S. M. Boles, K. McVeigh, and H. D. Kleber

The National Center on Addiction and Substance Abuse at Columbia University, New York, NY

Using data from a recent national survey of adolescent substance use, the present work examined whether adolescents with different patterns of alcohol and cigarette use differed in their estimates of the likelihood they would use an illegal drug in the future. While nonusers of either substance were the most likely to indicate that they would never use drugs in the future, users of both substances were the most likely to indicate that they would use drugs. In addition. while users of both were most likely to indicate that they were likely to use illegal substances, only-smokers were more likely than only-drinkers to indicate that they were likely to use such substances in the future. Results are discussed in terms of the gateway theory of drug sequencing and cognitive precursors of experimentation with illegal substances.

SMOKING EXPECTANCIES AND EXPERIMENTATION WITH CIGARETTES

H. L. Johnson and P. B. Johnson

Department of Elementary and Early Childhood Education, Queens College, Flushing, NY and The National Center on Addiction and Substance Abuse at Columbia University, New York, NY

While many studies have explored the role of alcohol expectancies in the development of adolescent alcohol use, less attention has been given to the study of cigarette or smoking expectancies and their relationship to early experimentation with cigarettes. The present research sought to determine the extent to which smoking expectancies differentiated sixth grade cigarette experimenters and nonexperimenters. One hundred sixyt-one males and 168 females completed an in-class survey regarding their expectancies about the likely effects of smoking cigarettes. They also reported whether they had previously smoked. Factor analyses identified positive and negative dimensions of the smoking expectancy items. Sixth grade experimenters possessed stronger positive and weaker negative expectancies than sixth grade nonexperimenters. Results are consistent with previous alcohol expectancy research and are discussed in terms of their diagnostic and treatment implications.

SMOKING AND COGNITION IN YOUNG ADULTS

S. M. Alessi, M. Kilbey*, and J. Mullennix*[++]

***Department of Psychology, Wayne State University, Detroit, MI and [++]Department of Psychology, University of Pittsburg, Johnstown, PA**

Previous research has reported a content-specific Stroop interference effect in a population of long-term smokers in treatment for alcohol and substance abuse (Gross *et al.* 1993). The present study was conducted to extend these findings to a sample of college students enrolled at Wayne State University, Detroit, MI. Subjects were classified as Nicotine Dependent (n = 48), Non-Dependent (n = 48), or Non-Smoker (n = 24) based on DSM-III-R criteria for nicotine dependence (Robins *et al.* 1989). All smokers were randomly assigned to either a satiated or abstinent smoking condition. There was a significant interaction between Sex and Dependence Status on the Negative Reinforcement/Negative Affect Reduction Scale of the SCQ (Brandon & Baker 1991). In addition, smokers scored significantly lower than non-smokers on the Negative Consequences Scale, and non-smokers scored significantly lower than smokers on the Positive Reinforcement/Sensory Satisfaction Scale of the CEQ. The experimental task consisted of a traditional Stroop Color Word Test (Stroop 1935) and a modified version of the Stroop Test using smoking-related and "neutral" words as stimuli. Average response times (ms) to color-congruent words were significantly faster than average response times (ms) to color-incongruent words on the traditional Stroop Test across groups. There were no main effects of Dependence Status, Smoking Condition, nor Word Category, nor were there interaction effects on the Content-Specific Stroop Test. These results suggest that while smokers and non-smokers differ with regard to their "expectations" of cigarette smoking, these individuals do not differentially process smoking-related words regardless of nicotine dependence status and abstinent/satiated factors.

REFERENCES: Furnished upon request from senior author.

DAY TREATMENT FOR ADJUDICATED DRUG DEPENDENT TEENS: DOES DOSE DETERMINE RESPONSE?

D. S. Festinger, D. B. Marlowe, V. Lidz, E. P. Merikle, B. M. Fishman, M. L. O'Neill, and J. J. Platt

Institute for Addictive Disorders, Allegheny University of the Health Sciences, Philadelphia, PA

Inner-city, adjudicated, drug dependent adolescents ages 14 to 18 were referred to our comprehensive drug-free day program. Participants were scheduled to receive 2 hours of individual cognitive-behavioral counseling, 10 hours of psychoeducational group therapy, and 1.5 hours of highschool remediation per week. Subjects attended the clinic from 8 to 3, Monday - Friday. Urine specimens were collected daily, two of which were randomly tested for alcohol, cannabis, cocaine, opiates, barbiturates, benzodiazapines, hallucinogens, amphetamines, and PCP. Of the 42 adolescents that entered our program, 9 subjects were excluded from the analysis for attending less than 10 hours (1 week) of group therapy, and 2 for attending less than 2 hours (1 week) of individual therapy, leaving a total N of 31. Plotting of a dose-response curve revealed a significant linear relationship between the number of group therapy hours received and drug abstinence intervals, accounting for 31% of the variance in outcome ($p<.005$). A separate curve plotted for individual therapy also revealed a significant linear relationship between hours and abstinence, accounting for 17% of the variance in outcome ($p < .05$). However, when both group and individual hours were entered into a hierarchical regression only total hours of group therapy was found to be a significant predictor of abstinence ($p < .05$). The addition of hours of individual therapy to the model accounted for only a 2% increase in explained variance, from 31% to 33%. These results suggest that group therapy may be a more effective treatment modality than individual therapy in inducing abstinence among drug dependent, adjudicated teens.

ACKNOWLEDGMENT: Supported by the Office of National Drug Control Policy.

THE MINI - A NEW SCREENING TOOL FOR THE DUALLY-DIAGNOSED

P. L. Donaldson

Medical and Health Research Association of New York City, Inc. NY, NY

There is a need for rapid assessment tools to screen for comorbid psychiatric disorders and expedite effective treatment at time of first evaluation. The MINI International Neuropsychiatric Interview (MINI) is a short, diagnostic interview for major Axis I psychiatric disorders in DSM-IV and ICD-10. The MINI focuses on the existence of current disorders, using one or two screening questions to rule out the diagnosis when answered negatively and then DSM-IV criteria type questions if answered positively. Previous validity studies using the MINI versus the SKID and the CIDI indicate very good reliability and validity with an average administration time of 21 minutes. The present study evaluated the feasibility and utility of the MINI as a screening instrument. Fifty-three newly admitted clients entering a therapeutic community had a psychiatric evaluation along with a MINI assessment. Results indicate that the MINI picked up 40 clients (75%) as potentially dually diagnosed. The psychiatric evaluation found 23 or (40%) with positive dual diagnoses. Conclusions reached were that the MINI may pick up psychiatric disorders missed by clinical interviews but it may also over-diagnose substance-induced disorders. Given that the MINI is a valid, reliable, inexpensive, quick and easy screening tool it should be used as part of a diagnostic assessment.

ACKNOWLEDGMENT: Supported by University of South Florida Creative Research Scholarship Award 6201943RO.

ASSESSING PSYCHIATRIC DISORDERS AMONG DRUG USERS: RELIABILITY OF THE REVISED DIS-IV

J. Horton, W. M. Campton, and L. Cottler

Washington University School of Medicine, Department of Psychiatry, St. Louis, MO

It has been estimated that up to 60% of substance users have a non-substance psychiatric disorder; yet, many of these dual diagnosed people go untreated or mistreated. To identify dual diagnosis, reliable and valid assessments are needed. Thus, this study aims to determine the reliability of the revised Diagnostic Interview Schedule Version IV (DIS-IV) for diagnosing psychiatric disorders among drug users. The revised DIS-IV was modified to cover DSM-IV diagnoses and criteria including: revisions based on feedback from the field and adding new questions to cover remission of symptoms and sequence of disorder onset. This is the first methodological study of the newly revised DIS-IV. The sample was recruited from lists of current and previous patients of three substance abuse and psychiatric treatment sites in the St. Louis area to provide a broad range of diagnoses with varying severity. Trained non-clinician interviewers administered the DIS-IV at test and retest. Preliminary results indicate reliability of lifetime disorders as measured by the kappa statistic were: major depression *k*=good, posttraumatic stress disorder *k*=fair, generalized anxiety *k*=poor, any phobia *k*=poor, social phobia *k*=good, attention-deficit hyperactivity disorder *k*=fair, panic *k*=fair, antisocial personality disorder *k*=good, alcohol dependence *k*=good, cocaine dependence *k*=good, cannabis dependence *k*=good and opiate dependence *k*=excellent. As expected based on prior studies, substance dependence disorders had the best reliability. Depression, antisocial personality, oppositional defiant disorder, and social phobia had good reliability. All the others had fair reliability, except for generalized anxiety and any phobia. We conclude that DIS-IV psychiatric disorders, except for generalized anxiety and any phobia, have adequate reliability among in-treatment or treatment-seeking substance users.

ACKNOWLEDGMENTS: Supported by NIDA grants DA00209 and DA05786.

THE RELIABILITY OF THE BSI AS AN INDICATOR OF PSYCHOPATHOLOGY AMONG ACTIVE SUBSTANCE ABUSERS

S. A. Wyatt, S. A. Ball, and B. Rounsaville

Yale University, New Haven, CT

The Brief Symptom Inventory (BSI) has been well established as an indicator of current symtomatology and predictor of psychopathology in the general population. Its reliability and validity as a screen for psychiatric symptoms and disorders in actively using substance dependent individuals has not been well established. We assessed 370 substance dependent individuals (male 44%, mean age 32.9, cauc. 56%) entering inpatient (49.1%) and outpatient treatment using three measures the BSI, ASI, and SCID I/II-R, at baseline and one year follow-up. We predicted that at baseline, the BSI grand total would be uniformly elevated. However, at follow-up assessment in subjects where there has been a decrease in substance use severity as measured by the ASI, we predicted a greater downward trend in BSI in subjects without a lifetime history of a depression or anxiety disorder in comparison with those positive for this history. The evaluation of this hypothesis was preformed by simple correlation, ANOVA, and multiple response analyses. The results indicate that at baseline there was a significantly greater elevation of BSI grand total in the patients with a history of mood or anxiety and there was a significant improvement in symptoms in both those with and without this history. In conclusion it appears by this analysis that the BSI, if adjusted for active substance use, remains a predictor of psychopathology for active substance abusers on entering treatment.

ACKNOWLEDGMENTS: Supported by NIDA grants RO1DA10012-01 and DA07238.

CLINICAL RESEARCH ON THE ASSESSMENT AND TREATMENT OF SUBSTANCE DEPENDENCE AND MENTAL DISORDERS

D. J. Geyen and J. M. Beal*

***Sam Houston State University, Huntsville, TX and Prairie View A & M University, Prairie View, TX**

Traditionally persons with a substance dependence were assessed and treated differently from those who were diagnosed with a mental disorder. Each group was considered mutually exclusive and classified under separate standards. In many respects this continues to be a widely accepted theory by many professionals practicing in the field. However as behavioral science progresses toward the next millennium, there is a growing need for researchers and practitioners to help those who suffer from substance dependence co-occurring with mental illness. This phenomenon is more commonly known as dual disorders. As a relatively young area of study, this form of cormobidity presents substantiated clinical issues related to assessment and treatment of persons with dual disorders. Some of these issues are: treatment of drug/alcohol addition with psychotropic medicine, deciding which disorder takes precedence in the assessment diagnostic phase; self medicating prescription drug abuse and non prescription drug abuse; and the residual effects of one type disorder exacerbating a related disorder. Achieving a valid diagnostic assessment and deciding on an appropriate treatment plan can be challenging. A qualitative analysis was conducted to investigate the nature of these topics ans they relate to assessment and treatment of dual disorders. The research presents data from a systematic, descriptive, replicable and cumulative perspective. It examines the concept in methods intended to reveal many facets of the human experience associated with the assessment and treatment of substance dependence and mental disorders.

COMPARISON OF PSYCHIATRIC SYMPTOMATOLOGY IN DUALLY DIAGNOSED VETERANS

M. Salinardi, D. Jameson, R. Snodgrass, and E. Hines, Jr.

VA Hospital, Hines IL

A pilot study (N=20) was conducted to measure the changes in psychiatric symptomatology in dually diagnosed veterans as measured by the Brief Symptom Inventory (BSI). Veterans were treated in a 4-week Dual Diagnosis Lodger program. The BSI was given at screening (BL) and after 3-weeks of treatment. Results indicated that the only significant decrease was in depressive symptoms from BL to the third week in treatment. None of the other 8 individual symptom scales, nor the Global Severity Index (GSI) decreased significantly over the 3-week period. As a result, the treatment program was extended from 4 to 6 weeks. The hypothesis was that the additional program time with this vulnerable group would result in more extensive decreases in psychiatric symptoms. Thirty-seven patients in a Dual Diagnosis Lodger program were given the BSI on the day of their screening (BL), after 3 weeks, and after 5 weeks in the program. Results of the nine symptom scales and the GSI were compared over the three points in time. Anxiety, depression, and the GSI all decreased significantly at 3 and 5 weeks. Psychosis, somatization and obsessive-compulsive decreased significantly from the 3 to 5 week time point. We conclude that this population report significant decreases in psychiatric symptomatology with a longer treatment program.

IMPACT OF ANTISOCIAL PERSONALITY DISORDER DURING LAAM MAINTENANCE TREATMENT

M. B. Mudric, A. R. Buchhalter, M. S. Kidorf, R. K. Brooner, and R. E. Johnson

Department of Psychiatry, Johns Hopkins University School of Medicine, Baltimore, MD

The diagnosis of antisocial personality disorder (APD) has been associated with poor treatment outcome. In the present study, the impact of APD on pre-treatment drug use and treatment outcome was examined for opioid dependent outpatients enrolled in a 29 week, randomized, stratified, double-blind study with LAAM. Patients were assigned to one of three conditions, each employing thrice weekly dosing: 25 mg/25 mg/35 mg (N = 62), 50 mg/50 mg/70 mg (N = 59), and 100 mg/100 mg/140 mg (N = 59). Patients completed the Structured Clinical Interview for the DSM III-R (SCID) at baseline and the Addiction Severity Index (ASI) at baseline and at weeks 5, 10, and 16. Data were collapsed across dosing conditions and analyzed for 84 patients (34 APD and 50 non-APD) who completed the maintenance phase of the study (weeks 5-17). Although both groups reported similar rates of pre treatment opioid use, APD patients reported more days of cocaine use (12.8 vs. 6.9 days; $p = .02$) during the month prior to treatment, and reported a trend of more total years of cocaine use (3.3 vs. 1.9 years; $p = .07$). APD and non-APD patients exhibited significant reductions in both cocaine and heroin use throughout the study ($p < .001$) despite the respective initial differences in pre treatment cocaine use (12.8 vs. 6.9 days). APD patients reported fewer days of cocaine use during the final ASI administration than non-APD patients (2.8 vs. 4.1 days). The results indicate, contrary to pre treatment differences, that both APD and non-APD patients similarly reduce opioid and cocaine use during LAAM maintenance treatment.

ACKNOWLEDGMENTS: Supported by grants P50 DA05273, K05 DA00050, K20 DA00166, and T32 DA07209 from USPHS/NIH/NIDA.

PSYCHOPATHOLOGY AND DRUG OF CHOICE, AFTERCARE COMPLIANCE AND RELAPSE PATTERNS AMONG CHRONIC NARCOTIC ABUSERS

W. Canter and C. Sannerud

VA Maryland Health Care System at Perry Point, MD and U.S. Drug Enforcement Administration

The relationship of psychopathology indices, initial motivational measures, prognostic ratings and demographics to drug preference, aftercare compliance and specific patterns of relapse were assessed using the MMPI-2, measures of prior personal and family psychopathology, reliable motivational measures and multiple aspects of demographic data. In the original sample, 190 consecutive admissions to a 21-day multimodal, inpatient treatment program were assessed at admission and discharge. Reliable aftercare compliance and abstinence data was collected at 3 and 10 months. Data was analyzed by means of discriminant function, cluster analysis and path analysis methodologies. Demographics and staff prognostic ratings showed no relationship to variables of interest. Specific empirical subtypes of psychopathology were very powerfully related to drug preference, initial aftercare compliance and specific longitudinal patterns of relapse. A second sample of 120 consecutive subsequent admissions and identical procedural and data analysis methodologies provided strongly corroborative cross-validation. These results support the need for explicit consideration of empirical and related DSM-IV psychopathology subtypes in aftercare compliance strategies and relapse likelihoods among narcotics abusers.

FAMILIAL RISK ANALYSIS OF THE ASSOCIATION BETWEEN ADHD AND PSUD

S. Milberger, S. V. Faraone, J. Biederman, M. P. Chu, and T. Wilens

Pediatric Psychopharmacology Unit, Massachusetts General Hospital, Harvard Medical School

Objective: To test hypotheses about patterns of familial association between Attention Deficit Hyperactivity Disorder (ADHD) and psychoactive substance use disorders (PSUD) using family study methodology. **Design: The** first-degree relatives of clinically referred children and adolescents with ADHD (131 probands, 413 relatives) and normal controls (106 probands, 323 relatives) were assessed by blind raters. **Results:** After stratifying the ADHD and normal control probands into those with PSUD (ADHD+PSUD and NC+PSUD) and those without PSUD (ADHD-PSUD and NC-PSUD), familial risk analyses revealed the following: 1) the risk for ADHD was not significantly different between relatives of ADHD and ADHD+PSUD (18% vs. 20%), but these two risks were significantly greater than the risk to relatives of normal controls with PSUD (1%) and without PSUD (7%); 2) there were no significant differences in the risk for PSUD between relatives of ADHD+PSUD (48%) and NC+PSUD probands (40%), but these risks were greater than the risk to relatives of ADHD probands without PSUD (30%) and normal controls without PSUD (21%); and 3) there was no evidence for nonrandom mating. **Conclusions:** These findings are consistent with the hypothesis that ADHD and PSUD are transmitted independently in families. Because the probands were young adolescents many have not lived through the age at risk for PSUD. Thus, the hypothesis stating that ADHD and PSUD represent variable expressions of a common underlying risk factor cannot be ruled out.

BUPROPION TREATMENT FOR ADULT ADHD AND COCAINE ABUSE

F. R. Levin, S. M. Evans, D. M. McDowell, D. Brooks, M. Rhum, and H. D. Kleber

Columbia University and NY State Psychiatric Institute, New York, NY

Although there is increased recognition of adult attention-deficit hyperactivity disorder (ADHD) among cocaine abusers, there are few studies targeting treatment for this dually-diagnosed population. Using the SCID for DSM-IV and a SCID-like module for child and adult ADHD symptoms, individuals with cocaine dependence and adult ADHD were enrolled in a 12-week open pilot study. Patients attended the clinic 3x/week. Individuals met weekly with the treating psychiatrist (FRL) who administered the Targeted Attention Deficit Disorder Scale (TADDS), a structured clinical interview to assess adult ADHD symptoms. Patients also completed the Adult Behavior Checklist (ABC), a self-report measure which incorporates the DSM-IV ADHD symptoms, on a weekly basis. Urine toxicology screens were collected 3x/week. All patients received weekly individual relapse prevention therapy. Of the 11 patients enrolled in the study, 9 completed at least 10 weeks of the trial. For these 9 patients, 9 were male; 8 were Caucasian. and 1 was Hispanic. The average age was 31.7 (5 years. Patients were maintained on divided daily doses of bupropion, ranging from 100 10 400 mg/day. Comparing the first 2 weeks of evaluation to the last 2 weeks of treatment, the average reduction in ADHD symptoms was 43% based on the ABC. Similarly, substantial improvements on the TADDS subscales were observed, with the greatest average reduction in inattentive symptoms (34%) and hyperactive symptoms (46%). Self-reported frequency of cocaine USC dropped an average of 12 to 2 days per month. The average reduction in cocaine-positive urines was 85%. These data suggest that bupropion may be an effective medication for treating ADHD symptoms and cocaine dependence. Further study of this medication under double-blind conditions for this dually-diagnosed population is warranted.

ACKNOWLEDGMENTS: Supported by NIDA grants P50 DA09236 and K20 00214-01A1

DOES ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IMPACT REMISSION FROM SUBSTANCE ABUSE?

J. Biedermon, T. E. Wilens, E. Mick, and S. Milberger

Pediatric Psychopharmacology Unit, Massachusetts General Hospital, Harvard Medical School, Boston, MA

Objective: Despite a growing literature on the developmental relationship between attention deficit hyperactivity disorder (ADHD) and the substance use disorders (SUD), little is known about SUD remission in ADHD adults. In this study we examine the effects of ADHD and psychiatric cotnorbidity on recovery from SUD. **Methods: We** studied 130 referred adults with ADHD and 71 nonADHD adults all of whom had a lifetime history of SUD. All psychiatric and substance use disorders were assessed by DSM III-R based structured psychiatric interviews including onset and offset data. Results: Although SUD remitted in 80% of both groups, the rate of remission and duration of SUD was quite different in the ADHD subjects relative to controls. The duration of PSUD was 37 months longer in the ADHD subjects compared to non-ADHD controls ($p<0.05$). The median titne to SUD remission was more than twice as long in the ADHD than in control subjects (144 vs 60 months, respectively). **Conclusions:** ADHD is associated with a longer duration of SUD and a significantly slower remission rate than that of controls. If confirmed such findings extend previous work showing that ADHD is a risk factor for early initiation and specific pathways of SUD providing further evidence of the relevance of this association.

CONNECTING CHILDHOOD VICTIMIZATION AND WOMEN'S DRUG PROBLEMS: THE ROLE OF PTSD

B. A. Miller, E. Maguin, and A. Browne

Research Institute on Addictions, Buffalo, NY

The connection between women's violent childhood victimization and their drug and alcohol (AOD problems has been postulated to be mediated by Post-Traumatic Stress Disorder (PTSD). To test these relationships, women were recruited from drug treatment settings (n = 141), shelters for battered women (n = 118) and two matched community samples (n = 285). Results showed that child sexual abuse (CSA) was related to both women's AOD problems and a PTSD diagnosis for the drug treatment and matched community comparison. Results were replicated for the shelter and its matched community comparison. However, PTSD did not completely mediate the relationship between CSA and AOD in either comparison. Father violence predicted AOD for the drug treatment and its comparison but not for the shelter and its comparison. Again, PTSD did not completely mediate the relationship between father violence and AOD. While PTSD plays a role in the relationship of childhood victimization and the development of AOD problems, there are other pathways and contributors that must be identified.

ACKNOWLEDGMENT: Supported by a NIDA grant RO1DA06795-04 (BAM).

PTSD IN HEROIN ADDICTS IN METHADONE TREATMENT

H. W. Clark, K. L. Sees, C. L. Masson, K. L. Delucchi, and S. M. Hall

University of California, San Francisco and VA Medical Center, San Francisco, CA

This study examined the occurrence of violent traumatic events leading to a DSM-III-R lifetime diagnosis of post-traumatic stress disorder (PTSD) and the impact of trauma on the severity of drug abuse. One hundred fifty opioid-dependent drug abusers who were participants in a clinical trial of methadone treatment were interviewed using the computerized version of the Diagnostic Interview Schedule, the Addiction Severity Index, and the Beck Depression Inventory. Thirty percent had a diagnosis of lifetime PTSD. The occurrence of PTSD-related symptoms was associated with gre ter drug use severity after controlling for gender and depression. Traumatic events of rape and seeing someone hurt or killed were associated with drug use severity suggesting that the experience of these events may lead to more severe drug use problems. Exposure to violent traumatic events may increase the risk for additional traumatic exposure, which in turn may lead to greater drug use severity. Given the high rate of PTSD among opioid-dependent patients, the study of the characteristics of traumatic events and subsequent violence-related psychiatric consequences may have important treatment implications.

ACKNOWLEDGMENT: Supported by NIDA grant P50DA09253.

DISORDERS AND DIMENSIONS OF PERSONALITY:TRAITS, STATES, SCHEMAS, COPING and PROBLEM SEVERITY

S. A. Bull, W. K. O'Neill, and L. B. Randolph

Department of Psychiatry, Division of Substance Abuse, Yale Medical School, The APT Foundation, Inc., New Haven, CT

Personality research in the addictions field has evaluated rates and clinical correlates of Axis II disorders, but few studies have provided a more comprehensive characterization of substance abusing individuals diagnosed with a wide range of DSM-IV personality disorders. Preliminary data on 31 methadonc maintained patients (48% female) is presented evaluating the association between structured interview diagnoses of Cluster A, B, and C personality disorders and normal and clinical personality dimensions. Axis I symptoms, interpersonal conflict, affect states, motivation to change, AIDS risk behaviors, addiction severity, and early maladaptive schemas. Correlational analyses indicated that the severity of each personality disorder was associated with a unique profile of these measures. Mistrust/abuse was the most common schema, and subjects most frequently reported: psychiatric symptoms of hostility, somatization. phobic anxiety, paranoia; interpersonal problems related to being vindictive and domineering. and; persistent HIV risk behaviors. Antisocial, Borderline. and Avoidant were the most common Axis II disorders (average 3.3 disorders per subject). Future research will evaluate whether individual differences in psychiatric symptoms, affect. interpersonal conflict, addiction severity. and schemas have important implications for planning treatment and predicting psychotherapy outcome. We are currently evaluating a 24-week individual therapy manual, Dual Focus Schema Therapy, which integrates relapse prevention with targeted intervention for early maladaptive schemus (enduring negative beliefs about oneself, others, and events) among personality disordered patients.

ACKNOWLEDGMENT: Supported by NIDA grant R01 DA10012-01.

EFFECTS OF VARYING RESPONSE REQUIREMENT AND ABSTINENCE ON CIGARETTE SMOKING BY SCHIZOPHRENICS

J. W. Tidey and S. T. Higgins^*

Departments of *^Psychiatry and ^Psychology, University of Vermont, Burlington, VT

Substance abuse is more prevalent among schizophrenics than the general population. It is unclear why schizophrenics are more likely to be substance abusers and whether drug abuse by this population is affected similarly by factors which affect drug use in non-schizophrenics. In this study, we examined the effects of varying smoking abstinence and response requirement on smoking by schizophrenic outpatients under controlled laboratory conditions. Six subjects, who had initial carbon monoxide (CO) readings indicative of heavy smoking, were recruited from a local mental health center. Before half of the experimental sessions, subjects were required to provide CO samples indicating recent (5-6 hrs) abstinence from smokin; subjects were non-abstinent in the remaining sessions. Subjects responded under a fixed ratio (FR)-1 or progressive ratio (PR) schedule of reinforcement for the opportunity to smoke. Subjects completed more ratios under the FR-1 schedule versus the PR schedule. Under both the FR-1 and PR schedules, subjects completed more ratios when abstinent versus non-abstinent. These results indicate that smoking by schizophrenics is sensitive to both response requirement and nicotine abstinence. Furthermore, these results are qualitatively similar to those reported previously for community volunteers without mental illness, suggesting that a common set of determinants affect cigarette smoking, and perhaps other forms of substance abuse. by these two populations.

ACKNOWLEDGMENTS: Supported by NIDA grants DA08076 and DA07242.

MEMORY IMPAIRMENT AND COCAINE CRAVING IN SCHIZOPHRENIA

M. L. Copersino[1], D. A. Richarme[1], R. Nazarian[2], M. Buzzanca,[2] and M. R. Serper[1,2]

[1]Hofstra University, Hempstead, NY and [2]New York University School of Medicine, New York, NY

Recent models of cocaine addiction posit that drug urges are mediated by cognitive processes such as learning and memory. Little is known, however, about how cocaine dependence interacts with schizophrenia (SZ). One of the hallmark features of SZ is impaired memory. Consequently, cognitive impairment in individuals with SZ may significantly alter their cocaine craving and dependence profiles. In the present study, we examined the relationship between verbal memory (using the California Verbal Learning Test; CVLT) and cocaine craving (using the Cocaine Craving Questionnaire- General Version; CCQ-GEN) in 21 patients with SZ and comorbid cocaine dependence and a control group of 25 non-SZ cocaine dependent patients presenting to the psychiatric emergency department. All subjects presented within 72 hours of last cocaine use and were required to have cocaine positive urine toxicology screens for study inclusion. Results revealed that patients with comorbid SZ and cocaine dependence reported significantly less cocaine craving ($p < .05$) and performed more poorly on a test of verbal memory (p's $< .01$) than their non-SZ counterparts. Differences between diagnostic groups were demonstrated for three out of five CCQ-GEN factor scores. Collectively, these three factor scores reflect reported subjective urges and drug seeking behavior, whereas the remaining two factors reflect expectation of improved functioning or relief from dysphoria. Consistent with existing cognitive craving models (e.g., Tiffany, 1994), subjects' reported craving measures were positively correlated with verbal memory performance.

READINESS FOR CHANGE IN A DUALLY-DIAGNOSED SAMPLE OF DEPRESSED COCAINE ABUSERS

A. L. Stotts, J. M. Schmitz, S. L. Day, A. K. Schwebel, and J. Grabowski

Substance Abuse Research Center, University of Texas - Houston

The Transtheoretical Model has been used extensively in addiction research as a framework with which to understand the process of change. Research evidence supports the idea that substance abusers can be classified into distinct stages of change representing various levels of readiness for change. While single-diagnosed (SD) substance abusers have been researched fairly extensively using this model, little is known about the process of change in the dually-diagnosed (DD). The addition of a second primary psychiatric disorder may influence readiness for changing substance use in various ways. This study compared SD (cocaine-dependent) and DD (cocaine-dependent and major depression) ambulatory, treatment-seeking patients at intake on readiness for changing drug use, as well as on experiential and behavioral process use and a decisional balance measure. It was hypothesized that the DD sample (N=39) would differ significantly from the SD sample (N=85) with regard to these variables. Although not statistically significant, results indicated that DD patients may be more ready for change than SD patients. The DD group was also significantly higher on the pros for drug use subscale of the decisional balance measure. This preliminary study suggests that depressed cocaine abusers may be more motivated for change; however, their focus on the positive aspects of drug use is likely to present a barrier to treatment and subsequent change. Further research is needed to explore these preliminary results.

ACKNOWLEDGMENTS: Supported by NIDA grants DA-09262-02 and DA-08654.

EVALUATING TREATMENTS FOR DUAL DIAGNOSIS: SMART AND 12-STEP

P. Penn, L. Winningham, R. Duran, S. McDavit, B. Dewitt, G. Mosley, and J. Wilson

La Frontera Center, Inc., Tucson, AZ

This research in progress evaluates the efficacy of two group treatment models adapted for adults with dual diagnosis: 12-STEP and SMART (REBT-based). The aims of the research are to determine to what extent these two treatment approaches and the general format are effective with this population, and whether client characteristics will interact. Except for treatment approach, the two intensive day treatment programs are equivalent and meet 25 hours a week for 6 months. Assignment is random, and over 100 clients have entered the programs so far. Assessments include diagnosis, the ASI, urinalyses, locus of control, strength of spiritual beliefs, quality of life, stage of change, satisfaction with treatment, and daily client logs that capture participation level and incidents. Assessment times are screening, intake, 3 months, 6 months, and 3- and 12-month follow-up. The clients are primarily Anglo and Hispanic Americans of both genders, and process evaluation suggests that these groups are being equally engaged. Multiple indicators suggest that this client population has many persistent mental and substance disorders, and severely impaired functioning. Preliminary results suggest that some predictors for success in both programs may include two or fewer times treated for alcohol abuse, primary psychiatric diagnosis of thought or mood disorder (vs. Axis II), using a primary substance (vs. polysubstance abuse), and absence of a chronic medical condition. Thus far, both programs significantly reduce the need for drug, alcohol, and psychological treatment (ASI scores) for those who complete the program, which continues at follow-up. However, at this time, SMART has a 50% higher completion rate than 12-Step. The combined completion rate is 40%, which is 5% higher than the entire agency rate and the citywide publicly funded population, suggesting that our general client-centered format is relatively effective.

ACKNOWLEDGMENTS: Supported by NIDA grant R01 DA08537 (PP) and by La Frontera Center. Inc.

COMPARISON OF DRUG RELATED ADMISSIONS TO A PSYCHIATRIC EMERGENCY ROOM IN 1995 AND 1997

S. L. Simon[1,2], C. K. Chung[4], J. Lau[4], R. Rawson[1,2,3], and W. Ling[1,2,3]

[1]L.A. Addiction Research Center, [2]Long Beach VA Medications Development Unit, [3]Matrix Institute on Addictions and [4]Harbor-UCLA Medical Center, Los Angeles, CA

Admissions to the Harbor-UCLA Psychiatric Emergency Room (ER) were examined for the first three months of 1995 (n=1414) and 1997 (n=1443). Fifteen percent of the admissions involved stimulant related problems with slightly more admissions for methamphetamine (MA) than for cocaine. Fifty six percent of the MA admissions had urine positive for other drugs as compared to 46% of cocaine admissions. Police brought in 80% of the MA admissions and 78% of admissions associated with cocaine. Both MA and cocaine admissions were predominantly male and significantly different ($f_{2,1819}$=4.67, p<.01) from the 56% males overall. MA admissions were younger than overall admissions (t_{307}=3.11, p=.002) and cocaine admissions were significantly older (t_{250}(0=5.12, p<.001). The ethnic composition of the MA admissions was predominantly Caucasian, while 'other' was the largest group of cocaine admissions in 1995 and African Americans predominated in 1997. Although the stimulant patients become asymptomatic more rapidly than overall admissions, the relapsing nature of stimulant abuse was apparent. Patients seen 2 or 3 times within a three month period were more likely to be admitted for cocaine or MA intoxication than any other diagnosis. MA admissions were also more likely to have been seen 5 times during a three month period and to have been seen both during 1995 and 1997. Both MA and cocaine differ from the other admissions in that their symptoms have a shorter duration, but occur more frequently. In spite of the changing ethnic composition of the admissions to the ER, the percent of stimulant admissions was relatively constant.

ACKNOWLEDGMENTS: Supported by inter-agency agreement no. 1 YO1 DA 50038-00 between NIDA and the Department of Veterans Affairs.

THE EFFECTS OF AMPHETAMINE ON COGNITIVE PERFORMANCE IN RHESUS MONKEYS

M. A. Taffe, M. R. Weed, I. Polls, and L H. Gold

Department of Neuropharmacology, The Scripps Research Institute, La Jolla, CA

Rhesus monkeys (6) were trained on a bimanual motor skill task as well as cognitive tests adapted from a human neuropsychological assessment battery (CANTAB; CAmbridge Neuropsychological Test Automated Battery; CeNeS, Cambridge, UK). The battery included tests of memory (delayed non-match to sample, DNMS; selfordered spatial search, SOSS), motivation (progressive ratio, PR) and reaction time (RT). The animals were trained to asymptotic performance in all tasks and then were administered two of the four CANTAB tasks on alternate weekdays (PR/SWM; DNMS/RT). The motor skills task was administered on each weekday. The effect of acute administration of d-amphetamine (0.03-0.56 mg/ kg, i.m.) on performance was then determined. Amphetamine speeded performance of the bimanual motor skill task after moderate doses in all subjects. RT task performance was speeded after higher doses in most subjects. Amphetamine produced an inverted-U shaped doseeffect curve for performance in the PR task with moderate doses increasing the last completed ratio in 4 subjects. Higher doses produced a decrease in last completed ratio relative to baseline in 4 subjects. Performance on the memory tasks (DNMS, SOSS) was relatively unaffected by amphetamine except at the highest dose which increased errors of omission in some individuals. To summarize, performance on tasks with significant motoric and attentional demands was improved, whereas performance on tests of memory was minimally affected by moderate doses of amphetamine. The highest doses of amphetamine produced poor performance in some individuals in all tasks. The results suggest that effects of amphetamine on cognitive performance in the monkey are highly variable with respect to potency but consistent in pattern.

ACKNOWLEDGMENTS: Supported by USPHS grants MH 19185 and DA 09111.

CARDIAC TOXICITY ELICITED BY REPEATED ADMINISTRATION OF 3,4-METHYL-ENEDIOXYMETHAMPHETAMINE (MDMA)

K. J. Varner, J. B. Delcarpi, and J. M. Moerschbaecher

Departments of Pharmacology and Cell Biology and Anatomy, LSU Medical Center, New Orleans, LA

There has been a dramatic increase in clinical reports of acute cardiovascular and cardiac toxicity associated with the recreational use of MDMA. However, the question of whether chronic or repeated use of MDMA, like other amphetamine analogues, can produce pathological cardiovascular/cardiac changes remains unanswered. Therefore, the purpose of this study was to determine whether repeated administration of MDMA produces pathological changes in the heart. For comparison, the cardiac effects elicited by repeated administration of methamphetamine (METH) were also characterized. Male Sprague-Dawley rats (275-300 g) were given daily injections of MDMA (20 mg/kg, s.c.) or METH (1 mg/kg, s.c.) for 28 days. Age and weight-matched control rats received saline. After 28 days, the rats were sacrificed and the hearts perfused with 2% glutaraldehyde/paraformaldehyde. The hearts were then embedded in paraffin, sectioned, stained with H&E or Mason's Tri-chrome and examined using light microscopy. MDMA-treated hearts showed areas of focal necrosis in the papillary muscles, atria and ventricles. These foci contained myocytes exhibiting contraction band necrosis, dilated sarcoplasmic reticulum and an increase in endomysial connective tissue. Also evident were areas of lymphocytic infiltrate indicative of active inflammation. The hearts from METH-treated rats showed a similar pattern of pathological changes. These results show that repeated administration of MDMA can produce serious and potentially life-threatening pathological changes in the myocardium.

ACKNOWLEDGMENTS: Supported by NIDA grants DA 08255 and DA 04775.

INDUCTION OF p53 mRNA BY METHAMPHETAMINE IS SUPRESSED BY (D-ALA^2-D-LEU^5)ENKEPHALIN IN VIVO

T. Hayashi, H. Hirata, M. Asanuma, L. I. Tsao, T. P. Su, and J. L. Cadet

Molecular Neuropsychiatry Section, Intramural Research Program, National Institute on Drug Abuse, NIH, Baltiomre, MD

We have recently shown that delta opioid agonist D-Ala^2-D-Leu^5 enkephalin (DADLE) inhibited the methamphetamine (METH)-induced decrease in dopamine transpoter (Tsao *et al.,* 1997). As p53 tumor-supressor gene is implicated in the neurotoxicity of METH (Hirata and Cadet, 1997), we examined the effects of DADLE on p53 mRNA levels altered by METH. Male CD-1 mice (25-30 g) received a single administration of METH (25 mg/kg; i.p.). DADLE (5, 20, or 40 mg/kg, i.p.) was injected 30 min before METH. p53 mRNA levels were determined by northern blot using a [^{32}P]dCTP-labeled mouse p53 cDNA probe. METH increased p53 mRNA significantly (N=4) in a time dependent manner. In the hippocumpus, the maximum increase of p53 mRNA was seen 24 hrs after the METH administration, whereas in the striatum, it occured at 72 hrs. DADLE (5-20 mg/kg) did not change the p53 mRNA level by itself, but dose-dependently abolished the increases of p53 mRNA caused by METH (N=10). A higher dose of DADLE (40 mg/kg), however, appeared to enhance the increase (N=5). Our results indicate that METH-induced increases of p53 mRNA in mouse brain can be attenuated by DADLE and suggest that DADLE may affect the expression of genes that are involved in the cell death process.

ACKNOWLEDGMENTS: Supported by Intramural Research Program, NIDA and Basic Neurobiological Systems Research Branch, DBR, NIDA.

FREE RADICAL SCAVENGING ACTIVITY OF THE DELTA OPIOID PEPTIDE [D-ALA^2, D-LEU^5]-ENKEPHALIN (DADLE)

L. I. Tsao[1], *C. C. Chiuek*[2], *J. L. Cadet', and T. P. Su*[1]

[1]**Intramural Research Programs, National Institute on Drug Abuse, NIH, Baltimore, MD and** [2]**National Institute of Mental Health, NIH, Bethesda, MD**

Delta opioid peptide DADLE has been demonstrated to prolong organ preservation and to attenuate the methamphetamine-induced neurotoxic damage to dopaminergic neurons in mice. Because the survival of organs depends largely on the oxidative state of tissue and because the neurotoxic effects of methamphetamine are known to involve reactive oxygen species, this study examined if DADLE might be an antioxidative agent *in vitro.* Superoxide anions were generated with the hypoxanthine and xanthine oxidase system and were measured spectrophotometrically by the anions reducing the ferribathophenanthroline disulfonic acid. Hydrogen peroxides were measured by the titanium and 4-(2-pyridylazo)resorcinol method. A salicylate hydroxylation trapping method was used to monitor the generation of hydroxyl radicals produced by ferrous citrate. Hydroxyl adducts of salicylate were assayed using a HPLC-EC procedure. Results showed that DADLE at micromolar concentrations dose-dependently inhibited the formation of both superoxide anions and hydroxyl radicals. DADLE was almost equipotent (IC50's = 100μM and 250μM respectively) to glutathione in sequestering those two free radicals. DADLE did not affect the reactivity of hydrogen peroxide. Thus, DADLE and, by extension, enkephalins might potentially protect the brain from oxidative damage by directly scavenging the toxic free radicals.

ACKNOWLEDGMENTS: Supported by Intramural Research Program, NIDA and Basic Neurobiological Systems Research Branch, DBR, NIDA.

EVIDENCE THAT MDMA AND METHAMPHETAMINE ARE NOT NEUROTOXIC TO SEROTONERGIC NERVES IN GUINEA PIG

C. M. Dersch*, J. L. Cadet*, H. Hirata*, M. H. Batmann*, A. M. Brockington*, F. I. Carroll†, K. C. Rice#, and R. B. Rothtnan*

***NIDA and #NIDDK, NIH, Baltimore and Bethesda, MD and †RTI, Research Triangle Park, NC**

The cocaine analog [^{125}I]RTI-55 labels three binding sites in guinea pig caudate: the 5-HT transporter (SERT), the DA transporter (DAT) and a third site (termed SERTsite2) measured when [^{125}I]RTI-55 binding to SERT and DAT are suppressed by 50 nM paroxetine and 100 nM GBR12935. The major purpose'of this study was to determine the neuronal localization of SERTsite2 in relation to the SERT and DAT. Male Hartley guinea pigs were pretreated with either saline (SAL) or fluoxetine (FLX) (10 mg/kg) 30 min before receiving SAL, MDMA (20 mg/kg), METH (10 mg/kg) or METH (20 mg/kg). This regimen was repeated four times every two hours. All injections were given i.p. The guinea pigs were sacrificed 7-days later and caudate membranes were prepared. The Kd and Bmax of [^{125}I]RTI-55 at all three sites was determined. SAL/MDMA and SAL/METH(10) had no significant effect on the Bmax of SERT, but increased the Kd value from 0.038 nM to 0.081 nM and 0.12 nM, respectively. This Kd change would decrease 0.01 nM [^{125}I]RTI-55 binding by about 64%. SAL/MDMA increased the Bmax of both DAT and SERTsite2 by about 70% with only minor increases in their Kd values. In contrast, SAL/METH(10) decreased the Bmax values of DAT and SERTsite2 by about 50% with only minor increases in their Kd values. Interestingly, FLX/METH10 increased the Bmax of the DAT and SERTsite2 by 2.1-fold and 1.4-fold, respectively, while decreasing the Bmax of SERT by 0.46-fold. Tissue levels of DA and 5-HT will be measured and presented at the meeting. Viewed collectively, these data indicate that SERTsite2 is regulated differently than DAT and SERT and is partially localized on DAergic nerve terminals. These data suggest that MDMA-induced decreases in SERT binding in the guinea pig caudate result from not a loss of SERT binding sites, but from adaptive changes in its Kd value for [^{125}I]RTI-55.

ECSTASY IN HUMANS: NEUROENDOCRINE EFFECTS AND PHARMACOKINETICS

J. Cami*, R. de la Torre, J. Ortuño, N. Pizarro, M. Farré, M. Mas, P. N. Roset, and J. Segura

Department of Pharmacology, Institut Municipal d'Investigació Mèdica. Universitat Autònoma, *Universitat Pompeu Fabra, Barcelona, Spain

The comsumption of 3,4-methylenedioxymethamphetamine (MDMA, ecstasy) and other designer drugs is increasing among young people. A double blind, randomized, placebo-controlled, cross-over design clinical trial was carried out to study the neuroendocrine effects of MDMA and its pharmacokinetics. Eight male volunteers received a single oral dose of MDMA (75 and 125 mg), d,l-amphetamine (40 mg) and placebo. All subjects were extensive metabolizers of dextromethorphan (CYP4502D6). Blood samples were obtained at predose, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, and 24 hours after drug administration. Cortisol, prolactin and growth hormone (GH) were determined by immunoassay techniques. Plasma was analyzed for MDMA and methylenedioxyamphetamine (MDA) using gas chromatography with nitrogen-phosphorous detection (GC/NPD). Cortisol and prolactin increased after the administration of MDMA, but GH after amphetamine administration. Pharmacokinetic parameters for plasma concentrations of MDMA 75 mg and 125 mg doses were as follows: Cmax (131 vs 236 ng/ml), tmax (1.8 vs 2.4 h), AUC0-24h (1332 vs 2623 ng/ml*h), and elimination half-life (7.7 vs 8.6 h), respectively. Concentrations'of MDA in plasma were about 5% of those of MDMA. Thus in humans, MDA seems to be a minor metabolite of MDMA.

ACKNOWLEDGMENTS: Supported by grants FIS 97/1198, CIRIT 95-SGR-00432, ISC-III 97/4344, and PNSD.

EFFECTS OF 17-ß-ESTRADIOL ON RESPONSE TO D-AMPHETAMINE IN WOMEN

A. Justice and H. de Wit

The University of Chicago, Department of Psychiatry, Chicago, IL

Recent evidence indicates that estrogen may play a role in mediating mood and behavior and may alter responses to drugs by modulating the activity of neurotransmitter systems. For example, studies with laboratory animals indicate that estrogen increases the activity of the dopamine system, which is thought to contribute the reinforcing efficacy of many drugs of abuse. Estrogen has also been shown to increase both neurochemical and behavioral responses to stimulant drugs, such as amphetamine, in rats. In the present study, two groups of healthy, regularly-cycling women participated in two sessions scheduled during the menses phases of two menstrual cycles. One group received estrogen patches (Estraderm TTS, 0.8 mg) which elevated plasma estradiol levels to approximately 750 pg/ml on both sessions; the other group received placebo patches on both sessions. Both groups received d-amphetamine (10.0 mg) and placebo, in a randomized and counterbalanced order, on the two sessions. Subjective and physiological effects were assessed throughout the sessions. Two hypotheses were tested: 1) that estrogen would increase self-reported ratings of stimulation and euphoria, and 2) that estrogen would increase response to amphetamine through interactions with the dopamine system. Results of preliminary analyses (N=10,7 in the two groups) failed to support the hypotheses. Estrogen did not increase subjective ratings of stimulation or euphoria. Furthermore, while amphetamine produced its prototypic effects, such as increased stimulation and friendliness, estrogen did not increase these effects.

ACKNOWLEDGMENT: Supported by DA-02812.

SUBJECTIVE AND BEHAVIORAL EFFECTS OF REPEATED D-AMPHETAMINE IN HEALTHY VOLUNTEERS.

S. R. Wachtel and H. de Wit

The University of Chicago, Department of Psychiatry, Chicago, IL

Behavioral sensitization is thought to be an important determinant of drug-taking and drug-seeking behaviors. Although there is abundant research characterizing behavioral sensitization in laboratory animals, there is little evidence for this phenomenon in humans. The aim of the present study was to determine if repeated oral d-amphetamine administration enhances self-reported mood and other behavioral indices of d-amphetamine effects in humans. Sixteen healthy volunteers, with no prior stimulant use, received two doses of d-amphetamine (20 mg, P.O.) and two doses of placebo in alternating order, on four consecutive days, under double-blind conditions. Subjective mood and drug effects were measured using standard self-report questionnaires. Heart rate, blood pressure, psychomotor performance, and tapping speed were also monitored. d-Amphetamine elicited prototypical increases on several measures including self-reported drug and mood effects, psychomotor performance, and physiological responses. However, except for a slight reduction in "feel" drug scores during the first two hours of the second d-amphetamine session, the majority of effects were not altered during the second d-amphetamine session. These results indicate that the subjective effects of d-amphetamine display only mild tolerance after a single exposure 48 hours earlier.

ACKNOWLEDGMENT: Supported by NIDA grant DA02812.

BEHAVIORAL EFFECTS OF THE D_1 AGONIST A 77636 IN SQUIRREL MONKEYS

J. Bergman E. Jutkiewicz, and N. H. Mutschler

Harvard Medical School/McLean Hospital ADARC, Belmont, MA

Dopamine D_1 receptor ligands with high agonist efficacy have behavioral effects that may overlap those of psychomotor stimulant drugs and have been proposed as candidate anti-cocaine medications. In the present experiments, behavioral effects of A 77636, an isochroman which has been reported to selectively activate dopamine D_1 receptors with high agonist efficacy, were compared with those of D, high-efficacy agonists from a different chemical class (e.g. the benzazepines). The effects of D_1 agonists on observable behavior were catalogued by determining changes in eyeblink frequency. In separate studies, the ratealtering effects of drugs-were determined in squirrel monkeys responding under a 30-response fixed-ratio (FR) schedule of stimulus-shock termination and their discriminativestimulus effects were evaluated in monkeys that distinguished between i.m. injections of 0.3 mg/kg methamphetamine and saline. Results indicate that A 77636 (0-3-3.0 mg/kg) produced dose-related increases in eyeblink frequency that were comparable in magnitude to those produced by other D_1 high-efficacy agonists. This effect was consistent among subjects and, at higher doses, long-lasting (24-48 hrs). As previously reported for the effects of D_1 high efficacy agonists (e.g., SKF 82958, SKF 81297 or dihydrexidine) in drug discrimination studies, A 77636 engendered responding on the methamphetamine-associated lever, albeit at doses that decreased response rate under the FR schedule. These data indicate that the behavioral effects of A 77636 overlap those of D_1 agonists from other chemical classes and are consistent with its characterization as a D_1 high efficacy agonist in monkeys.

ACKNOWLEDGMENTS: Supported by USPHS DA 03774, DA 10566, and MH 07658.

EFFECTS OF DOPAMINE AND OPIOID ANTAGONISTS ON EXPRESSION OF COCAINE-CONDITIONED LOCOMOTOR STIMULATION IN RATS

J. U. Adams, T. R. Efferen, and J. Rotrosen

New York NIDA/VA MDRU, Depts. of Psychiatry, NYU and VA Medical Centers, New York, NY

The locomotor stimulant effects of cocaine can be conditioned in rats by repeatedly pairing cocaine administration with a distinct environment. In the present study, the dopamine antagonists haloperidol (D2) and SCH-23390 (D1) and the opioid antagonist naloxone were tested for the capacity to disrupt the expression of cocaine's conditioned effects. Six conditioning sessions were conducted over a 10-day period. Either 10 mg/kg cocaine (paired group) or saline (unpaired group) was administered to male Sprague-Dawley rats immediately prior to a 1-hr session in activity boxes that differed in size, bedding and location from rats' home cages. A second injection, saline (paired) or cocaine (unpaired), was administered upon return to the rat colony room. Thus, all animals had the same history of cocaine exposure; only the environment in which it was experienced differed between groups. On test days, all animals received saline injections immediately prior to 30-min activity sessions. Rats who had previously received cocaine in the context of the activity chamber (paired) exhibited 110% greater activity than did control rats (unpaired). Twenty-min pretreatment (PT) with SCH-23390 (0.03-0.1 mg/kg ip) significantly inhibited this conditioned locomotor activity; neither naloxone (1-10 mg/kg sc, 20-min PT) nor haloperidol (0.1 mg/kg ip, 20-min PT) had any effect. In separate groups of rats, the antagonists were tested for their capacity to inhibit the direct effects of cocaine. Cocaine (5-10 mg/kg ip) stimulated locomotor activity in a dose-related manner. Haloperidol and SCH-23390 completely blocked, whereas naloxone partially attenuated, this effect. These results suggest that conditioned effects of cocaine are mediated, at least in part, by neuronal mechanisms distinct from those which mediate the direct effects of cocaine. As conditioned effects of cocaine likely play a role in its abuse, understanding the neurobiological bases of conditioning should permit development of novel treatment strategies.

ACKNOWLEDGMENT: Supported in part by NIDA grant DA 11700-01.

ACUTE BINGE COCAINE ELEVATES MU OPIOID RECEPTOR mRNA IN AREAS OF THE RAT MESOLIMBIC DOPAMINERGIC SYSTEM

V. Yuferov, Y. Zhou, C. E. Maggos, A. Ho, R. Spangler, and M. J. Kreek

Laboratory of Biology of Addictive Diseases, The Rockefeller University, New York, NY

Previous studies in our laboratory have shown that chronic 'binge' cocaine administration increased mu opioid receptor (MOR) density in dopaminergically innervated brain regions as measured by [3H]DAMGO binding (Unterwald *et al.,* 1992, 1994). Steady-state cocaine administration led to a transient increase in MOR mRNA levels in the nucleus accumbens, but not in the caudate-putamen. following 3 days of continuous cocaine administration. but not after 1, 2, 4, or 7 days (Azaryan, et al., 1996). The present study investigated effects of acute 'binge' pattern cocaine treatment on MOR mRNA levels in seven brain regions of male Fischer rats. Animals were injected with saline for 6 days prior to the test day. On day 7. rats received single 'binge' administration of cocaine (3 injections of 15 mg/kg. i.p., hourly, n=6) or saline (3 injections of 1 ml/kg, i.p., n=6). Rats were sacrificed 30 min after the final injection and the amount of MOR mRNA was detemined for selected brain regions by a quantitative solution hybridization RNasc protection assay. The significance of differences in MOR mRNA levels between groups was determined by t-test. MOR mRNA levels were significantly ($P<0.05$) increased in the frontal cortex, nucleus accumbens and amygdala, but not in the caudate-putamen, hippocampus, thalamus or hypothalamus. In conclusion. the acute intermittent ('binge') cocaine administration increased MOR mRNA with a regional pattern that is partly consistent with increases in MOR density previously determined by ligand binding experiments after chronic 'binge' cocaine.

ACKNOWLEDGMENTS: Supported by NIDA P50-DA 05130 and DA K05-00049.

NICOTINE+COCAINE AND HEROIN+COCAINE EFFECTS ON NUCLEUS ACCUMBENS DOPAMINE OVERFLOW

G. Zernig, I. A. O'Laughlin**, and H. C. Fibiger***

***Division of Neurochemistry, Department of Psychiatry, University of Innsbruck, Austria and **Division of Neurological Sciences, Department of Psychiatry, University of British Columbia, Vancouver, Canada**

Cigarette smoking increases the intake of cocaine and other drugs of abuse. In order to test if these epidemiological data re reflected in a neurochemical correlated of the reinforcing effects of drugs of abuse, i.e., dopamine overflow in the nucleus accumbens, *in vivo* brain microdialysis was used to examine the effects of nicotine and cocaine either alone or in combination in freely moving rats. Furthermore, the effects of the nicotinc+cocaine combination were compared to another drug combination of high abuse potential, i.e., heroin+cocaine ("speedball"). Both nicotine+cocaine as well as heroin+cocaine stimulated nucleus accumbens dopamine overflow in an additive manner. Repeated intermittent administration of nicotine did not significantly alter the effects of subsequent challenge with the nicotine+cocaine combination. Thus, no significant tolerance seems to develop to nicotine's effect. These neurochemical findings support behavioral data and clinical-epidemiological findings suggesting that the reinforcing effects of cocaine and heroine are additive and predict that nicotine will enhance the reinforcing efffects of cocaine.

MODULATION OF THE DISCRIMINATIVE STIMULUS EFFECTS OF COCAINE BY SNC 80 AND FENTANYL

J. K. Rowlett and R. D. Spealman

Harvard Medical School, New England Regional Primate Research Center, Southborough, MA

Previous research in squirrel monkeys has shown enhancement of the discriminative stimulus (DS) effects of cocaine by -opioid agonists, but not by the agonist BW373U86. The present study assessed the effects cocaine alone and combined with SNC 80, a selective agonist, and fentanyl, a selective agonist. Squirrel monkeys were trained to discriminate 0.3 mg/kg (i.m.) cocaine from saline under a fixed-ratio 10 schedule of food presentation. Cocaine (0.03-1.0 mg/kg) engendered dose-related increases in drug-lever responding to a maximum of 99%, with a decrease in response rate observed at 1.0 mg/kg. In contrast, SNC 80 (0.03-1.0 mg/kg) or fentanyl (0.001-0.01 mg/kg) resulted in a maximum of only 22% and 48% drug-lever responding, respectively, accompanied by pronounced decreases in response rate. SNC 80 (0.1-1.0 mg/kg) or fentanyl (0.001-0.01 mg/kg) given prior to cocaine enhanced the DS effects of cocaine, resulting in leftward shifts in the dose-response function. When the selective antagonist naltrindole (1.0 mg/kg) was combined with SNC 80 (1.0 mg/kg) or fentanyl (0.01 mg/kg) prior to cocaine, the leftward shift of the cocaine dose-response function produced by SNC 80 was blocked, whereas the leftward shift produced by fentanyl was not. By contrast, the antagonist naltrexone (0.3 mg/kg) blocked the cocaine-enhancing effects of fentanyl, but not of SNC 80. These results suggest that opioid enhancement of the DS effects of cocaine may be mediated by both - and -receptor mechanisms.

ACKNOWLEDGMENTS: Supported by NIDA grants DA00499, DA11054 and RR00168.

DIFFERENTIAL EFFECTS OF IBOGAINE AND COCAINE ON NEUROTENSIN AND DYNORPHIN SYSTEMS

M. E. Alburges and G. R. Hanson

Department of Pharmacology and Toxicology, University of Utah, Salt Lake City, UT

Ibogaine is currently being studied for its potential utility in the treatment of cocaine and methamphetamine abuse. Nevertheless, a molecular mechanism of action that explains its anti-addictive properties is still undefined. In previous studies, we characterized the differential effects of psychotomimetic drugs (cocaine and methamphetamine) on neuropeptide systems. These stimulants of abuse induce unique patterns of dopamine release which in turn alter the activity of the neurotensin and dynorphin systems. We have reported time-dependent and dose-dependent increases in neurotensin-like immunoreactivity (NTLI) in striatum, nucleus accumbens and substantia nigra as a result of repeated administrations of ibogaine which resemble the effects caused by similar cocaine treatment. In the present study, we examined and compared the effect of multiple doses of ibogaine or cocaine (40 mg/kg, i.p., daily, for 4 consecutive days) on the striatal, nigral, accumbens and cortical dynorphin (DYN) pathways. While both ibogaine and cocaine treatment similarly affected NT systems by increasing NTLI content in these brain areas as previously reported, the effect of these two drugs on DYN concentrations were dissimilar. Thus, dynorphin-like immunoreactivity was significantly increased in striatum, nucleus accumbens and substantia nigra after cocaine, but not after ibogaine, administration. The responses from these two extrapyramidal and limbic neuropeptide systems suggest that the pharmacological actions of ibogaine and cocaine have both similarities as well as major differences.

ACKNOWLEDGMENT: Supported by a minority supplement to NIDA grant DA09407.

CAPSAICIN INCREASES THE LETHALITY OF COCAINE

*J. Mendelson, *B. Tolliver, K. Delucchi, and *P. Berger*

Drug Dependence Research Center, Langley Porter Institute, University of California, San Francisco and the *Veterans Affairs Medical Center, San Francisco, CA

Oleoresin capsaicin (OC), a vanillylamide responsible for the pungent taste of chili peppers, is the primary ingredient in pepper spray. Since 1992, California police have been using OC sprays as a non-lethal method to subdue delirious or violent individuals. From 1/93 to 6/95, 26 deaths were associated with OC. Twenty-four of the 26 deaths occurred in stimulant intoxicated individuals; 13/24 involved methamphetamine and 8/24 cocaine. Because both cocaine and capsaicin are pharmacologically active, are metabolizcd by CYP 3A4, and modulate neurotransmission (capsaicin via substance P). we hypothesized a direct potentiation of cocaine toxicity. The effects of capsaicin (8-methyl-N-vanillyl-6-nonenamide, 0, 1 and 10 mg/kg) on cocaine (0, 50, 60, 75 and 100 mg/kg) induced lethality were assessed in 12 groups of ~30 male Swiss-Webster mice. Drugs were administered in 5% v/v ethanol/ saline in a volume of 10 µl/g of body weight. Capsaicin 0 and 1 mg/kg did not affect lethality. Capsaicin 10 mg/kg increased the lethality of the 60 mg/kg cocaine condition from 13 to 53% ($p<0.01$) and of the 75 mg/kg cocaine condition from 53 to 90% ($p<0.001$). Cocaine 100 mg/kg alone was lethal in 97% of the animals. We conclude that exposure to pepper spray in cocaine intoxicated individuals may potentiate cocaine lethality. Further study is needed to define the mechanism (metabolic, autonomic or CNS) of this pharmacologic interaction.

ACKNOWLEDGMENT: Supported in part by USPHS Grant DA01696

INTERACTION OF COCAINE AND ALCOHOL; AN ASSESSMENT OF THE COMBINATIONS OF COCAINE AND COCAINE, ALCOHOL AND ALCOHOL AND COCAETHYLENE AND COCAETHYLENE

B.-F. X. Sobel, N. Sundararaman, and A. L. Riley

Psychopharmacology Laboratory, American University, Washington, DC

The combination of cocaine and alcohol yields greater response-suppressing effects on schedule-controlled responding than either cocaine or alcohol alone (Sobel & Riley, NIDA Monograph 153:94; 1995). Although it is possible that this apparent synergism is a result of the summation of the effects of cocaine, alcohol and cocaethylene, the unique cocaine metabolite produced in the presence of alcohol, a more parsimonious basis may be dose additivity. According to dose additivity, the enhanced effects of the combination reflect a summation of the doses of two drugs. As such, the combination of two drugs is equivalent to administering the same drug twice. If so, it might be expected that same drug combinations would produce similar effects as the combination of cocaine and alcohol. The present study addressed this possibility by assessing the interaction of cocaine and cocaine, of alcohol and alcohol and of cocaethylene and cocaethylene. Seventeen female Long-Evans rats were trained to respond on an FR20 schedule for a water reinforcer. Subjects were first administered cumulative doses of cocaine, alcohol or cocaethylene. They were then administered an ineffective dose of cocaine, alcohol or cocaethylene prior to further dose-response assessments with itself. The cocaine/cocaine, alcohol/alcohol and cocaethylene/cocaethylene combinations yielded similar shifts in dose-response functions as the combinations of cocaine and alcohol, suggesting that all these combinations share a similar process, i.e., dose additivity. This position was supported by isobolographic analyses which revealed that the enhanced suppression of cocaethylene by cocaethylene and of alcohol by alcohol was additive in nature. The increased suppressing effect of the combination of cocaine and cocaine was less than additive, possibly due to within-session partial metabolism.

ACKNOWLEDGMENT: Supported by a grant from the Mellon Foundation (ALR).

ACUTE AND CHRONIC NEUROCHEMICAL AND BEHAVIORAL STUDIES COMPARING COCAETHYLENE AND COCAINE

E. F. McCance-Katz, T. T. Lee, P. Jatlow, and C. W. Bradberry

Departments of Psychiatry and Laboratory Medicine, Yale University School of Medicine

Cocaethylene, the psychoactive metabolite resulting from concurrent alcohol and cocaine use, was compared to cocaine because of its use in clinical studies of drug reward mechanisms, and its potential as a model compound for cocaine substitution therapy. In awake rats with microdialysis probes in place, a three hour bolus/i.v. infusion of both cocaine and cocaethylene resulted in an initial behavioral activation followed by a striking difference. The cocaethylene group displayed a return to predrug levels of activity, while the cocaine group showed a progressive increase in activity throughout the three hour period. Both cocaethylene and cocaine result in an initial increase in the extracellular concentration of dopamine. However, following that initial increase, levels of dopamine dropped in the cocaethylene group while the cocaine group levels remained elevated. Chronic i.v. treatment with cocaine, cocaethylene, and a water control was done for 7 days using minipumps. Animals were then challenged with an i.v. bolus of 1 mg/kg cocaine. A one week infusion of cocaine resulted in tolerance to the behavioral activating effects of a cocaine challenge, as did treatment with cocaethylene. These results demonstrate a rapid induction of tolerance to the behavioral and neurochemical properties of cocaethylene, resulting in a diminished behavioral response to a cocaine challenge both acutely, and after 7 days. These results demonstrate we are able to induce tolerance to the activating properties of cocaine with a compound lacking the full behavioral and neurochemical toxicological profile of cocaine.

ACKNOWLEDGMENTS: Supported by DA 08073 and DA 04060.

EFFECTS OF INTRAVENOUS COCAETHYLENE IN HUMANS

C. L. Hart, P. I. Jatlow, T. R. Kosten, and E. F. McCance-Katz

Departments of Psychiatry and Laboratory Medicine, Yale University, New Haven, CT

Cocaethylene is a pharmacologically active homolog of cocaine, formed by transesterification of cocaine in the presence of alcohol. Previously we reported that intranasal cocaethylene had behavioral and cardiovascular effects similar to cocaine, but cocaethylene had a longer elimination half-life and appeared to be less potent than cocaine. Here we relate findings from a randomized placebo-controlled, double-blind study, in which we examined the pharmacokinetics and behavioral and physiological effects of intravenous cocaethylene in humans. Cocaine-dependent participants randomly received one study drug, either cocaethylene (0.25 or 0.5 mg/kg), cocaine (0.25 or 0.5 mg/kg), or placebo, during each experimental session. Experimental sessions occurred on separate days. While drug plasma concentrations did not differ, cocaethylene was less potent in producing tachycardia than an equivalent dose of cocaine. Similar results were found for behavioral measures (cocaine high and rush). All active drug conditions produced significant increases in systolic blood pressure, but no significant effect on diastolic blood pressure was observed. Additionally, cocaethylene had a longer elimination half-life than cocaine. The slower clearance of cocaethylene may contribute to direct toxic effects of cocaine and alcohol during binge use of these substances. These findings confirm results from our previous study showing that cocaethylene is less potent than cocaine. Furthermore, the properties of cocaethylene make it a candidate compound to test as a potential cocaine agonist pharmacotherapy.

ACKNOWLEDGMENTS: Supported by K20-DA00216 (EFMK), R-29-DA09573 (EFMK), P50-DA04060 and NIH-M01-RRR00125.

PLASMA COCAINE AND METABOLITE LEVELS IN SUBJECTS WITH AND WITHOUT A FAMILY HISTORY OF ALCOHOLISM

J. F. McNeil, E. M. Kouri, L. H. Lundahl, and S. E. Lukas

Behavioral Psychopharmacology Laboratory, McLean Hospital/ Harvard Medical School, Belmont, MA

Although many studies have been conducted to document the association between a positive family history of alcoholism (FHP) and subsequent development of alcoholism, few studies have focused on whether FHP subjects respond differently to other drugs. We have previously shown that FHP subjects experience slightly higher subjective effects after acute cocaine administration than subjects without such a history (FHN). The present study was conducted to determine if these effects could be explained by different pharmacokinetic profiles between the FHP and FHN subjects. Healthy male occasional cocaine users (average 1-2 times/month) with (n=11) and without (n=13) a family history of alcoholism provided informed consent and volunteered to participate in this study. Subjects served as their own control and were tested on two separate days during which they received either 0.9 mg/kg cocaine or placebo via the intranasal route. Blood samples were collected in tubes with sodium fluoride as a preservative at 5 min intervals over the 4 hr study. Plasma samples were frozen for subsequent analysis using a GC/MS procedure to simultaneously determine cocaine, benzoylecgonine (BE) and ecgonine methyl ester (EME) levels in each sample. Peak plasma cocaine (45-105 min) levels were significantly higher in the FHP subjects; there were no differences in BE or EME levels. These results suggest that cocaine pharmacokinetics differ in FHP and FHN subjects and may contribute to the subtle differences in subjective responses after cocaine.

ACKNOWLEDGMENTS: Supported by grants DA03994 and DA00343

ACUTE PHYSIOLOGICAL AND BEHAVIORAL EFFECTS OF ASCENDING DOSES OF ORAL COCAINE IN HUMANS

C. A. Hayes, C. R. Rush, R. W. Baker, and K. Wright

Department of Psychiatry, University of Mississippi Medical Center, Jackson, MS

The present study was designed to assess the acute physiological and behavioral effects of a wide range of doses of oral cocaine HCL (placebo, 50, 100, 200 and 300 mg). Nine volunteers (8 males and 1 female) with recent histories of cocaine use resided on a general inpatient psychiatry unit while they participated. Drug doses were administered in a double-blind fashion under medical supervision, but for safety purposes, they were administered in ascending order. The physiological, subject-rated and perfomance effects of oral cocaine HCL were assessed before drug administration and periodically afterwards for 5 hours. Oral cocaine HCL increased heart rate and blood pressure as a graded function of dose, but the magnitude of these effects were not clinically significant. Oral cocaine HCL produced positive subject-rated drug effects (e.g., increased ratings of Good Effects, Like Drug and Willing to Take Again), but did not affect performance. Consistent with the pharmacokinetics of oral cocaine HCL, drug effects were generally discernible from placebo 0.5-1 hour after administration, peaked approximately 1 hour after administration, and progressively abated during the remainder of the experimental session. The results of this experiment demonstrate that across a six-fold range of doses oral cocaine HCL is well tolerated by individuals with recent histories of cocaine use and can be safely administered under controlled laboratory and medical conditions.

ACKNOWLEDGMENT: Supported by NIDA grant DA 10325.

THE DETERMINANTS OF CARDIOVASCULAR RESPONSE TO SMOKED-COCAINE IN HUMANS

D. K. Hatsukami, M. Sofuoglu[1], S. Dudish-Poulsen, D. Nelson, and P. R. Pentel[2]

Departments of Psychiatry, Pharmacology[1] and Medicine[2], University of Minnesota, Minneapolis, MN

The purpose of this analyses is to examine the individual factors in determining the acute cardiovascular response to cocaine in humans in laboratory setting. Data from twenty-four female and 38 male crack cocaine users who were enrolled in different protocols were analyzed. All subjects were housed in the General Clinical Research Center and experienced similar admission and adaptation days. Subjects received a single 0.4 mg/kg dose of smoked cocaine during their first laboratory session. Physiological measures were obtained at baseline and -2, 2.5, 4.5, 9.5, 14.5, 19.5 and 24.5 minutes in relation to cocaine administration. Multiple regression models were used to identify useful subject variables to predict changes in heart rate and blood pressure in response to cocaine. Several variables including race, gender, weight, height, baseline physiological variables, amount of cocaine use, use of nicotine, alcohol and marijuana were found to be significantly associated with cardiovascular response to cocaine. The importance of these factors in determining the cardiovascular response to cocaine and their role as risk factors for the cardiovascular complications of cocaine needs to be studied further.

ACKNOWLEDGMENTS: Supported by NIH grants P-50 DA09259 and MO1-RR00400.

SIMILAR INCREASE IN VONWILLEBRAND FACTOR AFTER INTRAVENOUS COCAINE IN MEN AND WOMEN

A. J. Siegel*, M. B. Sholar, J. H. Mendelson, G. H. Tofler, J. J. Stec, I. Lipinska, and P. M. Ridker

***Department of Medicine and Alcohol and Drug Abuse Research Center, McLean Hospital—Harvard Medical School, Belmont, MA**

The pathogenesis of cocaine-associated heart attack and stroke is uncertain. Since thrombosis may play a role, we examined the effect of a moderate dose of intravenous (i.v.) cocaine on thrombotic and fibrinolytic potential in 18 adult subjects who fulfilled DSM-IV criteria for cocaine abuse and provided informed consent. Cocaine 0.4 mg/kg i.v. was infused over 1 min. to six male and six female subjects matched for age and body mass index, while six others received placebo. Cardiovascular status was continuously monitored in a semi-supine position. Blood samples were collected in tubes containing sodium citrate from the opposite arm at baseline, 30, 60, 120, 180, and 240 minutes after cocaine or placebo injection. Plasma was analyzed for vonWillebrand Factor (vWF), fibrinogen, fibrinolytic activity, plasminogen activator inhibitor and tissue plasminogen antigens. There was a significant increase ($p<.02$) in vWF in the post-cocaine group versus placebo, but no significant difference with respect to gender. There were no significant changes in the other hemostatic factors. The similar increase in vWF following acute i.v. cocaine may enhance platelet deposition and account for an increase in risk of thrombotic events in men and women.

ACKNOWLEDGMENTS: Supported in part by NIDA grants P50-DA04059, K05-DA00064, K05-DA00101 and T32-DA-7252.

HIGHER INCIDENCE OF RESPIRATORY EVENTS DURING SLEEP IN CRACK COCAINE SMOKERS

*S. E. Lukas and C. M. Dorsey**

Behavioral Psychopharmacology Research Laboratory, Sleep Research Program*, McLean Hospital/Harvard Medical School, Belmont, MA

Sleep apnea (cessation of breathing during sleep) is of great concern among sleep clinicians because the amount of oxygen that is available to the heart is reduced and arrhythmias may result. Because of cocaine's local anesthetic effects, we conducted a study to determine if crack cocaine smokers have a higher incidence of hypopnea and apnea events than the general population. After providing informed consent, healthy male and female crack smokers (age 30.3 ± 2.3) agreed to participate in this study. Subjects met criteria for cocaine dependence and currently used crack cocaine (average $300/week). Subjects agreed not to use cocaine or other drugs for 3 days prior to the study. They arrived at the lab at 8:30 p.m. and were prepared for standard sleep recordings and respiratory monitoring; subjects slept in the laboratory for two consecutive nights. Polysomnographic records were scored under blind conditions. Total sleep time and the percentage of time spent in the various sleep stages did not differ from an age-matched control database. Compared to controls who had an apnea/hypopnea index (AHI) of <0.2/hr, crack smokers had an AHI of 5.28 ± 2.52 /hr. Further, one third of the crack smokers had an AHI of >10/hour, which is clinically significant. These results suggest that individuals who smoke crack cocaine may be at risk for breathing-related disorders during sleep. When combined with cocaine's acute cardiovascular effects, this interaction may account for the high incidence of adverse reactions to cocaine, particularly when the doses are not excessive.

ACKNOWLEDGMENTS: Supported by grants DA03994 and DA00343.

SAFETY OF BUPRENORPHINE: CEILING FOR CARDIO-RESPIRATORY EFFECTS AT HIGH IV DOSES

A. Umbricht, M. A. Huestis, E. J Cone, and K. L. Preston

NIDA Intramural Research Program, Baltimore, MD

Buprenorphine is a partial μ opioid agonist and a κ antagonist that is used for the treatment of opioid dependence. The safety of sublingual buprenorphine in experienced opioid users without physical dependence has been reported at doses up to 32 mg. Concerns have been raised about the potential acute health risk of buprenorphine if diverted and used by the IV route at doses equivalent to those used for maintenance. In this dose-ranging study, the safety of buprenorphine was tested in a single-blind, double-dummy design, according to the following schedule: SL:12 mg/placebo; IV bolus: 0, 2, 4, 8, 12, and 16 mg, in sessions separated by at least 72 hours. SL doses (or placebo) were held in the mouth for 5 min., followed immediately by an IV injection (1 minute) in 6 experienced opioid users without opioid dependence. (Sixteen mg IV buprenorphine is equivalent to 4 - 11 times Fentanyl doses used to induce apnea during opioid anesthesia.) Vital signs and oxygen saturation were monitored continuously for 3 hours while the subject remained in a sitting position performing computer tasks and later on a residential unit. Analysis of the Area Under the Curve showed a statistically significant increase from baseline in Systolic Blood Pressure for the 8 mg IV dose compared to the placebo condition (+ 13.5 mm Hg). There were no other statistically significant changes in blood pressure, heart rate or oxygen saturation among the 7 drug conditions. The mean (± SD) maximum decrease in 02 saturation from baseline was greatest for the 8 mg IV dose: -7.3 (±4.3). The main side effects were sedation, mild irritability, nausea, and itching. One subject's participation was discontinued after the 12 mg IV dose because of severe nausea, which persisted for 24 hours. Subjects remained responsive to low voice and computer prompts for tasks performances. Buprenorphine appears to have a ceiling for cardio-respiratory effects and a high safety margin when administered by the IV route in the absence of other drugs.

THE MASS BALANCE OF BUPRENORPHINE IN HUMANS

E. T. Everhart, P. Cheung, E. Lin, I. Fernandez, P. Jacob III, J. Mendelson, R. Upton, and R. T. Jones

Drug Dependence Research Center, Langley Porter Institute, University of California, San Francisco

Determination of the metabolic disposition of buprenorphine in humans has been difficult due to low administered doses and presumed hepatic clearance with fecal elimination. To assess the metabolic disposition of buprenorphine in humans, six opiate-experienced subjects received 1 mg of tritiated (200 μCi) buprenorphine intravenously over 60 minutes. Subjects were housed on the UCSF-GCRC and plasma, urine, and feces were collected for seven days. Buprenorphine and its known metabolites, norbuprenorphine and buprenorphine-3-glucuronide, were quantitatively assessed. Almost all (99±13%) of the radioactive dose of buprenorphine was recovered in urine and feces. Only small amounts of buprenorphine and metabolites were found in plasma (<3% of the radioactive dose per liter, even at peak concentrations). In urine, almost all buprenorphine was conjugated as was most of the norbuprenorphine. In contrast, almost all the buprenorphine and norbuprenorphine in feces was free. Fecal unconjugated buprenorphine and norbuprenorphine may result from elimination of the conjugated material in the bile with hydrolysis in the gastrointestinal contents to regenerate free buprenorphine and metabolite. Two unknown polar metabolites were identified in urine samples.

ACKNOWLEDGMENT: Supported in part by NIDA grant N01DA 48306.

DOUBLE-BLIND RANDOMISED TRIAL OF BUPRENORPHINE AND METHADONE IN OPIATE DEPENDENCE

S. Petitjean, D. Ladewig, C. Uehlinger, D. Waldvogel, J. Déglon, S. Livoti, and R. Stohler

Department of Psychiatry, University of Basel and Psychiatric Outpatient Clinic, Fribourg and Methadone Outpatient Clinic, Geneva, Switzerland

The safety and efficacy of sublingual buprenorphine compared to methadone was evaluated in a double-blind controlled study over six weeks. Patients meeting DSM-IV criteria for opiate dependence were randomly assigned to receive either methadone or buprenorphine (SL tablets) in a flexible dosing procedure (buprenorphine: 4, 8, 12, 16mg/d; methadone: 30, 60, 90, 120mg/d). Dose changes were possible throughout the first 3 weeks of the study. The buprenorphine (n=27) and the methadone (n=31) group did not differ regarding baseline demographic variables and measures of drug use (mean age 28±5.4 yrs, 81% male, 45% IDU). Doses were increased if the urinalysis continued to be opiate positive. Mean doses were 10mg/d for buprenorphine, and 69mg/d for methadone respectively. Outcome measures included retention in treatment and heroin use. The retention rate for methadone was significantly longer than for buprenorphine (mean days in treatment: 30 days for buprenorphine and 40 for methadone; $p<0.001$). Dropout rates were 44% and 10% in the buprenorphine and methadone group respectively. In the buprenorphine group, 4 patients experienced adverse events (headache, allergic reactions). The two groups did not differ in the ratio of opiate positive urine samples (buprenorphine: 65%, methadone: 56%; $p>0.5$). The number of opiate positive urine specimens decreased over the study period in both groups. In conclusion, these results suggest greater efficacy of methadone maintenance in terms of retention in treatment compared to buprenorphine in a flexible dosing procedure.

ACKNOWLEDGMENT: Supported by the Federal Office of Public Health, Switzerland.

BUPRENORPHINE AND NORBUPRENORPHINE IN HUMAN HAIR OF SUBSTANCE ABUSE TREATMENT SUBJECTS

A. S. Valdez, D. G. Wilkins, M. H. Slawsott, C. Sison, A. Huber*, W. Ling*, and D. E. Rollins*

Center for Human Toxicology, University of Utah, Salt Lake City, UT and *Friends Research Institute, Los Angeles, CA

Hair analysis may be a useful tool for monitoring therapeutic compliance in drug treatment programs. In this study. subjects (n=32) initiating buprenorphine (BUP) treatment were randomly assigned to one of two treatment conditions: 8 mg oral liquid or 16 mg tablet once daily. Hair and plasma specimens were collected weekly and urine collected three times weekly for up to 16 weeks. Buprenorphine concentrations in hair and plasma were measured by LC/MS/MS. Urine specimens were analyzed by radioimmunoassay. For subject #1, hair concentrations of BUP ranged from 4.51 (3 weeks) to 45.59 pg/mg (16 weeks); for norbuprenorphine (NBUP) ranged from 4.83 to 54.55 pg/mg. For subject #2, hair concentrations of BUP ranged from 17.8 (3 weeks) to 113.6 pg/mg (14 weeks); NBUP ranged from 67.7 to 884.0 pg/mg. Although measured hair concentrations of BUP and NBUP varied substantially from week to week, a gradual trend of increasing hair concentrations over time was observed. These data demonstrate that hair may be a useful adjunct specimen to plasma and urine for the monitoring of BUP treatment compliance.

ACKNOWLEDGMENT: Supported by NIDA grant DA 09096.

SEMIQUANTITATIVE OPIATE URINALYSIS: EFFECTS OF HYDROMORPHONE DOSE VERSUS UNSANCTIONED OPIATE USE

E. Schoener, M. K. Greenwald, and C. E. Johanson

Department of Psychiatry and Behavioral Neurosciences, Wayne State University, Detroit, MI

Semiquantitative analyses of monitored urine samples from healthy male (4) and female (4) buprenorphine (BUP)-maintained volunteers, ages 40-49, were performed with fluorescence polarization immunoassay (FPIA; Abbott ADx instrument and standard reagents). Fresh urine samples were gently swirled; each aliquot was pipetted from the middle of the specimen and transferred to the sample cup. During BUP treatment, various doses of hydromorphone (HYD: 0. 4, 8, and 16 mg/70 kg, im), a short-acting mu-opioid agonist, were administered to each volunteer in randomized order at 1:00 pm on four consecutive weekdays. This sequence was repeated five times at BUP doses of 2, 4, 8. 4 and 2 mg sl (note: BUP does not cross-react with the opiate assay.) Urine samples were obtained before the first HYD dose (control sample) to verify drug abstinence and 20 hrs after HYD injection. Unsanctioned opiate use (always heroin or codeine) resulted in rescheduling test sessions. In these volunteers, unsanctioned use yielded raw values in excess of 1000 ng/ml ("high" threshold for total opiate concentration). In contrast, the mean (SEM) control sample value before the first HYD dose of the test week was 40 (9) ng/ml, and mean (SEM) values 20 hrs after the 0, 4, 8 and 16 mg/70 kg HYD doses were 146 (32), 345 (30), 394 (43), and 554 (75) ng/ml, respectively. This linear HYD dose-effect function was reliable and highly statistically significant across the 8 volunteers (no gender difference), although there were modest carryover effects of higher HYD doses depending on the order of administration. These data indicate that short-acting opiate administration can be discriminated from unsanctioned opiate use with semiquantitative urinalysis (without creatinine correction) and that HYD produces dose-related increases in urine opiate levels during a 24-hr period using FPIA detection methods. The apparent sensitivity of this technique suggests it could be implemented 'as is' to address certain research questions.

GRADUAL BUPRENORPHINE DETOXIFICATION IN AN OUTPATIENT CLINIC

T. D. Mudric, E. C. Strain, M. L. Stitzer, and G. E. Bigelow

Department of Psychiatry, Johns Hopkins University School of Medicine, Baltimore, MD

Buprenorphine has been shown to be an effective maintenance treatment for opioid dependence and has promising characteristics for use in detoxification treatment. This study examined clinical outcomes during an 10-wk outpatient detoxification with sublingual buprenorphine following 16 wks of buprenorphine maintenance treatment. Participants (N=42) were those who entered the detoxification phase. Double-blind dose reduction was 12.5%/wk of the participants' final buprenorphine maintenance dose (mean = 9.4 mg; range = 8-16 mg). Primary outcome measures were: weekly percent positive opioid urines, self-reported IV heroin use, and total withdrawal symptom scores. Data analyses were conducted with the participants (n=24) who remained in treatment through the first week of placebo dosing. The outcome measures gradually changed for the first 7 weeks of the detoxification but increased abruptly during the first placebo week. During the first 7 weeks of detoxification, participants had a mean of 29.8% opioid positive urines per week (wk 1 = 18.1%, wk 7 = 38.9%), a reported mean of .4 injections of heroin per week (wk 1 = .33, wk 7 = .63), and a mean total withdrawal symptom score of 30 (maximum possible score being 180; wk 1 = 25, wk 7 = 39). During the first placebo week participants submitted 60.4% opioid positive urines on average, reported a mean of 2.6 heroin injections, and increased their total withdrawal scores to a mean of 64. These results suggest that gradual buprenorphine detoxification (12.5%/wk) is associated with modest illicit drug use and withdrawal symptoms; however these outcomes deteriorate upon initiation of placebo dosing.

ACKNOWLEDGMENTS: Supported by NIDA grants K02 DA00332, K05 DA0050, and R18 DA05792.

OUTPATIENT-BASED PHARMACOKINETIC STUDIES OF BUPRENORPHINE

D. Ling[1], A. Huber[1,2], C. Charuvastra[1], N. Chiang[3] and W. Ling,[1,2]

[1]L.A. Addiction Treatment Research Center, [2]Long Beach VA MDRU and [3]NIDA Medications Development Division

Most pharmacokinetic studies of medications have been conducted in inpatient settings. This strategy provides more control over intervening variables so those conclusions regarding the pharmacokinetic profile can be more precise. However, this approach can be costly, especially in studies of substance dependent patients where the dropout rate is high and the management of patient behavior is arduous. Also, while conclusions about the generalizability of the results to relevant clinical populations remain. We implemented a pharmacokinetic study as an addendum to a 16-week double-blind double-dummy outpatient study comparing the safety and efficacy of two formulations of buprenorphine. The study design includes a one-week dose run-up stabilization period, maintenance for four weeks each at 8, 12, and 16 mg for liquid formulation (or at 16, 24, and 32 mg for the tablet formulation), followed by a crossover to the maximum dosage of the other formulation for 4 weeks. Pharmacokinetic data was collected during the fourth week of each dosage and formulation. Measures of global intoxication, drug craving, test drug liking, and opiate withdrawal scale were completed at each blood draw. Participants received grocery vouchers for each session successfully completed with payment totaling $280. The cost to run one session using this outpatient study design is approximately $650 compared to a similar inpatient study at a cost of $3200 per session. Participant satisfaction data indicates that patients enjoyed the study, thought the clinic environment was very comfortable, did not have trouble interacting with clinic staff, and were very interested in future studies of this nature. High satisfaction ratings were also given to quality of meals and level of monetary compensation. An examination of the results with respect to patient participation, data collection, study completion, and personnel requirements, suggest that outpatient studies are feasible at considerable cost savings.

SENSITIVE CAPILLARY GC/MS METHOD FOR SIMULTANEOUS QUANTITATION OF BUPRENORPHINE AND NORBUPRENORPHINE IN HUMAN PLASMA

S. Gopall, M. Borenstein[1], A. Cowan[2], and T.-B. Tzeng

School of Pharmacy and Medicine[2], Temple University, Philadelphia, PA

A sensitive, specific, and robust capillary CC-MS method has been developed and validated for simultaneous determination of buprenorphine and its active metabolite, norbuprenorphine in human plasma using buprenorphine-D4 as the internal standard. Sample preparation involved a clean-up procedure using a Bond Elut Certify cartridge followed by derivatization with pentafluoropropionic anhydride. Separation was carried out on a HP-1 fused silica capillary column using helium as the carrier gas. The oven temperature was programmed from 120°C to 280°C. The injector temperature was 280°C. Selected ion monitoring was used in the electron impact mode. The retention times for buprenorphine (m/z = 524, 556) and norbuprenorphine (m/z = 616, 648) were 9.7 and 10.6 mins, respectively, with baseline separation and no interference from blank plasma. Excellent linearity was found between 0.1 and 20.0 ng/mL with a limit of quantitation of 0.05 and 0.1 ng/ml for buprenorphine and norbuprenorphine respectively. Intra-day assay precisions were within 11.0% for buprenorphine and 16.0% for norbuprenorphine. and accuracies were within 5.0% for buprenorphine and 19.0% for norbuprenorphine. Inter-day assay precisions were within 10.0% for buprenorphine and norbuprenorphine, and accuracies were within 0.4% for buprenorphine and 3.0% for norbuprenorphine. Absolute recoveries were quantitative (> 80.0% for buprenorphine and > 92.0% for norbuprenorphine) and concentration-independent. This method will be applied to pharmacokinetic/ pharmacodynamic/bioequivalence studies of buprenorphine in humans.

Keywords: Bioanalysis, Buprenorphine, Norbuprenorphine, Human plasma, GC/MS

BUPRENORPHINE-NALOXONE INTERACTIONS AT PEAK BUPRENORPHINE EFFECTS

E. A. Jacobs, W. K. Bickel, N. M. Petry, and G. Badger*

University of Vermont, Burlington, VT and *University of Connecticut, Farmington, CT

Buprenorphine (BUP)-naloxone interactions were examined at peak buprenorphine effects in opioid-dependent outpatients. After being stabilized on a maintenance dose of 8 mg/ 70 kg (n=1) or 16 mg/ 70 kg (n=9) of BUP every other day, subjects participated in challenge sessions every other week. Challenge sessions were conducted at Low (half maintenance), Medium (maintenance), and High (double maintenance) BUP doses, in either an ascending (n= 5) or descending (n=5) sequence. One placebo and one active naloxone challenge session were conducted in random order at each condition. Subjects received each BUP dose for at least 10 days prior to the first challenge session at each condition. Subjects received 3 injections (i.m.) spaced 45 min apart during each challenge session. BUP was administered 150 min before the first injection. During active sessions, a saline placebo injection was followed by 3.0 mg/ 70 kg and 13 mg/ 70 kg doses of naloxone using a cumulative dosing procedure. All injections contained saline during placebo sessions. Dependent measures included an Adjective Withdrawal Scale. Visual Analog Scale, Observer Ratings of opioid withdrawal and agonist effects, Addiction Research Center Inventory, Digit-Symbol Substitution Test, vital signs, and pupil diameter. Measures of precipitated withdrawal were directly related to naloxone dose across all BUP doses. Across measures of withdrawal, significant effects of naloxone dose and significant BUP-naloxone dose interactions were more frequently obtained in subjects experiencing the BUP doses in an ascending sequence. Data from these subjects suggest precipitated withdrawal may be less pronounced at lower BUP doses.

EFFICACY OF THE BUPRENORPHINE-NALOXONE TABLET FOR DAILY VS. ALTERNATE-DAY OPIOID DEPENDENCE TREATMENT

J. B. Kamien, S. K. Mikulich, and L. Amass*

Department of Psychiatry, Addiction Research and Treatment Services, University of Colorado School of Medicine, Denver, CO and *BioPsych Consulting, Denver, CO

A combination buprenorphine-naloxone tablet was developed to mitigate against potential diversion and abuse of buprenorphine (BUP). One of BUP's unique features is that it can be used as both a daily and alternate-day treatment. This study determined whether a combination tablet containing 8 mg of BUP and 2 mg of naloxone could be administered safely and effectively every other day and whether increasing the dose is essential for maintaining an efficacious alternate-day treatment. Twenty-six opioid-dependent outpatients entered a double-blind, placebocontrolled, triple crossover trial. Twenty-one days of daily combination tablet administration were compared to two different 21day periods of alternate-day BUP administration where patients received either 8 or 16 mg of the combination tablet every other day with placebo on the interposed day. Outcome measures included treatment retention, medication compliance, drug use, and daily ratings of opioid effects and pupillary diameter. Fifty-four percent (14/26) of patients completed the study. Of the 12 subjects who dropped out, only 2 did so during the 16 mg alternate-day condition. The remainder of the drop-outs (10/12) were evenly distributed between the 8 mg daily and 8 mg alternate-day condition. Clients were medicated on 86%, 84% and 88% of days during the 8 mg daily, 8 mg and 16 mg alternateday conditions, respectively. Rates of illicit opioid use were 53%, 60% and 54% for the 8 mg daily, 8 mg and 16 mg alternate-day conditions, respectively. Subject- and observer-rated measures of opioid effects did not distinguish daily from alternate-day treatments, but pupillary diameter was significantly decreased during the 16 mg as compared to 8 mg alternate-day treatment. These data replicate earlier findings of similar efficacy of daily and alternate day BUP dosing, extends these findings to the combination buprenorphine-naloxone tablet and suggests slightly improved outcomes during alternate-day treatment using multiples of the daily dose.

ACKNOWLEDGMENT: Supported by NIDA grant DAI 1160.

BUPRENORPHINE/NALOXONE COMBINATION TABLET: EFFECTS IN OPIOID-DEPENDENT VOLUNTEERS

K. B. Stoller, E. C. Strain, and G. E. Bigelow

Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD

Buprenorphine, a mixed agonist-antagonist opioid (or partial agonist), is a safe and effective treatment for opioid dependence. However, there is concern that it may be abused. A sublingual (SL) buprenorphine/naloxone (B/N) combination tablet may reduce this risk by capitalizing on the differentially poor SL bioavailability of the opioid antagonist naloxone. While discouraging parenteral injection due to the possibility of precipitated withdrawal in opioid-dependent individuals, naloxone should have little or no biodelivery or effect if the B/N is taken sublingually. This study characterizes the effects of B/N combinations in opioid-dependent volunteers. During a 10-week residential research unit admission, subjects were maintained on oral hydromorphone (10 mg q.i.d.). In twice-weekly experimental sessions, subjects received SL tablets, intramuscular (IM) injections, or control (double-blind, double-dummy). The 15 conditions included: B/N SL or IM (1/0.25, 2/0.5, 4/1, 8/2, 16/4 mg), 0.25 mg naloxone IM (antagonist control), 10 mg hydromorphone IM (agonist control), 8 mg buprenorphine monotherapy SL tablet or IM (buprenorphine control), and placebo. SL B/N produced, at most, mild effects at all dose conditions. IM B/N produced robust dose-related antagonist effects within minutes of administration, and some modest delayed agonist effects. Similar effects were observed for 8 mg B/N vs. 8 mg buprenorphine SL tablets. The 8 mg B/N combination, but not 8 mg buprenorphine alone, produced intense antagonist effects when given IM. In summary, the combination of buprenorphine and naloxone produces antagonist effects when taken parenterally, but not sublingually.

ACKNOWLEDGMENTS: Supported by NIDA grants R01 DA 08045, K05 DA 00050, K02 DA00332, and T32 DA 07209.

ANTINOCICEPTIVE PROFILES OF KAPPA OPIATE AGONISTS

P. J. Little, L. Cortes-Burgos, S. L. Gottshall, M. Koblish, S. Long, and D. L. DeHaven-Hudkins

Adolor Corporation, Malvern, PA

The development of clinically useful analgesics that act through kappa (κ) receptors has been limited by the dysphoria produced by centrally acting κ agonists. The efficacy of κ agonists in animal models of antinociception may be dependent on the strength and types of nociceptive stimuli. The goal of these studies was to determine the potency and efficacy of κ agonists in a variety of antinociceptive models in rats or mice in order to determine the ability of these compounds to alleviate inflammatory pain. Formalin-induced flinching and FCA-induced hyperalgesia were assessed in rats, and acetic acid-induced writhing was measured in mice. Following intrapaw injections, GR 89696, ICI 199441, spiradoline and U-50,488H were active in both the early and late phases of the formalin test with ED_{50}s in late phase formalin of 0.42, 0.74, 5.8 and 91 μg, respectively. These compounds were also active in late phase formalin following s.c. administration with the same rank order of potency and ED_{50}s of 0.003, 0.05, 0.83 and 1.2 mg/kg, respectively. These κ agonists increased paw pressure thresholds in the inflamed paw of rats injected with FCA. The intraplantar ED_{50}s (in parentheses) in this model of chronic inflammatory pain were similar to values obtained with intrapaw administration in the formalin assay for GR 89696 (0.4 μg), ICI 199441 (2.5 μg) and spiradoline (14 μg) U-50,488H increased paw pressure thresholds by 170% at 300 μg. In the mouse acetic acid writhing test, all of the κ agonists were very potent. The ED_{50}s for inhibition of writhing were 0.0003, 0.004, 0.07 and 0.19 mg/kg following s.c. administration of GR89696, ICI 199441, U-50,488H and spiradoline, respectively. These data indicate that κ agonists are potent and fully efficacious in animal models of antinociception that involve an inflammatory component, suggesting that κ agonists may be most useful as therapeutics for pain associated with inflammatory conditions.

TOLERANCE TO THE ANTINOCICEPTIVE EFFECTS OF MU OPIOIDS IN BUTORPHANOL-TREATED RATS

M. A. Smith, A. C. Barett, and M. J. Picker

Department of Psychology, University of North Carolina, Chapel Hill, NC

The present investigation examined the antinociceptive effects of opioid analgesics following acute and chronic administration of the low-efficacy opioid butorphanol. In a warm-water, tail-withdrawal procedure, rats were restrained and the latencies to remove their tails from either 50° (low) or 55° (high) Celsius water were measured. Under acute conditions, etorphine, levorphanol, morphine, dezocine, (-)-pentazocine and nalbuphine increased tail-withdrawal latencies at the low water temperature, whereas only etorphine, levorphanol, morphine and dezocine increased latencies at the high water temperature. A dose of 30 mg/kg butorphanol enhanced the effects produced by these opioids at the low temperature, but antagonized their effects at the high temperature. During chronic treatment with 30 mg/kg/day butorphanol, tolerance was conferred to the antinociceptive effects of all the opioids examined, with greater degrees of tolerance conferred to those drugs possessing low efficacy at the mu receptor. During butorphanol treatment, etorphine, levorphanol and morphine increased tail-withdrawal latencies at both water temperatures, dezocine increased latencies at only the low temperature, and (-)-pentazocine, nalbuphine and butorphanol failed to increase latencies at either temperature. A dose of 30 mg/kg butorphanol antagonized the antinociceptive effects of etorphine, levorphanol, morphine and dezocine during chronic treatment, and these effects were observed at both low and high water temperatures. These findings suggest that the level of antinociception produced by opioid analgesics depend upon (1) their relative efficacy at the mu receptor (2) the intensity of the nociceptive stimulus and (3) whether behavioral testing follows acute or chronic drug administration.

ACKNOWLEDGMENTS: Supported by DA10277 and DA05713.

MORPHINE-LIKE STIMULUS EFFECTS OF NMDA ANTAGONISTS MAY BE DUE TO DISRUPTION OF STIMULUS CONTROL

C. Willmore, A. Bespalov, R. L. Balster, and P. M. Beardsley*

Virginia Commonwealth University, Richmond, VA and *Pavlov Medical University, St. Petersburg, Russia

Antagonists to the NMDA receptor complex have been repotted to partially generalize from the discriminative stimulus effects of a large number of pharmacologically dissimilar compounds including pentylenetetrazol, NMDA, morphine, THC, pentobarbital, and select dopaminergic agents. These effects could represent either a true commonality in their discriminative stimulus effects or, possibly, a generalized disruption of stimulus control. To test the hypothesis that NMDA antagonists which generalize from the morphine stimulus also nonspecifically disrupt stimulus control we evaluated NMDA antagonists in rats trained to discriminate 3.2mg/kg s.c. morphine from vehicle, and in other rats reinforced according to a Fixed Consecutive Number 8 (FCN8) schedule of food reinforcement. The FCN schedule required at least 8 consecutive presses on one lever followed by a single press at an alternate lever for food pellet delivery, and was used as an instrument to detect non-specific disruption of stimulus control. Drugs tested included MK-801, phencyclidine, D-CPPene, NPC 17742, (+)HA966, kynurenic acid, eliprodil, ifenprodil, and memantine. Several of the drugs produced "partial " generalization from the morphine cue with D-CPPene yielding the highest levels (70% morphine lever selection at 5.6mg/kg). Only NMDA-active compounds which disrupted FCN performance, however, were able to produce apparent morphine-like stimulus effects. These data suggest that nonspecific disruption of stimulus control by NMDA antagonists may be a determinant of their partial generalization from the morphine stimulus.

ACKNOWLEDGMENTS: Supported by NIDA grant DA 01442 and DA 07027 .

THE MAGNITUDE OF MORPHINE TOLERANCE IS ATTENUATED BY AN NMDA RECEPTOR ANTAGONIST

R. M. Allen[1] and L. A. Dykstra[2]

[1]Curriculum in Neurobiology and [2]Department of Psychology, University of North Carolina, Chapel Hill, NC

Previous research demonstrates that antagonists of the N-Methyl-D-Aspartate (NMDA) glutamate receptor attenuate opioid tolerance in rodent antinociceptive assays. The present study used a rat warm-water tail-withdrawal procedure to determine the role of morphine (MS) maintenance dose in the tolerance-attenuating effects of the competitive NMDA receptor antagonist, LY235959 (LY). In this procedure, the lower 8 cm of each rats tail is placed in 55°C water, and the latency to removal is measured. Prior to chronic drug administration, MS produced dose-dependent increases in tail-withdrawal latencies, with maximal antinociception at 10 mg/kg MS. Following administration of 10, 20, and 40 mg/kg MS twice-daily for 7 days, the MS dose effect curves shifted rightward 0.38, 0.69, and 1.10 log units, respectively. Thus, higher maintenance doses produced greater degrees of tolerance. The concurrent administration of LY (1, 3, or 5.6 mg/kg) with 10 mg/kg MS twice-daily for 7 days resulted in a dose-dependent attenuation of MS tolerance, with complete attenuation observed with 3 and 5.6 mg/kg LY. In contrast, the 0.69 and 1.10 log unit shifts observed with twice-daily administration of 20 and 40 mg/kg MS were only partially attenuated by 3 mg/kg LY. When 3 mg/kg LY was co-administered with 20 and 40 mg/kg MS the rightward shifts were 0.41 and 0.76 log unit, respectively. In summary, 3 mg/kg LY attenuated approximately 0.3 log unit of the total magnitude of MS tolerance, independent of the MS maintenance dose.

ACKNOWLEDGMENTS: Supported by USPHS grants DA-02749, DA-00033 and DA-53701.

INTERACTIONS FOLLOWING COMBINED ADMINISTRATION OF NMDA ANTAGONISTS AND MORPHINE IN MONKEYS

J. S. Rodefer, M. J. Tiano, R. M. Allen, and L. A. Dykstra

Department of Psychology, University of North Carolina at Chapel Hill, Chapel Hill, NC

The present experiment evaluated acute drug interactions resulting from the combined administration of several non-competitive NMDA antagonists and morphine. The rate-decreasing effects of dizocilpine (MK-801; 0.003-0.056 mg/kg), phencyclidine (PCP; 0.03-0.3 mg/kg), and ketamine (0.3-5.6 mg/kg) were evaluated in combination with morphine (0.3-1.0 mg/kg) under an fixed-ratio (FR) 30 schedule of food presentation in 4 squirrel monkeys *(Saimiri sciureus)*. Cumulative dose-effect functions were first examined for each of the NMDA antagonists alone. for morphine alone, then in combination with dizocilpine (0.01-0.02 mg/kg), PCP (0.03-0.08 mg/kg), and ketamine (1.0-2.0 mg/kg) pretreatment. Finally, dose-effect curves were redetermined for NMDA antagonists alone and in combination with morphine (0.03-0.3 mg/kg) pretreatment. Pretreatment with dizocilpine, PCP, and ketamine markedly decreased the ED50 for morphine across all dizocilpine, PCP and ketamine doses examined. When monkeys were pretreated with morphine the ED50 values for ketamine, PCP and dizocilpine also decreased and in a dose-dependent fashion. Isobolographic analysis of these data suggest that across most dose-combinations, acute administration of PCP, dizocilpine, or ketamine and morphine produced additive interactions.

ACKNOWLEDGMENTS: Supported by PHS grants DA02749, DA00033 and DA 07244 (LAD).

SUPRASPINAL Δ^9-THC, WIN 55,212-2, AND ANANDAMIDE ANTINOCICEPTION IN MICE IS DIFFERENTIATED BY CHOLERA TOXIN

D. J. Stone, Jr.[1,2], S. J. Hipp[2,3], and R. B. Raffa[1,3]

[1]Drug Discovery, The R.W. Johnson Pharmaceutical Research Institute, Spring House, PA; [2]Drexel University Biomedical Sciences Program and [3]Temple University School of Pharmacy and School of Medicine, Philadelphia, PA

The supraspinal (intracerebroventricular; *i.c.v.*) administration to mice of Δ^9-terahydrocannabinol (Δ^9-THC), WIN 55,212-2 mesylate (WIN; a high affinity cannabinoid receptor agonist), or of the endogenous ligand anandamide (arachidonyl ethanolamide; AEA) induces an antinociceptive effect, presumably through the central CB_1 cannabinoid receptor type. The purpose of the present study was to determine whether the antinociceptive effects of Δ^9-THC, WIN and AEA, although not distinguishable at the behavioral (antinociceptive) and receptor level, could be distinguished at the level of second messenger transduction in vivo. Male, Swiss-derived Crl:CD-1 (ICR) mice, 18 - 24 g, were injected *i.c.v.* with either Δ^9-THC (160 nmol), WIN (30 nmol), or with AEA (860 nmol) 24 hours after *i.c.v.* administration of vehicle (sterile water), pertussis toxin (PTX; which catalyzes ADP-ribosylation of a cysteine side chain on a subunits of inhibitory G-proteins and disables activation by ligand-receptor complex) or cholera toxin (CTX; which modifies stimula-tory G_s proteins such that they are persistently activated). Antinociception was measured 5 min after administration of Δ^9-THC, WIN or anandamide (peak time determined in pilot studies) using the warm-water tail-flick test. PTX dose-dependently reduced the antinociceptive effects of both Δ^9-THC. WIN and AEA with similar IC_{50} values (0.13, 0.20 and 0.32 nmol, respectively), consist-ent with mediation *via* $G_{i/o}$-coupled CB receptors. CTX (0.1 - 3.0 μg) had no effect on the anti-nociceptive effect of Δ^9-THC. In contrast, CTX dose-dependently increased the antinociceptive effect of i.c.v. AEA (ED_{50} = 0.50 nmol). These data suggest a slight difference in the receptor-effector coupling between Δ^9-THC. WIN 55,212-2 and the endogenous ligand anandamide.

GAMMA-HYDROXYBUTYRIC ACID AUGMENTS MORPHINE (M)-INDUCED ANALGESIA AND INVERTS TOLERANCE TO M IN MICE

E. R. Bowman and M. D. Aceto

Virginia Commonwealth University, School of Medicine, Richmond, VA

Gamma-hydroxybutyric acid (GHBA), a precursor and metabolite of gamma-aminobutyric acid, which has been used in Europe, as a general anesthetic and hypnotic, as an aid in childbirth, in the treatment of alcoholism and in anxiety attendant with detoxication from cocaine and amphetamines, depression and other conditions, has also gained popularity as a fashionable recreational drug. Because little is known about its interaction with opioids, this study was initiated. GHBA, per se, (at 30, 60, 80, and 100 mg/kg s.c.) had little effect on the normal reaction time in the tail-flick test. When these doses of GHBA were coadministered with the ED25 of M, dose-related synergism was observed. In mice made completely tolerant to M antinociceptively (25 mg/kg.s.c., 4 times a day for 4 days), GHBA (60 mg/kg s.c.) in combination with M partially restored antinociception. Naloxone (1 mg/kg s.c.) nearly abolished this effect. These results suggest possible therapeutic applications and potential safety issues for GHBA in abusers.

ACKNOWELDGMENT: Supported by NIDA grant DA 5-8059.

BENZODIAZEPINE MODULATION OF ACUTE AND CHRONIC ETHANOL-INDUCED CHANGES IN NOCICEPTION

M. B. Gatch and H. Lal

Department of Pharmacology and Substance Abuse Institute of North Texas, University of North Texas Health Science Center, Fort Worth, TX

Ethanol produces antinociception when administered acutely or chronically in rats, and acute withdrawal from ethanol induces hyperalgesia. This study examines the effects of ligands for the benzodiazepine site on the GABA receptor on ethanol-induced changes in nociception. A radiant heat tail-flick assay was used to assess changes in nociception in rats. Acute activity of cumulative doses of ethanol (0.5 – 2.0 g/kg) and diazepam (0.1 – 10 mg/kg), a benzodiazepine site agonist were tested alone and after pretreatment with flumazenil (10 mg/kg), a benzodiazepine site antagonist. Chronic effects of ethanol were tested in three groups of rats which received 10 days of exposure to a liquid diet. One group received ethanol alone, one group received ethanol and twice daily injections of flumazenil (10 mg/kg) and one received a dextrin control diet. Acute withdrawal was tested at 12 hr after removal of the liquid diet. Effects of cumulative doses of diazepam (1.0 – 10 mg/kg) were tested during withdrawal in the ethanol alone group. Acute doses of ethanol produced a small but significant degree of antinociception which was fully suppressed by flumazenil. Acute doses of diazepam did not produce antinociception. Chronic exposure to ethanol produced antinociception on days 2-8. Tolerance developed by day 10 and hyperalgesia was seen 12 hr after removal of ethanol. Administration of diazepam during withdrawal reversed the hyperalgesia induced by ethanol withdrawal. However, flumazenil (10 mg/kg) failed to reverse this effect of diazepam. No antinociception was seen in either the ethanol/ flumazenil or dextrin control groups. These results suggest that the antinociceptive effects of both acute and chronic ethanol are at least partially mediated by GABA receptors, and that diazepam's anti-hyperalgesic effects may not be mediated by the GABA receptor.

ACKNOWLEDGMENT: Supported in part by NIH grant AA09567-05.

INADEQUATE MORPHINE SERUM LEVELS DESPITE HIGH ORAL DOSAGES IN SEVERE, CHRONIC INTRACTABLE PAIN PATIENTS

F. S. Tennant

Community Health Projects Medical Group, West Covina, CA

Patients with severe, chronic intractable pain (SCIP) due to incurable, nonmalignant causes will frequently. for unknown reasons, escalate their daily, oral morphine intake to very high levels. Thirty-two (32) SCIP patients who were treated with daily, oral morphine (N=26) or methadone (N=6) had blood samples collected within three hours after ingesting their usual. oral dose. All self-administered their opioid on a regular 4-6 hour interval. Total daily intake of morphine ranged from 60 to 1100 mg. (mean 541.3 + 355.0 S.D.) and that of methadone from 80 to 200 mg. (mean = 112.0 + 50.2 S.D.). The serum concentrations ranged in the morphine group from 0 to 720 ng/ml (mean = 116.2 + 189.3 S.D.). Fifteen (15;57.7%) patients in the morphine group demonstrated a serum concentration less than 50 ng/ml, and only 8 (30.8%) showed a serum concentration over 100 ng/ml. Eight (830.8%) showed zero concentration. While all methadone patients reported pain relief for at least four hours following their usual oral dosage, no morphine patient with a serum concentration below 50 ng/ml reported pain relief for longer than two hours following their usual dosage. The serum morphine concentrations in over half of the morphine patients showed a level so low as to indicate that oral morphine in the SCIP patients was being deactivated and converted to metabolites so rapidly that adequate pain relief was not achieved for even four hours.

PREVENTION OF OPIOID DOSAGE ESCALATION BY THE CLONIDINE PATCH IN SEVERE, CHRONIC INTRACTABLE PAIN

D. Duncombe and F. S. Tennant

Community Health Projects Medical Group, West Covina, CA

Patients with severe, chronic intractable pain (SCIP) due to incurable, nonmalignant causes will frequently escalate their daily opioid intake to high levels and resort to ancillary drug use giving the appearance of abuse. The reasons for dosage escalation and ancillary drug use is unclear, but it may be, in part, due to the onset of opioid withdrawal symptoms which occur between opioid dosages. Since high dose opioids have multiple neuroendocrine and other complications, minimizing the opioid dosage is advisable. To minimize opioid daily dosage and prevent dosage escalation, 30 patients with SCIP who were taking Schedule II opioids at a minimum daily morphine equivalence of 100 mg. were selected. Clonidine patches containing 1 to 3 mg. were placed on each patient. Daily opioid dosages was determined by assessing the number of oral dosages required to achieve pain control. Over a 12 week period every patient either eased dosage escalation or reduced their daily opioid intake up to 50% without loss of pain control. Some patients reported enhanced pain relief. The clonidine patch likely provides a constant blood level of clonidine which prevents opioid withdrawal symptoms and pain exacerbation between opioid dosages.

BEHAVIORAL EFFECTS OF REMIFENTANIL IN NON-DRUG ABUSING VOLUNTEERS

M. L. Black, J. L. Hill, C. J. Young, P. A. Klock, J. M. Klafta, D. W. Coalson, and J. P. Zacny

Department of Anesthesia and Critical Care, The University of Chicago, Chicago, IL

Remifentanil is an ultrashort-acting opioid agonist that is used in both inpatient and outpatient surgical procedures. The drug is administered via an infusion because nonspecific blood and tissue esterases metabolize the drug rapidly. The purpose of this study was to characterize remifentanil's psychopharmacological effects both during and after its infusion. Ten healthy volunteers (mean age: 24.6±3.0 yrs) were enrolled in a randomized, double-blind, placebo-controlled, crossover trial. In a semi-recumbent position, subjects received an infusion of saline or remifentanil over 120 min in an upper-extremity vein. The age- and weight-adjusted infusion (determined with Stanpump®, a computer modeling software package) targeted three constant remifentanil plasma levels for 40 min each: 0.75, 1.5, and 3.0 ng/ml. Mood forms and psychomotor tests were completed, and miosis was assessed, during and after the infusions. In addition, analgesia was tested at each dose level using a cold pressor test. Remifentanil dose-related effects were observed by increased VAS ratings of sleepy, coasting, high, dizzy, and heavy, increased miosis, decreased psychomotor performance, and decreased pain reports during the cold pressor test. There was intersubject variability on the VAS rating of drug liking. After the remifentanil infusion was discontinued, recovery as measured by mood indices and miosis was rapid. Psychomotor impairment, however, continued for up to 60 min ($p<0.05$) after the infusion was terminated. The intersubject variability of drug liking may indicate some potential for remifentanil abuse with anesthesia personnel.

ACKNOWLEDGMENT: Supported in part by NIDA grant DA-08573.

STATE-DEPENDENCY RESEARCH: A REVIEW OF RECENT LITERATURE

J. M. Stahl and K. E. Brakke

Department of Psychology, Morris Brown College, Atlanta, GA

State-dependent learning (SDL) received a great deal of attention in the 1970's, but research effort directed toward this topic has declined in more recent years as related drug discrimination paradigms assumed prominence. There has been a mild resurgence in state-dependency research in the mid-1990's; however, several issues surrounding the existence and nature of SDL remain unresolved, and these could play a role in interpretation of the results of related drug effect studies. A review of 110 abstracts of SDL articles published in the last 30 years suggests that alcohol, barbituates, and benzodiazepines are associated with SDL moreso than many other drugs. Also, the term "state-dependent learning" may be misleading because it appears that the presence of a drug alters cues used to retrieve information rather than disrupting learning or acquisition. New approaches to studying state-dependency should further the renewed interest in the phenomena associated with state-dependency.

ACKNOWLEDGMENT: Supported by NIDA-MIRD grant 5R24DA07256.

RAT STRAIN DIFFERENCES IN SENSITIVITY TO THE DISCRIMINATIVE STIMULUS EFFECTS OF OPIOIDS: COMPARISON TO THE ANTINOCICEPTIVE EFFECTS

D. Morgan and M. J. Picker

Department of Psychology, University of North Carolina, Chapel Hill, NC

Data were recently presented demonstrating that rat strains differ in sensitivity to the antinociceptive effects of mu opioids and these differences were influenced by the intrinsic efficacy of the test drug and the stimulus intensity used (Morgan *et al.,* NIDA Research Monograph, 1998). The rank order of sensitivity to the antinociceptive effects of the mu opioids was F344 > Sprague-Dawley > Long-Evans > Lewis. The present study examined the sensitivity to the discriminative stimulus and rate-decreasing effects of mu opioids. As in the antinociception procedure, the efficacy of the opioid and the stimulus intensity (i.e. training dose) was systematically altered. To this end, rats were trained to discriminate morphine from water in a standard, two-lever drug discrimination procedure. The following strains of rats (and training doses) were used: F344 (3.0 or 5.6 mg/kg morphine), Lewis (3.0 or 5.6 mg/kg), Sprague-Dawley (3.0 mg/kg), and Long-Evans (3.0 mg/kg). The drugs tested included the higher efficacy opioids morphine and levorphanol, the intermediate efficacy opioid buprenorphine and the lower efficacy opioids butorphanol and nalbuphine. In general, all drugs substituted completely for the morphine stimulus and there were no substantial differences in sensitivity across strains, regardless of training dose. Furthermore, there were no differences across strains in the time course of morphine, sensitivity to antagonism by naloxone, or sensitivity to the rate-decreasing effects of these opioids.

ACKNOWLEDGMENTS: Supported by NIDA grants DA05669 and DA10277.

DISCRIMINATIVE STIMULUS EFFECTS OF HEROIN IN RATS: ROLE OF MU, DELTA and KAPPA OPIOID RECEPTORS

K. E. D'Anci, S. S. Negus, and N. K. Mello

Alcohol and Drug Abuse Research Center, McLean Hospital-Harvard Medical School, Belmont, MA

Heroin (3,6 diacetylmorphine) is metabolized *in vivo* to 6-monoacetylmorphine and subsequently to the prototype mu agonist morphine. These metabolites, and especially morphine, are thought to mediate many of the behavioral effects of heroin by acting at mu opioid receptors. However, several recent preclinical studies suggest that heroin and/or 6-monoacetylmorphine may act on delta opioid receptors or other non-mu opioid receptors. The present experiment is the first in a series of studies designed to characterize more fully the pharmacological profile of heroin in the rat. Nine adult male Sprague-Dawley (CD outbred) rats were trained to discriminate heroin (0.56 mg/kg, ip) from saline in a two-lever, food-maintained drug discrimination procedure. Heroin (0.018-1.8 mg/kg) dose-dependently increased heroin appropriate responding and decreased response rates in all rats. Pretreatment with the opioid antagonist naltrexone (0.0032-0.1 mg/kg, ip) dose- dependently blocked the discriminative effects and the rate decreasing effects of 0.56 mg/kg heroin. These data confirm previous findings and indicate that heroin serves as a salient discriminative stimulus in rats. These findings also indicate that the discriminative stimulus effects of heroin are mediated by opioid receptors. Further studies indicated that the mu-selective agonist fentanyl substituted completely for heroin in four of five rats. However, the delta agonist SNC80 and the kappa agonist U50,488 produced primarily saline-appropriate responding up to doses that eliminated responding. Taken together, these results suggest a role for mu receptors, but not kappa or delta receptors in mediating the discriminative stimulus effects of heroin in rats.

ACKNOWLEDGMENTS: Supported in part by grants RO1-DA02519, P50-DA04059, T32-DA077252, and K05-DA00101 from NIDA, NIH.

DISCRIMINATIVE STIMULUS EFFECTS OF THE DELTA OPIOID AGONIST SNC80 IN RHESUS MONKEYS

M. R. Brandt, S. S. Negus, N. K Mello, X. Zhang, and K. Rice**

Alcohol and Drug Abuse Research Center, McLean Hospital - Harvard Medical School, Belmont, MA and *LMC, NIDDK, NIH, Bethesda, MD

Four rhesus monkeys were trained to discriminate the non-peptidic, delta opioid agonist SNC80 (0.32 mg/kg, i.m.) from saline using a food-reinforced drug discrimination procedure. Criteria for adequate stimulus control were satisfied following an average of 85 training sessions (range: 59-119). Cumulative doses of SNC80 produced a dose-dependent increase in SNC80 appropriate responding and a dose-dependent decrease in response rate. In time course studies, peak effects of the training dose of SNC80 were observed after 15 min and these effects diminished over 120 min. Both the discriminative stimulus effects and rate-decreasing effects of SNCSO were antagonized by the delta-selective antagonist naltrindole (0.1 mg/kg) and not by the mu-selective antagonist quadazocine (0.1 mg/kg). In substitution studies, the other delta agonists SNC86 (0.01-1.0 mg/kg), SNC 162 (0.01-1.0 mg/kg), SNC243A (0.01-1.0 mg/kg) and SNC89 (0.32-17.8) produced dose-dependent increases in SNC80 appropriate responding and substituted completely for SNC80. However, the mu agonist morphine (0.32-5.6 mg/kg) and the kappa agonist U-50,488 (0.1 -1.0 mg/kg) produced primarily saline appropriate responding up to doses that eliminated responding. Two other non-opioids (the N-methyl-D-aspartate antagonist ketamine, 0.1-3.2 mg/kg and the monoamine reuptake inhibitor cocaine, 0.032-1.0 mg/kg) also produced primarily saline-appropriate responding. These data demonstrate that monkeys can learn to discriminate SNC80 from saline and support the view that the discriminative stimulus effects of SNC80 are mediated by delta opioid receptors. This procedure can be used to further characterize the behavioral effects of SNC80 and provide an effective means to evaluate other delta opioid agonists and antagonists.

ACKNOWLEDGMENTS: Supported in part by grants R0-DA02519, P50-DA04059, T32-DA0752 and K05-DA00101 from NIDA, NIH.

MULTI-ELEMENTAL DISCRIMINATIVE STIMULUS CONTROL: EFFECTS OF LITHIUM (UCS) CONCENTRATION

R. J. Lamb and T. U. C. Järbe

Allegheny University of the Health Sciences, Department of Psychiatry, Institute of Addictive Disorders, Broad and Vine, Philadelphia, PA

The effects of the lithium chloride (LiCl; UCS) concentration used to assess the stimulus control exerted by a morphine (5.6 mg/kg) stimulus in a discriminated taste aversion procedure was examined. In this discriminated taste (DTA) aversion procedure, male Taconic Sprague-Dawley rats received injections of LiCl (range: 30 to 180 mg/kg) following morphine presentations, and injections of saline (10 ml/kg) following saline (1 ml/kg) pretreatment. These 5 paired groups (n=8) were compared to unpaired rats (n=8) that received saline injections rather than LiCl injections following presentation of the drug stimulus. Morphine and saline (1 ml/kg) were injected i.p. 20 minutes before drinking. Results suggested that the formation of DTA was a function of the LiCl concentration and most rapid for the highest concentration. The lowest dose of LiCl, 30 mg/kg, did not reliably maintain a DTA. Suppression of drinking was orderly related to the morphine dose (range: 0.3 to 10 mg/kg) in the paired rats whereas no significant decline in drinking occurred for the controls. The control of drinking was pharmacologically specific because both paired and unpaired animals were equally affected in tests with Δ^9-THC (range: 0.3 to 10 mg/kg, injected i.p., 2 ml/kg, 30 min prior to the drinking session). Subsequently the DTA's were extinguished. Extinction revealed no major UCS concentration dependent effect. Thus, rate of extinction was similar across groups. The reaction to morphine was attenuated in tests with 3 and 10 mg/kg after extinction.

ACKNOWLEDGMENTS: Supported by NIDA grants DA 08395, 09064 and 00253

OPIOID ANTAGONISM IN A MORPHINE-NALBUPHINE-SALINE THREE-CHOICE DISCRIMINATION

M. J. Tiano, L. A. Dykstra, and E. A. Walker

Department of Psychology, University of North Carolina, Chapel Hill, NC

A three-choice discrimination was established among the high-efficacy opioid morphine, the low-efficacy opioid nalbuphine, and saline. The potency of naltrexone as an antagonist of morphine- and nalbuphine-like responding was then examined. Seven White Carneau pigeons were trained to discriminate among 3.2 mg/kg morphine, 5.6 mg/kg nalbuphine and saline under FR30 schedules of food presentation. A low dose of morphine (0.01 mg/kg) produced saline-like responding; intermediate doses of morphine (0.1-1.0 mg/kg) produced nalbuphine-like responding and high doses of morphine (3.2-10 mg/kg) produced morphine-like responding. A low dose of nalbuphine (0.01 mg/kg) produced saline-like responding and intermediate and high doses of nalbuphine (0.1-100 mg/kg) produced nalbuphine-like responding. No dose of nalbuphine produced morphine-like responding. The *kappa* agonist spiradoline produced partial nalbuphine-like responding and the *delta* agonists BW373 (0.01-3.2 mg/kg) and SNC80 (0.03-3.0 mg/kg) produced saline-like responding. Low doses of naltrexone (0.01 and 0.1 mg/kg) antagonized the discriminative stimulus effects of both the morphine and nulbuphine training doses. Naltrcxone partially antagonizcd the nalbuphine-like responding produced by 1.0 mg/kg spiradoline. Taken together, these data suggest that morphine and nalbuphine produce stimulus effects through a common, *mu* opioid receptor in this three-choice discrimination.

ACKNOWLEDGMENTS: Supported by NIDA grant DA00033 and DA02749 (LAD) and DA10776 (EAW).

DELTA OPIOID-LIKE STIMULUS EFFECTS OF MU OPIOIDS IN PIGEONS DISCRIMINATING BW373U86 FROM SALINE

M. J. Picker and C. D. Cook

Department of Psychology, University of North Carolina, Chapel Hill, NC

The present study examined the substitution patterns produced by opioids with activity at the mu receptor in pigeons trained to discriminate the delta opioid BW373U86 from saline. A low dose of naltrindole (0.1 mg/kg) produced a 16-fold rightward shift in the dose-effect curve for BW373U86's stimulus effects, whereas a relatively high dose of naloxone (1.0 mg/kg) produced only a 2.0-fold rightward shift. The delta opioid SNC80 and the mixed mu/kappa opioids ethylkctocyclazocine and ketocyclazocine substituted completely for the BW373U86 stimulus. Various opioids with activity at the mu receptor (levallorphan, [-]-cyclazocine, [-]-n-allylnormetazocine, butorphanol, nalbuphine, [+]-propoxyphene, etorphine, fentanyl) substituted partially for the BW373U86 stimulus. There was no relationship between the substitution patterns produced by these opioids and their relative intrinsic efficacy at the mu receptor, their relative selectivity for the mu receptor or their relative affinity for the delta receptor. Naloxone (1.0 mg/kg) was considerably more effective than naltrindole (0.1 mg/kg) in antagonizing the effects of etorphine, ethylketocyclazocine, ketocyclazocine and butorphanol, suggesting that these effects were not mediated by activity at the delta receptor. There was no evidence that the opioids tested antagonized the BW373U86 stimulus, suggesting that these opioids were not functioning as low efficacy agonists at the delta receptor. The kappa opioids bremazocine and U50,488 and the non-opioids cocaine and pentobarbital failed to produce appreciable levels of BW373U86 responding. The present findings indicate that in pigeons mu opioids most likely produce delta-like discriminative stimulus effects by activation of mu and not delta or kappa receptors.

ACKNOWLEDGMENTS: Supported by NIDA grant DA10277 and DA07244.

CHARACTERIZATION OF BUPRENORPHINE IN PIGEONS TRAINED TO DISCRIMINATE BUPRENORPHINE FROM SALINE

R. Galici, M. R. Brandt, and C. P. France

Department of Pharmacology, Louisiana State University Medical Center, New Orleans, LA

The discriminative stimulus effects of buprenorphine were evaluated in 6 pigeons trained to discriminate 0.178 mg/kg of buprenorphine from saline while responding under a fixed ratio 20 schedule of food presentation. With increasing doses of buprenorphine, pigeons switched responding from the saline to the buprenorphine key with a dose of 0.1 mg/kg occasioning > 90% drug-key responding; up to a dose of 10 mg/kg, buprenorphine did not alter rates of key pecking. Morphine, heroin and nalbuphine completely substituted for the discriminative stimulus effect of buprenorphine. Enadoline partially substituted for the buprenorphine discriminative stimulus effect in 2 pigeons and did not substitute in the other birds. The NMDA antagonist ketamine did not substitute for the discriminative stimulus effect of buprenorphine in any bird up to a dose of 10 mg/kg. The order of potency for discriminative stimulus effects was buprenorphine 2 nalbuphine > morphine. The buprenorphine and morphine ED_{50}s for discriminative stimulus effects were 373 and 4 times smaller, respectively, than the EDsos for decreasing rate of responding. The duration of action of buprenorphine (0.032-0.32) was dose-related and drugappropriate responding was not evident 24 hours later. Ten mg/kg of buprenorphine produced discriminative stimulus effects which lasted for 48 hours in some pigeons. Naltrexone prevented the discriminative stimulus effects of buprenorphine and morphine with equal potency; naltrexone fully reversed the discriminative stimulus effects of morphine and failed to reverse an established effect of buprenorphine. The long duration of action of buprenorphine and its pseudo-irreversible actions are thought to account for its apparent effectiveness in the clinic, though the specific mechanism that accounts for this unusual profile of effects is not fully understood.

ACKNOWLEDGMENT: Supported by USPHS grant DA 05018.

DIZOCILPINE MODIFIES THE RATE-DECREASING EFFECTS OF MORPHINE AND NALTREXONE IN LAAM-TREATED PIGEONS

C. A. Gauthier and C. P. France

Louisiana State University Medical Center, New Orleans, LA

There is a growing literature describing the effects of NMDA antagonists on tolerance to and dependence on morphine. Most of these studies have been conducted in rodents and have measured changes in tail flick latency or behavioral signs of precipitated withdrawal (i.e., jumping). In order to test the generality of these findings, the current study evaluated the effects of dizocilpine on changes in sensitivity to the rate-decreasing effects of morphine and naltrexone in 1-alpha-acetylmethadol (LAAM)-treated pigeons. Dose-effect curves for morphine and naltrexone were determined before, during and after periods of chronic treatment with either morphine (10-100.0 mg/kg/day) or LAAM (0.32-3.2 and 0.56-5.6 mg/kg/day) administered alone or in combination with dizocilpine (0.32 or 1.0 mg/kg/day). Tolerance to morphine and an increased sensitivity to naltrexone were demonstrated during treatment with morphine and LAAM. Tolerance to morphine and an increased sensitivity to naltrexone was attenuated when dizocilpine (1.0 mg/kg/day) was co-administered with LAAM, and not when a smaller dose of dizocilpine (0.32 mg/kg/day) was administered. These data suggest that concurrent administration of NMDA antagonists could attenuate the development of tolerance and dependence, under certain conditions. However the degree of tolerance and dependence might directly effect whether this interaction will occur. To the extent that these data are predictive of the interactions between NMDA antagonists and opioids in humans, they suggest that under some conditions, non-competitive NMDA antagonists might be useful as adjunct drug therapy in the management of opioid tolerance and dependence.

ACKNOWLEDGMENT: Supported by USPHS grant DA05018.

OPIOID ANTAGONISTS ATTENUATE THE BEHAVIORAL EFFECTS OF COCAINE AND AMPHETAMINE IN RATS: PROGRESSIVE RATIO ICSS

K. W. Easterling, R. J. Pearson, and S. G. Holtzman

Emory University School of Medicine, Atlanta, GA

While having only minor behavioral effects alone, lower doses (< 3.0 mg/kg) of the opioid antagonist naltrexone (NTX) can attenuate the effects of several non-opioid drugs of abuse (e.g., alcohol, cocaine, or amphetamine). The present experiments characterized the effects of cocaine (COC) and d-amphetamine (AMPH), alone or in combination with NTX, under a progressive ratio schedule of intracranial self-stimulation (ICSS). Adult male Sprague-Dawley rats (N=6) received bipolar electrodes aimed at the lateral hypothalamus and were then trained to press a lever to receive a 250 msec train of bipolar square-wave electrical stimulation (100 Hz, 6.5-80 μA). Once subjects acquired the behavior, contingencies required that progressively more lever presses be made to obtain each stimulation -- until responding ceased, thereby defining rewarding efficacy as behavioral "break point". After responding was stable (≅ 1.65 resp/sec, 10 sessions), a cumulative dose-respoase curve for NTX (1.0 - 56 mg/kp, SC was determined. Higher doses of NTX (10 - 56 mg/kg) significantly decreased ICSS response rates (≥ 50%) and the rewarding efficacy of the stimulation (breakpoint, ≥ 30%). When schedule contingencies supported lower baseline response rates (≅ 0.6 resp/sec), dose-response curves for COC (3.0 - 30 mg/kg, i.p), and AMPH (0.03 - 3.0 mg/kg, s.c.) were determined. Both COC and AMPH significantly increased ICSS response rates (≅ 3.4x) and increased breakpoints (≅ 4.5x). NTX (0.3 or 1.0 mg/kg) given 15 min prior to either COC or AMPH attenuated their effects on ICSS. Another opioid antagonist, naloxone (1.0 mg/kg) attenuated the effects of COC. Therefore, opioid antagonists attenuated the response-rate-increasing effects of COC and AMPH and their ability to enhance the rewarding efficacy of brain stimulation, as measured by progressive ratio breakpoint.

ACKNOWLEDGMENTS: Supported in part by NIH grants DA00541 and K05DA00008.

DAILY MORPHINE INJECTIONS SENSITIZE NIGRAL-LESIONED RATS TO TURNING INDUCED BY MORPHINE

L. A. Volpicelli, K. W. Easterling, H. L. Kimmel, and S. G. Holtzman

Emory University, School of Medicine, Atlanta, GA

Morphine-like opioids enhance dopaminergic activity in the nigrostriatal system indirectly and can induce turning in unilaterally nigral-lesioned rats. The objectives of this study were to determine 1) if morphine-induced turning increases progressively over the course of daily morphine (MOR) injections and 2) if this MOR regimen produces cross-sensitization to the effects of amphetamine or cocaine. Two groups (n = 7) of adult male Sprague-Dawley rats received daily s.c. injections of saline (SAL) or MOR (10 mg/kg). The MOR-treated group showed a significant and progressive increase in turning over the course of daily injections, while the SAL-treated group did not. After 14 days, a MOR dose-response curve (1.0 - 30 mg/kg) was determined. MOR produced dose-dependent increases in ipsilateral turning over a 4 hr period in both groups. However, the peak of the dose-response curve of the MOR group was higher than that of the SAL group, indicative of sensitization. While daily injections of SAL or MOR continued, dose-response curves for amphetamine (0.1-3 mg/kg) or cocaine (1.0-30 mg/kg) were determined. Both drugs produced equivalent dose-dependent increases in turning in the two treatment groups (i.e. no cross-sensitization). By the end of the study, 71 days after daily injections began, the MOR-treated group turned 6X more than the SAL group in response to a challenge injection of MOR (10 mg/kg).

ACKNOWLEDGMENTS: Supported in part by NIH grants DA00541 and K05DA00008

EFFECTS OF MORPHINE AND NALOXONE ON FIXED-RATIO AND PROGRESSIVE RATIO RESPONDING MAINTAINED FOOD OR FENTANYL IN RHESUS MONKEYS

J. R. Glowa and D. Stafford

Department of Pharmacology and Therapeutics, LSUMC, Shreveport, LA

These studies were undertaken to see if pretreatment with a mu agonist would decrease responding maintained by an opioid. Three adult male rhesus monkeys weighing 6.8-9 kg were maintained at 90% of their free-feeding weight and trained under either a multiple (mult) FR30 food, FR30 fentanyl, TO schedule or, a progressive-ratio (PR) schedule of fentanyl (0.03-1.0 µg/kg/inj, i.v.) delivery. Responding maintained at 'peak' unit doses of fentanyl under each procedure were used to assess the effects of morphine (0.03-5.6 mg/kg, i.m.) or naloxone (0.01 - 0.3 mg/kg, i.m.). The unit dose-effect function under the mult schedule was shaped like an inverted-U, low rates of responding occurred with unit doses of 0.03 µg/kg/inj and peak rates were maintained at either 0.1 (5TV) or 0.3 (8616) µg/kg/inj fentanyl. With higher unit doses, rates of fentanyl-maintained responding were decreased. When saline was substituted for fentanyl, rates of responding decreased almost completely. Rates of responding in the food component did not vary as a function of the unit dose of fentanyl , and were higher. When the peak unit dose of fentanyl (0.1 µg/kg/inj) was used to maintain responding, morphine decreased fentanyl-maintained responding while having little effect or no effect on food-maintained responding. Naloxone decreased both food- and fentanyl-maintained responding. Under the PR schedule of fentanyl delivery, the number of ratios completed for fentanyl monotonically increased with increasing unit dose of fentanyl (0.01 to 0.3 µg/kg/inj). When a unit dose of 0.3 µg/kg/inj fentanyl maintained PR responding, morphine dose-dependently decreased the number of ratios completed. In contrast, low-to-intermediate doses of naloxone had little effect on fentanyl-maintained PR responding, whereas a higher dose (0.1 mg/kg) decreased the number of ratios completed about 50%. These studies show that mu agonist morphine could selectively decrease fentanyl-maintained responding, whereas the effects of the opioid antagonist naloxone were less selective. These results are similar to previous reports showing dopamine agonists can selectively decrease cocaine-maintained responding, and support the notion that agonists can be used to decrease drug self-administration.

ACKNOWLEDGMENT: Supported by NIDA grant RO1 DA 09820.

EFFECTS OF NALTREXONE ON BEHAVIOR REINFORCED BY ORALLY DELIVERED METHADONE

N.-S. Wang, M. J. Macenski, and R. A. Meisch

Department of Psychiatry and Behavioral Sciences, UT-Houston, TX

The effects of naltrexone were studied on behavior reinforced by oral delivery of methadone in two rhesus monkeys. Methadone and water were available under concurrent FR 8 schedules during daily 3-hr sessions. Naltrexone doses (0.003, 0.01, 0.03 and 0.1 mg/kg, in an ascending-descending sequence of doses) were administered IM daily until behavior stabilized for six sessions. A block of saline administration separated each naltrexone dose. With M-NL, drug responding decreased as the naltrexone dose increased. Subsequently when the dose was decreased, there was a progressive increase in responding With M-JS, the greatest decrease (73%) occurred at 0.01 mg/kg dose. Subsequent doses resulted in a progressively less percent decrease in responding. At all test doses, methadone maintained responding was above the vehicle values. In a second experiment the methadone concentration was varied in the sequence: 0.1, 0.2, 0.4, 0.8, 0.4, 0.2, 0.1 mg/ml. For both monkeys there was an inverted U-relation between methadone concentration and number of drug deliveries. In M-NL, naltrexone (0.1 mg/kg) suppressed methadone reinforced responding. In M-JS, naltrexone (1.0 mg/kg) also decreased all methadone reinforced responding with the largest decrease at 0.2 mg/ml. Similar effects occurred with both the ascending and descending methadone concentration. Responding maintained by water was very low and was not systematically altered by either change in methadone concentration or the naltrexone dose. These two ex-periments showed that the responding maintained by orally delivered methadone was sensitive to naltrexone pretreatment.

ACKNOWLEDGMENT: Supported by NIDA grants DA 08398, DA 04972 and DA 00159.

COMPARSION OF HIGH VS LOW CONCENTRATION ETHANOL + METHADONE COMBINATIONS

K. L. Shelton, M. J. Macenski, and R. A. Meisch

Department of Psychiatry and Behavioral Sciences, SARC, University of Texas Health Science Center at Houston, Houston, TX

The reinforcing effects of combinations of orally self-administered ethanol + methadone were examined in 4 rhesus monkeys that failed to self-administer oral methadone alone. Ethanol concentrations of 1, 2, 4, 8, 16 and 32% were combined with .2 mg/ml methadone and compared to concurrently available water. under an FR 8 schedule in daily. 3 hr, sessions. All of these combinations were strongly preferred to water, with an inverted. U-shaped, dose-response function being observed. The 0.2 mg/ml methadone + ethanol combinations were then concurrently compared to one another. Higher ethanol concentration combinations were generally preferred to lower ethanol concentration combinations. In a second series of manipulations, combinations of 2% ethanol + .2, .4 and .8 mg/ml methadone were concurrently compared to water. All three combinations were preferred to water. When the combinations of 2% ethanol + methadone were compared to each other, the intermediate (0.4 mg/ml) methadone concentration combination was preferred to the high (.8 mg/ml) methadone concentration by all four animals. The results show that ethanol + methadone combinations are orally self-administered by monkeys and that orderly dose-response relationships can be generated. The findings also suggest that intermediate ethanol + methadone combinations are preferred to high and/or low concentration combinations.

ACKNOWLEDGMENTS: Supported by NIDA grant DA 08398, DA 04972 and DA 00159.

CHRONIC SCOPOLAMINE ATTENUATES REINSTATEMENT OF MORPHINE SELF-ADMINISTRATION BY MORPHINE OR PAIRED LIGHT PRIMING

F. Zhang, W. Zhou, Z. Wang, and G. Yang

Ningbo Institute of Microcirculation and Henbane, Ningbo, China

Two rhesus monkeys were trained to press lever for intravenous morphine self-administration on a daily 4 hr session, second order schedule FI10 min (FR10:S). No significant changes of total response rate and total morphine injection were found after 5 min pre-session treatment with scopolamine (0.001-0.075 mg/kg). However, when session began with a priming injection of morphine (0.25 mg/kg), 5 min pre-session treatment with scopolamine (0.025-0.25 mg/kg) caused a significant delay of morphine injection (156.8 ± 10.1 min). Considering the delayed morphine metabolism in the blood with a similar time course after scopolamine treatment as our another research showed, the present results suggested that mechanism of blood morphine transferring may play an important role in delaying morphine injection after scopolamine treatment when session began with a priming dose of morphine injection. Results also showed that chronic treatment with scopolamine could significantly attenuates the effects of both morphine priming and paired light priming to reinstate responding after chronic extinction under or not under the presence of ACTH or dexamethasone. This suggested that muscarinic cholinergic system played an important role in mediating the drug-seeking behavior.

USING MATCHING THEORY TO PREDICT THE DEGREE OF BEHAVIORAL TOLERANCE

J. Dallery, J. S. Lancaster, and T. S. Guest

Department of Psychology, Morris Brown College, Atlanta, GA

The economic context (i.e., an enriched vs. impoverished environment) affects many drug-induced phenomena. The present study examined if the economic context of operant responding predicts the degree of tolerance to the behavioral effects of amphetamine. Matching theory was used to quantify the economic context for each subject. Eight rats lever pressed for food reinforcement under several variable-interval (VI) schedules. Amphetamine was first administered acutely (0.2, 0.8, 1.6, and 3.2 mg/kg), then chronically (dose tailored for each subject) over thirty consecutive sessions. Control saline injections were also administered during the acute regimen. Hermstein's (1970) single-alternative matching equation described the rats' response rate data well under all conditions. A parameter in Herrnstein's matching equation *(r_e)* indexed the economic context for each subject under baseline conditions. The variability in the degree of tolerance between subjects was accounted for by the value of each subject's economic context index. Enriched environments reduced the degree of tolerance, while impoverished environments increased the degree of tolerance. In terms of the reinforcement loss hypothesis, the results suggest that tolerance is not determined by reinforcement loss per se, but by how much the animal loses relative to the economic context in which the operant task is embedded.

ACKNOWLEDGMENT: Supported by a NIDA, Minority Institutions Research Development Program grant 5R24DA07256-7.

IDENTIFICATION OF THE N-SUBSTITUENT CONFORMATION GOVERNING POTENCY AND MU RECEPTOR SUBTYPE-SELECTIVITY IN (+)-(3R,4R)-DIMETHYL-4- (3-HYDROXYPHENYL)PIPERIDINE OPIOID ANTAGONISTS

J. B. Thomas,[†] S. W. Mascarella,[†] R. B. Rothman,[‡] J. S. Partilla,[‡] H. Xu[†,‡] K B. McCullough[‡] C. M. Dersch,[‡] B. E. Cantrell[§], D. M. Zimmerman[§], and F. I. Carroll[†]

[†]Research Triangle Institute, Research Triangle Park, NC; [‡]NIDA Addiction Research Section, Baltimore, MD; and [§]Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN

A study of the binding site associated with the N-substituent of (+)-(3R,4R)-dimethyl-4-(3-hydroxyphenyl)piperidine **(4)** derivatives, which is proposed to be different from the site bound by the N-substituent of naltrexone, was undertaken using a set of rigid versus flexible N-substituents. The results showed that the high binding affinity, selectivity, and antagonist potency of N-propylphenyl or N-propylcyclohexyl analogs of (+)-(3R,4R)-dimethyl-4(3-hydroxyphenyl)piperidine **(4)** are achieved via a conformation wherein the N-substituent' connecting chain is extended away from piperidine nitrogen with the appended ring system rotated out-of-plane relative to the connecting chain atoms.

ACKNOWLEDGMENT: Supported by NIDA grant DA09045.

DESIGN OF A OPIOID RECEPTOR SPECIFIC PEPTIDOMIMETIC BASED ON THE PHARMACOPHORE OF A OPIOID PEPTIDE

V. J. Hruby[+], S. Liao[+], J. Alfaro-Lopez[+], P. Davis[‡], K. Hosohata[‡], F. Porreca[‡], and H. I. Yamamura[‡]

Departments of Chemistry[+] and Pharmacology[‡], University of Arizona, Tucson, AZ

Opioids currently utilized for the treatment of pain have toxic side effects including constipation and respiratory depression. These side effects appear to be related to their μ opioid receptor selectivity. We have been developing potent, receptor selective, and biologically stable peptide agonist analogues of the enkephalins and deltorphins selective for the δ opioid receptor using conformational and topographical constraints. De novo design of potent, receptor selective, and stable non-peptide agonist ligands based on a peptide pharmacophore has proven to he difficult. On the basis of the three dimensional bioactive pharmacophore conformation for the highly potent and δ opioid receptor selective, topographically constrained cyclic enkephalin analogue c[(2S,3R)TMT[1],DPen[2],-DPen[5]]enkephalin, we have designed, de novo, a series of non-peptide peptidomimetics that can mimic key pharmacophore elements including the Tyr[1] phenol group, the Phe[4] phenyl group, the α-amino group, and the bulky hydrophobic substituents in the 2 and 5 position, using a piperazine scaffold. A series of 1,4-disubstituted piperazine analogues with increasing lipophilic bulky substituents in the l-position lead to the design and syntheses of SL-3111 which has 8nM binding affinity for the δ opioid receptor, nearly 2000 fold selectivity for the δ opioid receptor, and agonist activity in the MVD assay. Based on its structure-activity relationships and on its interactions with site specific mutant receptors, the new δ ligand's bioactivities paralleled peptide but not non-peptide biological activities. Careful attention to both conformational and topographical properties are necessary for de novo design.

ACKNOWLEDGMENTS: Supported by grants from the U.S. Public Health Service (NIDA) DAO6284 and DAO8657.

DELTA OPIOID SELECTIVITY OF *N*-SUBSTITUTED NOROXYMORPHINDOLES

S. D. McLamore*, A. Coop*, C. M. Dersch[±], K. McCullough[±], R. Horel[±], R. B. Rothman[±], and K. C. Rice*

LMC, NIDDK, NIH, Bethesda, MD[*] and Clinical Psychopharmacology Sect. IRP, NIDA, NIH, Baltimore, MD[±]

Naltrindole (NTI) is a potent and selective, non peptide δ opioid receptor antagonist introduced by Portoghese and coworkers in 1988. It has been proposed that the binding of NTI and the enkephalins to δ receptors involves similar arrangement of the aromatic rings. Of the three opioid receptors (μ, κ and δ) the functions of the δ receptors are least understood. Accordingly, the discovery of NTI has provided a significant tool for study of δ receptors. In an effort to prepare compounds with improved selectivity, we have investigated the effects of altering the basic *N*-substituent of noroxymorphinindole. The nature of the *N*-substituent is known to have a dramatic effect on the pharmacological profiles of many classes of opioids, but has not been thoroughly studied for this series of compounds. Recent findings Dondio and coworkers indicated that *N*-Et substituted naltrindole-like compound displayed a greater δ selectivity than the traditional N-Me or N-CPM derivatives. This suggest that the traditional *N*-substituents may not produce optimal for δ selectivity for these compounds. The results of this study suggest that the N-substitiuent has a major effect on the δ selectivity and affinity in the indole 4,5-epoxymorphinan series. Furthermore, the results indicate that an increase in the carbon chain length causes a decrease in selectivity and a maximum selectivity was observed when a carbon length of 2-3 was employed. Finally, we concluded that the *N*-methylallyl substituted compound appears to be one of the most selective morphinans described thus far.

DESIGN AND PHARMACOLOGICAL PROPERTIES OF A NOVEL KAPPA-OPIOID AGONIST, TRK-820

K. Kawarnura, K. Kawai, H. Hayakawa, Y. Takezawa*, H. Matsuura*, C. Tajima*, T. Endo*, and H. Nagase

Department of Medicinal Chemistry, *Department of 2nd Pharmacology, Basic Research Laboratories, Toray Industries, Inc., Japan

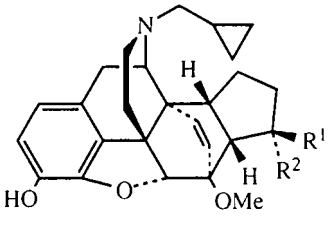
A structurally novel kappa-opioid agonist, (-)-17-cyclopropylmethyl-3,14b-dihydroxy-4,5a-epoxy-6b[*N* -methyl-*trans*-3-(3-furyl)acrylamido]morphinan hydrochloride (TRK-820), was designed and synthesized by applying two working hypothesis: the "Message-address concept" for opioid antagonist and the "Accessory site hypothesis" in the structural relationship between agonist and antagonist on G-protein coupled receptor. The kappa-agonist TRK-820, modified from kappa-opioid antagonist nor-BNI, has a structure corresponding to a Tyr-Gly moiety of endogenous opioid peptides in its 4,5-epoxymorphinan core as an opioid message moiety and a suitable length of C6-*N*-methylamide side chain as an opioid address moiety for kappa-receptor. Thus, the structure of TRK-820 is different from prototypical kappa-opioid agonists having a N-C-C-N(SP2) pharmacophore sequence such as U-50488H. TRK-820 exhibited high potency and kappa-selectivity in GPI(IC50=0.0048nM) and MVD(IC50=0.036nM) preparation[Ke ratio: mu(GPI)/kappa(GPI)=279, delta(MVD)/kappa(GPI)=517]. On acetic-acid-induced writhing model (Ac-WR) and tail flick model in mice, antinociceptive effects of TRK-820 were 85-140 times more potent than morphine and 85-350 times more potent than U-50488H. Interestingly, this kappa-agonist, TRK-820, showed neither aversion nor preference in the CPP test (rats) within the dose range, 0.003-0.3mg/kg s.c.[ED50=0.0033mg/kg s.c.(Ac-WR)], in spite of U-50488H showed severe aversion within the dose range, 0.3-10mg/kg s.c.[ED50= 1.16mg/kg s.c.(Ac-WR)]. Consequently, we successfully applied the "Message-address concept" for opioid antagonist to opioid kappa-agonist by combination with the "Accessory site hypothesis".

ETHERS OF RING-CONSTRAINED ORVINOLS. REQUIREMENTS FOR OPIOID RECEPTOR AGONIST ACTIVITY IN THE ORVINOL SERIES

J. W. Lewis, C. E. Miller, and A. Coop

School of Chemistry, University of Bristol, UK; Laboratory of Medicinal Chemistry, NIDDK, NIH, Bethesda, MD

In studies of constrained analogues of buprenorphine, the 7,8-cyclopentanol derivatives **(1, 2)** were shown to have k/d-agonist activity in *in vitro* assays. *In vivo* the differences between the epimers was quite marked with only 1 showing k-agonist effects. It was of interest to investigate the effect of masking the 20-OH group in 1 and 2 by O-alkylation. Thus ethers (3-6) were prepared and evaluated in opioid receptor binding assays in guinea pig brain homogenates and in MVD and GPI. The epimeric ethoxy derivatives **(3, 4)** showed high affinity non-selective binding, k-agonism in GPI and m/d-antagonism in MVD. The effect of masking the OH group in **1** was to substantially reduce both k and d efficacy, whereas similar masking in 2 also reduced d efficacy, but appeared to have relatively little effect on k efficacy. The iso-butyl and benzyl ethers of **1** resembled buprenorphine in having non-reversible agonist activity in the functional assays.



1 R^1 = OH, R^2= H 2 R^1 = H, R^2= OH
3 R^1=OEt, R^2= H 4 R^1 = H, R^2 = OEt
5 R^1 = O^{i}Bu, R^2 = H
6 R^1 = OBn, R^2 = H

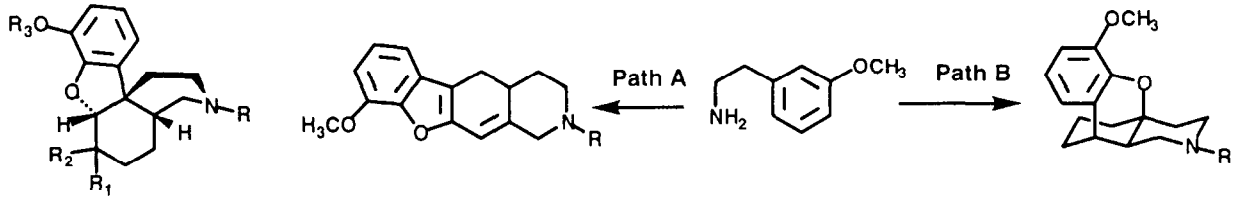
ACKNOWLEDGMENT: Supported by NIDA grant DA-07315 and NIDA contract 8307 (SRI).

SYNTHETIC STUDIES TOWARD THE OCTAHYDROBENZOFURO[3,2-e]ISOQUINOLINES

T. Fursy, J. L. Flippen-Anderson, and K. C. Rice*

LMC, NIDDK, NIH, Bethesda, MD and *NRL, Washington, DC

Development of synthetic methodology for numerous classes of compounds related to morphine has continued to attract much attention. Compounds of the general structure 1 containing a tetracyclic ring system show significant opioid activity. Several methods for the preparation of 1 and related derivatives have been developed, where O-ring closure is a major step in their construction. In continuation of our research in using intramolecular electrophilic Grewe type cyclization for O-ring formation, we now report application of the reaction in an approach to novel synthesis of the isomeric ring system 2 and 1 from the commercially available 3-methoxyphenethyl amine. The structures of synthesized compounds were unambiguously established by X-ray analysis. and revealed the *trans*-decahydroisoquinoline configuration of 3 (R=H) as the oxalate salt.



1 2 3

SYNTHESIS OF 14-(3'-PHENYLPROPYL) OPIOID LIGANDS AND THEIR BINDING ON THE OPIOID RECEPTORS

*X. Tian, C. M. Dersch†, K. McCullough†, R. Horel†, R. B. Rothrnan†, and K. C. Rice**

LMC, NIDDK, NIH, Bethesda, MD and †Clinical Psychopharmacology Sect. IRP, NIDA, NIH, Baltimore, MD

Naltrindole (NTI) is the first non-peptide delta opioid antagonist which was designed based on the message-address concept and has become an important pharmacological tool. NTI shows high affinity and reasonable selectivity for the delta receptor. Many attempts have been centered around the structural modification of NTI to improve the affinity and selectivity. The effect of a 14-hetero substituent (O, N, S) on the pharmacological profile of opioid ligands has been extensively investigated. In contrast, only a few C14 alkyl substituted examples appear in the literature. It has been found that the introduction of a simple alkyl group (i.e. ethyl) at the 14-position of morphinone greatly increases its agonist potency. During the continuing study on potent and selective opioid receptor ligands, we have synthesized 14-(3'-phenylpropyl)-dihydrocodeinone, dihydromorphinone, their N-cyclopropylmethyl analogs and the corresponding indole derivatives by using a thebaine Diels-Alder reaction with phenyl vinyl ketone. The binding data of these ligands indicate that replacement of the 14-hydroxyl function of NTI by a 3'-phenylpropyl group dramatically reduces the binding affinity and selectivity on delta receptor.

AMINO ACID SUBSTITUTIONS OF THE TERMINAL TYROSINE IN THE CYCLIC TETRAPEPTIDE JOM-6

I. J. McFadyen*†, M. J. Schaefer*, H. I. Mosberg#, J. R. Omnaas#, K. Sobczyk-Kojiro#, J. C. Ho#, and J. R. Traynor* †

Schools of *Medicine and #Pharmacy, University of Michigan, Ann Arbor, MI and †Department of Chemistry, Loughborough University, Leics UK

JOM-13 is a cyclic tetrapeptide constrained by a disulfide linkage which has good selectivity for the δ-- over μ-opioid receptors. Conversion of this linkage to the dithioether and amidation of the terminal carboxyl group (to afford JOM-6) reverses the selectivity (μK_i 0.3nM; δ K_i 25nM). In order to investigate conformational features of the pharmacophore elements in the μ receptor-bound state the *in-vitro* pharmacology of JOM-6 and derivatives in which the terminal Tyr has been replaced with various amino acids has been studied. Compounds were evaluated for affinity in ligand binding assays at cloned μ and δ opioid receptors and for efficacy using a [^{35}S]-GTPγS binding assay at the μ receptor. Replacement of the Tyr in JOM-6 with Phe still gave a potent p-agonist (K_i 24nM. EC_{50} 19nM), but this activity was lost if the dithioether linkage was replaced with a direct disulfide link. Replacement of the Phel with cyclohexylalanine only reduced activity slightly (K_i 33nM, EC_{50} 74nM), but replacement with diphenylalanine or phenylglycine was detrimental.

JOM-6 Tyr-[D-Cys-Phe-D-Pen]NH_2

└─S-(CH2)2-S─┘

ACKNOWLEDGMENTS: Supported by DA 00254, DA 03910 and the EPSRC UK.

MORPHINAN CYCLIC PYROLLIDINES: IN VIVO SELECTIVITY AND EFFICACY AT OPIOID RECEPTORS

S. M. Husbands*, S. Breedon*, C. L. Neilan, J. H. Woods, J. Broadbear, J. R. Traynor, and J. W. Lewis*

***School of Chemistry, University of Bristol, Bristol, England, UK and Department of Pharmacology, University of Michigan, Ann Arbor, USA**

We have reported previously that morphinan derivatives BU72 and BU74 are of high potency in the GPI while only BU72 is a potent agonist in MVD, BU74 displaying only partial agonism and potent antagonistic effects in this preparation. Of interest was the pseudo-irreversible nature of the agonism, with no standard opioid antagonists able to reverse the effects. We have recently found (C. L. Neilan *et al,* this meeting) that BU72 is an extremely potent μ-agonist *in-vivo,* again displaying an antagonist resistant profile and long duration of action. As a potential treatment for opiate abuse/dependence, we felt that the lower efficacy of BU74 would be desirable and thus have studied the *in-vivo* profile of BU74. Results indicate that the agonist activity of BU74 in the mouse tail withdrawal assay is antagonist resistant, while in the abdominal stretch assay BU74 is in fact a κ agonist. Thus the simple exchange of a NMe group in BU72 for a NCPM group in BU74 appears to have caused a total loss of μ-agonist activity resulting in a κ-agonist profile. We also prepared the *p*-Me derivative of BU72, due to our findings in the related series of 14-cinnamoylamino ligands (eg MC-CAM etc.) where a *p*-Me group was the moiety most associated with μ antagonism. In the current series introduction of a *p*-Me substituent appears to have had little or no effect on the profile, with *p*-Me BU72 also displaying long lived, highly efficacious agonist activity, followed by extremely long duration antagonist effects.

ACKNOWLEDGMENTS: Supported by NIDA grant 073 15 and 00254.

SYNTHESIS OF TRITIUM LABELLED SR144528 BY METALLATION AND tri-n-BUTYLTIN TRITIDE QUENCHING

H. H. Seltzman, M. C. Foster, C. D. Wyrick, and F. I. Carroll

Research Triangle Institute, Research Triangle Park, NC

The selective antagonist for the peripheral cannabinoid receptor (CB2), recently introduced by Sanofi Recherche, was synthesized by two approaches that differed from that reported by Sanofi. The first involved condensation of the appropriate 2,4-diketoester with 4-methylbenzylhydrazine followed by amidation. The second employed unsubstituted hydrazine, followed by amidation and final benzylation. A new tritiation approach was developed for this compound to circumvent the problematic catalytic tritium reduction which results in cleavage of the chlorine atom as well as debenzylation. This new method involved dimetallation of SR144528 at the pyrazole C-4 and at the benzylic carbon with n-butyllithium followed by quenching with tri-n-butyltin tritide as a tritium acid. Model studies with tri-n-butyltin deuteride showed deuterium incorporation at the C-4 and benzylic sites by NMR, and an incorporation level that would be equivalent to specific activities ranging from 15 to 45 Ci/mmol depending on the ratio of tri-n-butyltin deuteride to dimetallated SR144528 employed. The corresponding procedure with tri-n-butyltin tritide afforded the tritiated ligand at a specific activity of 0.35 Ci/mmol, likely due to competing quenching of the metallated SR144528 by contaminating moisture. A quenching with higher ratios of tri-n-butyltin deuteride to dimetallated SR144528 under strict control of anhydrous conditions is anticipated to provide the high specific activity tritiated ligand for pharmacological studies.

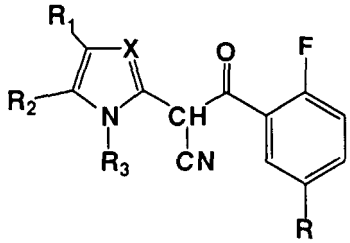
ACKNOWLEDGMENT: Supported by NIDA N01DA-6-7054.

SUBSTITUTED HETARYLACETONITRILES AS A POTENT NON-NUCLEOSIDE ANTI-HIV AGENTS

A. Nemazany, B. L. Robeson, and K. C. Rice*

LMC, NIDDK, NIH, Bethesda, MD and *Starks C.P., Rockville, MD

Problems with the clinically approved anti-HIV drugs which are nucleosides involve toxicity, significant side effects and high cost. Also, the development of these agents has been limited by the difficulties in synthetic modification of such molecules. By contrast, the non-nucleoside anti-HIV agents exhibit structural diversity and their chemical synthesis is generally less complicated. Recently, imidazole derivatives have been recognized as an antiviral agents. In order to further explore this class compounds, we report the synthesis and anti-HIV *in vitro* activity of the new substituted hetarylacetonitriles 1. The compound 1 (R=H, R1,R2=C6H4, R3=H) shows moderate anti-HIV activity and thus provides a lead for further development of potential anti-HIV agents.



ACKNOWLEDGMENT: Supported by the National Cancer Institute's Drug Discovery Program.

GENERATION OF MONOCLONAL ANTIBODIES TO THE KAPPA OPIOID RECEPTOR

L. E. McCarthy*, W. K. Long*, L.-Y. Liu-Chen, T. K. Eisenstein*, M. W. Adler, and T. J. Rogers*

Departments of *Microbiology and Immunology, and Pharmacology, Temple University School of Medicine, Philadelphia, PA

Opioid peptides and alkaloids can modulate a variety of immune functions. The effects of opioids are partly attributed to the activation of opioid receptors on cells of the immune system. Radioligand binding studies generally support the existence of opioid receptors on immune cells, though inconsistencies are reported. Recently, RT-PCR has shown that immune cells express mRNA for opioid receptors, but it does not necessarily establish the presence of cell surface receptors. Therefore, a method enabling detection of cell surface opioid receptors would be useful. Currently, we are generating monoclonal antibodies specific for the kappa opioid receptor. The second extracellular loop of the kappa receptor was selected for use as an antigen because this domain exhibits significant dissimilarity among receptor subtypes as well as very highly conserved sequence homology among the mouse, rat, and human. Following repeated immunizations of Balb/c mice with the E2 loop peptide-KLH, splenocytes were harvested for hybridoma production. Culture supernatants from these hybridomas were assessed for immunoreactivity to the E2 loop of the kappa receptor. Antibodies from immunoreactive hybridomas will be utilized in conjunction with a FITC-labeled anti-mouse IgG mab to detect surface kappa opioid receptors on immune cells by flow cytometry.

ACKNOWLEDGMENT: Supported by NIDA grants DA06650, DA11130 and T32DA07237.

THE EFFECTS OF A KAPPA-OPIOID RECEPTOR AGONIST ON T-LYMPHOCYTE DIFFERENTIATION

J. K. Sliker*, T. K. Eisenstein*, M. W. Adler, and T. J. Rogers*

Departments of *Microbiology and Immunology, and Pharmacology, Temple University School of Medicine, Philadelphia, PA

Endogenous and exogenous opioids have been shown to exert a direct effect on both the central nervous system and the immune system. Previous studies from this laboratory have shown that k-opioid receptor mRNA is present in the immature murine T-cell lines R1.1 and DPK. DPK cells express both CD4 and CD8 and differentiate to the $CD4^{+}CD8^{-}$ stage following stimulation with the superantigen staphylococcal enterotoxin A (SEA). These cells also exhibit an increase in the expression of MHC class I and a decrease in the expression of the heat stable antigen (HSA) upon exposure to SEA. The alterations in the expression of these cell-surface molecules and the presence of kappa-opioid receptor mRNA in these cells led us to examine the effects of the k-opioid receptor agonist, U50,488H, on SEA-stimulated DPK cells. We have used RNase protection analysis to detect the expression of cytokine, cytokine receptor, and chemokine mRNA levels in DPK cells following treatment with U50,488H and/or SEA in the presence of antigen presenting cells (APCs). Our results show that DPK cells produce little cytokine or chemokine mRNA. However, after stimulation with superantigen, levels of cytokine receptors IL-2Ra, IL-2Rb, IL-7Ra, and IL-15Ra mRNAs are elevated. We report here that treatment with U50,488H results in significant modulation of cytokine receptor expression.

ACKNOWLEDGMENT: Supported by NIDA grants DA06650, DA11130 and T32DA07237.

MORPHINE INHIBITS MHC CLASS II EXPRESSION AND ANTIGEN PRESENTATION IN MOUSE CELLS

J. J. Meissler, Jr., M. E. Hilburger, T. J. Rogers, M. W. Adler, and T. K. Eisenstein*

Departments of Microbiology and Immunology and *Pharmacology, Temple University School of Medicine, Philadelphia, PA

Mice implanted with slow release 75 mg morphine pellets have previously been shown to have impaired capacity of their spleen cells to make in vitro antibody responses to sheep red blood cells and reduced ability of their peritoneal macrophages to phagocytize pathogenic yeast. In the present studies, using flow cytometery. peritoneal cells of morphine-treated mice were shown to have decreased expression of MHC class II antigens and to have reduced capacity to present the antigen hen egg white lysozymc (HEL) to a T-cell hybridoma (3A9) which responds to this antigen. Simultaneous implantation of a naltrexone pellet with the morphine pellet blocked the suppressive effect. A similar protocol of morphine treatment was tested for the effect on spleen cell expression of MHC class II antigen and presentation of the antigen pigeon cytochrome C (PCC). Morphine was found to suppress spleen cell class II expression and to inhibit antigen presentation, and naltrexone blocked the suppression. Thus. morphine given in vivo suppresses the capacity of antigen-presenting cells to present antigen to T-cells. providing at least one mechanism by which morphine induces immunosuppression.

ACKNOWLEDGMENTS: Supported by NIDA grants DA06650 and T32 DA07237.

IMMUNE, ENDOCRINE, AND BEHAVIORAL EFFECTS OF PRECIPITATED AND DEPRIVATION-INDUCED WITHDRAWAL IN LAAM-TREATED MONKEYS

N. C. Alonzo, D. J. J. Carr, and C. P. France*

Departments of Pharmacology and Microbiology, Immunology and Parasitology*, Louisiana State University Medical Center, New Orleans, LA

Naltrexone-precipitated withdrawal and deprivation-induced withdrawal were compared using measures of immune function, plasma cortisol concentration, body temperature, and discriminative behavior in rhesus monkeys receiving 1.0 mg/kg of 1-alpha-acetylmethadol (LAAM) s.c twice daily and discritninating between saline and 0.0178 mg/kg of naltrexone under a schedule of stimulus-shock termination. When LAAM-treated subjects received 0.1 mg/kg of naltrexone, they responded >90% on the naltrexone lever; however, when daily LAAM injections were replaced by vehicle, monkeys responded a maximum of 60% on the drug lever. Naltrexone had no effect on mitogen-induced IFNγ, IL-10, or IL-12 production; however, there was a significant increase in natural killer (NK) cell cytotoxicity and a decrease in the percentage of $CD4^+$ lymphocytes after 0.1 mg/kg of naltrexone. In contrast. drug deprivation had no effect on mitogen-induced IL-12 production, NK activity, or the percentage of $CD4^+$ lymphocytes, while mitogen-induced IFNγ and IL-10 production significantly increased. There was a trend towards a decrease in body temperature and an increase in plasma cortisol levels after administration of naltrexone and not during LAAM deprivation. These data collectively demonstrate both qualitative and quantitative differences between antagonist-precipitated and deprivation-induced opioid withdrawal; they further suggest that acute (precipitated) withdrawal studies might not be predictive of the physiologic and behavioral conditions that emerge when LAAM treatment is terminated.

ACKNOWLEDGMENTS: Supported by USPHS grants DA05018 and US35470.

PRENATAL NICOTINE CAUSES LONG-TERM IMMUNOSUPPRESSION IN RAT OFFSPRING

H. Navarro, K. Basham, A. Adcock, W. Ross, M. E. Brust, and P. Basta

Research Triangle Institute, Research Triangle Park, NC

Prenatal nicotine exposure in rats is known to alter offspring development causing peripheral functional deficits, especially in organ systems under sympathetic nervous system (SND) control. Since the SNS plays an important role in normal immune function, we determined the effects of prenatal nicotine on the development of immune responsiveness. Time-mated rats were exposed to nicotine (6 mg/kg/day via minipump; gestational days [GD] 4-20) or vehicle and the development of splenocyte responsiveness to Con A (1 ug/mL) or LPS (50 ug/mL) stimulation was measured by [^{3}H]thymidine incorporation on postnatal days (PND) 9, 15, 22, 29, 64 and 86. These results were compared to the effects of gestational ethanol exposure (15% wt:vol in drinking water; GD 10-19) which is known to disrupt normal development of immune function. Nicotine caused consistent and long-lasting suppression of splenocyte proliferation following either ConA or LPS exposure. [^{3}H]thymidine incorporation was decreased 53-58% during the first two postnatal weeks and remained 50-60% below normal in adulthood (PDN 64 and 86). These deficits were similar in magnitude to those caused by ethanol. Our results indicate prenatal nicotine exposure has the potential to permanently compromise offspring immune function.

GLUCOCORTICOID SELF ADMINISTRATION IN RHESUS MONKEYS

J. H. Broadbear, G. D. Winger, T. J. Cicero, and J. H. Woods*

Department of Pharmacology, University of Michigan, Ann Arbor, MI and *Department of Psychiatry, Washington University, St. Louis, MO

In rats, corticosterone maintains self-administration (SA) behavior (Piazza *et al.,* 1993). There are also a number of cases reported in the human literature in which glucocorticoids have beer abused, leading to dependence, withdrawal and relapse (e.g. Dixon and Christy, 1980). This study investigated wnether glucocorticoids would maintain SA behavior in monkeys. Four male rhesus monkeys (Macaca mulatta), each with a surgically-implanted venous catheter, were used in this study. The baseline was 0.1 mg/kg/inj methohexital or saline, with a fixed-ratio 10 time-out 10 (FR 10 TO 10) schedule. The glucocorticoids tested were hydrocortisone (0.001-3.0 mg/kg/inj), methyl prednisolone (0.01-1.0 mg/kg/inj) and dexamethasone (0.03-0.3 mg/kg/inj). Preliminary studies indicated that dexamethasone (0.3 mg/kg/inj) was initially self-administered by 3 of 4 monkeys, but not on subsequent occasions. One in 4 monkeys self-administered methyl prednisolone (1.0 mg/kg/inj) but only the first time it was offered. Hydrocortisone did not maintain responding above saline rates. In humans, dexamethasone is potent, long-acting and selective for glucocorticoid over mineralocorticoid receptors; methyl prednisolone is somewhat less so. Hydrocortisone, on the other hand, is short-acting and non-selective. The examination of dexamethasone suppression of HPA activity in these monkeys indicated that its long duration of action may have interfered with testing. Subsequently, blood was drawn each morning and cortisol was measured by RIA to determine that normal basal HPA activity had resumed prior to each glucocorticoid substitution. Of the four monkeys tested in this later series of experiments, one reliably self-administered dexamethasone and methyl prednisolone.

REFERENCES: Dixon, R. B. and Christy, N. P. On the various forms of corticosteroid withdrawal syndrome. Am J Med 68:224-230, 1980.

Piazza, P. V.; Deroche, V.; Deminiere, J-M.; Maccari, S.; Le Moal, M.; and Simon, H. Corticosterone in the range of stress-induced levels possesses reinforcing properties: Implications for sensation-seeking behaviors. Proc Natl Acad Sci USA 90:11738-11742, 1993.

ACKNOWLEDGMENT: Supported in part by USPHS Research grant DA 09161.

COCAINE PRE-EXPOSURE ENHANCES ACQUISITION AND PROLONGS EXTINCTION OF FOOD REINFORCED RESPONDING IN FISCHER 344 RATS

T. A. Kosten, T. J. GrandPre, and C. N. Haile

Department of Psychiatry, Yale University School of Medicine, New Haven, CT

Acquisition and extinction of drug self-administration (SA) are models of drug abuse liability and relapse. Lewis (Lew) rats more readily acquire cocaine (Coc) SA compared to Fischer 344 (F344) rats with no strain differences in extinction. Because this may reflect learning differences, we examined acquisition and extinction of foodreinforced responding. Since drug pre-exposure enhances acquisition of drug SA in outbred rats, we assessed the effects of Coc pre-exposure (30 mg/kg IP/hr for 3 hr for 3 d) vs saline exposure. F344 rats show greater corticosterone (CORT) responsivity than Lew rats and Coc increases CORT levels. Thus, we examined the effects of metyrapone (MTP; 100 mg/kg SC in DMSO), a CORT synthesis inhibitor, pretreatment in F344 rats. Finally, because locomotor sensitization to psychostimulants is stronger if there is a delay between drug exposure and testing, other F344 rats began training 25 days after Coc exposure. Rats were given access to operant chambers (Coulbourn) for 30 min/d, 5 d/wk and allowed to bar press for food (45 mg; Bio-Serv) on a continuous reinforcement schedule (50 pellets/session max). After 24 acquisition sessions, food was removed for 8 extinction sessions and restored for 3 reinstatement days. Acquisition of food-reinforced responding was enhanced by Coc pre-exposure in F344, but not Lew rats. Coc exposure also led to prolonged extinction responding, resembling "frustrative non-reward" or a partial reinforcement extinction effect in F344, but not Lew rats. There were no strain or Coc effects on reinstatement. MTP attenuated these effects of Coc. Finally, the fastest rates of acquisition and extinction were seen in F344 rats that had a delay between Coc exposure and training. Coc may overactivate glucocorticoid receptors in hippocampus or other areas causing neuronal atrophy. Alternatively, Coc pre-exposure may enhance the saliency of context cues in F344 rats. These data suggest that drug "craving" may reflect Coc-induced alterations in ability to extinguish appetitive responses.

ACKNOWLEDGMENT: Supported by NIDA 04060.

STRESS MODULATES REPEATED COCAINE-INDUCED BEHAVIOR IN A SEXUALLY DIMORPHIC MANNER

R. Sircar, S. Biswas, T. Scipione, S. Bennett, and S. Schwimmer

Laboratory for Developmental Neuroscience, Departments of Psychiatry, Neurology, Pathology, Albert Einstein College of Medicine, Bronx, NY

Both repeated exposure to psychostimulants (cocaine, amphetamine) and stressors (novel environment, restraint, repeated foot shock) produce behavioral sensitization. The present study explored the effects of exposure to cold water stress prior to cocaine administration on acute as well as repeated cocaine behavior in male and estrogenprimed progesterone-treated ovariectomized (OVX+EB/P) female rats. Male and OVX+EB/P female Sprague Dawley rats were divided into two groups one group was subjected to cold water stress while the other group remained in their home cages All rats received five days of cocaine (15 mg/kg, i p.) and behavioral scoring was done on Day I (first day of cocaine injection), Day 5 (last day of cocaine injection) and Day 15 (10-day withdrawal) For cold water stress, each animal was placed individually in cold water at 2-6°C for 5 min. Following cold water stress, rats were dried and injected with cocaine in the test cage. Control rats received daily cocaine without any stress exposure As reported earlier (Sircar *et al.,* Soc. Neuro. Abs 23 (2) 430 17, 1997), both male and OVX+EB/P female rats exhibited acute cocaine-induced increase in behavioral score as well as repeated cocaine-induced behavioral sensitization, and the OVX+EB/P rats scored higher than the males on both behavior Stresspretreatment significantly increased acute cocaine scores in both male and OVX+EB/P female rats Behavioral scores of male rats treated daily with cocaine and pre-exposed daily to cold water stress showed significant reduction in behavioral scores on Day 5 and Day 15 compared to Day 1. In the female OVX+EB/P rats, the scores on Day 1, Day 5 and Day 15 did not differ from each other. Pre-exposing rats to cold water stress daily prior to cocaine administrations inhibited repeated cocaine-induced behavioral sensitization in female rats and induced significant behavioral tolerance in male rats.

THE EFFECT OF SALINE SUBSTITUTION TESTS ON PLASMA CORTICOSTERONE IN RATS TRAINED TO SELF-ADMINISTER COCAINE

R. L. Peltier, G. F. Guerin, N. R. Dorairaj, B. D. Irby, and N. E. Goeders

Departments of Pharmacology and Therapeutics and Psychiatry, LSU Medical Center, Shreveport, LA

Previous research from this laboratory has explored the role of the hypothalamic-pituitary-adrenal (HPA) axis in the reinforcing and discriminative stimulus effects of cocaine. For example, we found that noncontingent electric footshock facilitates the acquisition of cocaine self-administration. The current experiments were designed to further determine the involvement of the HPA axis in the reinforcing properties of both cocaine and food. Male Wistar rats were first implanted with indwelling jugular catheters, after which they were trained to self-administer cocaine (0.125, 0.25 or 0.5 mg/kg/inf) under a multiple, alternating (cocaine/food) schedule of reinforcement. Training and testing sessions lasted for 2 hr, during which time either cocaine (fixed-ratio; FR 4), or food (FR10) was available as a reinforcer. When baseline self-administration behavior did not vary by more than 10% over three consecutive days, saline was substituted for cocaine. At the end of the saline substitution tests, plasma was taken through the intravenous catheters and plasma corticosterone was measured using radioimmunoassays. There was a significant decrease in the total number of saline infusions obtained in a single session for the lowest dose of cocaine tested (0.125 mg/kg), and a significant increase in the total number of saline infusions obtained in a single session for the highest dose of cocaine tested (0.5 mg/kg). In contrast, there were no significant differences in plasma corticosterone levels.

ACKNOWLEGMENT: Supported by USPHS grant DA06013 from NIDA.

ETOCONAZOLE BLOCKS THE REINSTATEMENT OF EXTINGUISHED COCAINE-SEEKING BEHAVIOR BY ELECTRIC FOOTSHOCK BUT NOT COCAINE IN RATS

*J. R. Mantsch and N. E. Goeders**

Departments of Pharmacology and Therapeutics and *Psychiatry, Louisiana State University Medical Center, Shreveport, LA

The role of corticosterone (CORT) in the reinstatement of extinguished cocaine-seeking behavior by electric-footshock (EFS) and cocaine was investigated. Male Wistar rats were implanted with jugular catheters and trained to self-administer cocaine (0.5 mg/kg/inf, iv) by pressing a lever under a fixed-ratio 4 schedule of reinforcement with a 90-sec lmited hold during daily 2-hour sessions. After 15 days of stable self-administration, this behavior was extinguished by presenting no consequences of lever-pressing for 10 consecutive sessions. Following extinction, the ability of intermittent EFS (15 min) or cocaine (0 - 20 mg/kg, ip) to reinstate behavior previously reinforced by cocaine was determined by presenting these stimuli prior to the subsequent sessions. EFS and cocaine (10 and 20 mg/kg, ip) both produced significant reinstatement as observed by increased responding on the cocaine lever compared to the previous extinction sessions. The role of CORT in the reinstatement of cocaine-seeking behavior by EFS and cocaine was investigated using the CORT synthesis inhibitor/Type II receptor antagonist ketoconazole (KETO). KETO (25 and 50 mg/kg, ip) prevented the reinstatement by EFS but not cocaine despite significantly attenuating the CORT responses to both stimuli. The relationships between EFS- and cocaine-induced reinstatement and the discriminative stimulus effects of cocaine were also investigated. KETO (25 or 50 mg/kg) failed to block the ability of cocaine (0 - 20 mg/kg, ip) or EFS to generalize to 10 mg/kg cocaine in rats trained to discriminate the drug from saline.

ACKNOWLEDGMENT: Supported by NIDA USPHS grants DA06013 and DA05836-01.

COMPARABLE LEVELS OF HPA ACTIVATION WITH STRESS-INDUCED AND DRUG CUE-INDUCED COCAINE CRAVING

R. Sinha and S. O'Malley

Department of Psychiatry, Yale University School of Medicine, New Haven, CT

Exposure to environmental stressors and drug-related cues are known to increase drug craving. In this study. we examined the psychobiological responses associated with these two craving states. Fifteen cocaine dependent subjects participated in a laboratory session in which subjective and psychobiological responses to neutral, stress and drug cues imagery conditions were compared. Stress imagery and drug cues imagery was based on personally experienced situations while the neutral imagery was based on a standard neutral, relaxing situation. Stress and drug cues imagery produced significant increases in cocaine craving when compared to neutral imagery. Further, salivary cortisol and heart rate increases were observed with both stress and drug cues imagery. Comparable increases in cortisol with stress and drug cues exposure indicates that HPA activation may be a component of the neurobiological state of drug craving. These findings are consistent with the preclinical literature demonstrating the significance of corticosterone in facilitating the acquisition of psychostimulant self-administration in laboratory animals.

ACKNOWLEDGMENT: Supported by NIDA grant P50-DA09241.

ATTENUATION OF COCAINE-INDUCED ACTH AND CORTISOL RELEASE, BUT NOT SUBJECTIVE EFFECTS, IN HUMANS

A. S. Ward, E. D. Collins, M. Haney, R. W. Foltin, and M. W. Fischman

Columbia University and NYS Psychiatric Institute, New York, NY

Surgical or pharmacological attenuation of HPA function reduces the discriminative stimulus and reinforcing effects of cocaine in laboratory rodents. To examine the role of the HPA axis on cocaine's effects in humans, experienced cocaine users received either ketoconazole (0, 600 and 1200 mg p.o.), which reduces cortisol release, or dexamethasone (0 and 2 mg p.o.), which reduces ACTH release, before smoking cocaine base (0.0, 12.5, and 50 mg). Experimental sessions began one hour after ketoconazole administration and nine hours after dexamethasone administration; sessions were conducted in the morning, to correspond to the daily maximal basal cortisol level. Cardiovascular activity was measured continuously, and mood scales were completed repeatedly throughout the sessions. Blood was drawn for determination of plasma ACTH and cortisol levels. Under placebo ketoconazole and dexamethasone conditions, cocaine dose-dependently induced ACTH and cortisol release, and increased cardiovascular activity and several subjective effects. Ketoconazole dose-dependently reduced cocaine's effects on cortisol release without affecting ACTH levels or the subjective effects of cocaine. Dexamethasone blocked cocaine's effects on ACTH and cortisol release without affecting the subjective effects of cocaine. Ketoconazole significantly decreased some cocaine-induced increases in cardiovascular activity, while dexamethasone significantly increased the cocaine-induced increase in heart rate. These results contradict the drug discrimination data obtained in laboratory animals and indicate that attenuation of HPA function does not reduce the subjective effects of cocaine in humans.

ACKNOWLEDGMENTS: Supported by NIDA grant DA-06234 and NIH grant MOI-RR-00645.

DIFFERENTIAL SUBJECTIVE RESPONSE TO CRF IN PATIENTS WITH ADDICTIONS COMPARED WITH NORMAL VOLUNTEERS

S. H. Kellogg, A. Ho, J. H. Schluger, G. Perret, L. Borg, K. McClary, D. West, and M. J. Kreek

The Laboratory on the Biology of the Addictive Disease, The Rockefeller University, New York, NY

This study is part of an ongoing series exploring the role of stress responsivity and changes in hypothalamic pituitary-adrenal axis (HPA) functioning that may accompany drug addiction. We explored, in conjunction with a series of neuroendocrine studies (see Schluger *et al.,* this volume), the subjective responses to intravenously administered corticotrophin releasing factor (CRF) and its impact on normal and addicted subjects. In an inpatient study at the Rockefeller University Hospital, nineteen normal volunteers (NVs) and seven methadone-maintained, cocaine dependent (but illicit opiate-free) subjects (MMCDs) received a complete or partial protocol consisting of placebo, 0.5 mg/kg CRF (low CRF), and 2.0 or 4.0 mg/kg CRF (high CRF) on different days in varying order. Each subject was asked to indicate the drug effect that they felt on a visual analog scale (DVAS) at 10 and 30 minutes after placebo or CRF administration. The endpoints of the line were marked "Cold Turkey"/"Sick" and "High"/Euphoria. Subjects were also informed that the middle of the line represented their "normal" state. Separate analyses were done for each level of intervention. In all three conditions, there was a main effect for drug status in which the MMCD subjects were significantly closer to the "Cold Turkey"/"Sick" pole than the NVs (in all conditions, $p. < .02$). There was a significant addiction-status-by-CRF-dose interaction in each of the analyses. In the placebo condition, there was no significant difference in DVAS scores for either MMCDs or NVs at 10 and 30 minutes. In both the low and high CRF conditions, there were significant interactions in which the methadone patients reported significantly greater feelings of withdrawal at 30 minutes than the NVs (in both studies, $p. < .05$). These preliminary results point to a differential and subjectively more negative effect in response to stimulation of the HPA axis by CRF for MMCD subjects than for Nvs.

ACKNOWLEDGMENTS: Supported in part by grants DA-P50-05 130, DA00049 and M01-RR00102.

ENHANCED SENSITIVITY TO NEGATIVE GLUCOCORTICOID FEEDBACK IN PATIENTS WITH ONGOING COCAINE DEPENDENCE

B. Aouizerate*, J. H. Schluger, G. Perret, K. McClary, A. Ho, P. V. Piazza*, and M. J. Kreek

The Laboratory on the Biology of the Addictive Disease, The Rockefeller University, New York, NY and *University of Bordeaux II, Bordeaux, France

We examined the hypothesis that patients with addicitive diseases may have an enhanced sensitivity of the HPA axis to negative feedback control by glucocortcoids, by performing inpatient dexamethasone (DEX) suppression tests in 8 methadone maintained former heroin addicts with ongoing cocaine dependence (MMC) (3 males, 5 females:mean age 33 yrs, range 18 - 46 yrs) and in 19 normal healthy volunteers (NV) (12 males, 7 females: mean age 32 yrs, range 19 - 46 yrs). Three doses of DEX were administered at 11pm on separate evenings: the standard, 2mg, and two lower doses, 0.125 and 0.5 mg. Plasma ACTH and cortisol levels were determined by RIA in blood sampled at 9am, 1 pm, and 5pm the following day. Baseline ACTH and cortisol levels served as controls. Cocaine dependent patients were studied after a period of abstinence from cocaine ranging from 1 to 26 days. Two way ANOVA's were used to determine differences in hormonal levels at 1 and 5pm. Basal ACTH and cortisol levels were within normal ranges, however, levels were significantly lower in MMC than NV (basal ACTH: $p<0.01$, cortisol: $p<0.001$). Further, MMC showed a greater suppression of ACTH and cortisol in response to the lowest doses of DEX than NV (DEX 0.125mg: ACTH: $p<0.01$, cortisol: $p<0.001$; DEX 0.5mg: ACTH: $p<0.001$, cortisol: $p<0.03$). These results indicate that the abnormal HPA axis activity seen in patients with cocaine addiction may be due in part, to an increased sensitivity to the negative feedback exerted by glucocorticoids.

ACKNOWLEDGMENTS: Supported in part by grants DA-P50-05130 and DA00049.

DIFFERENTIAL STIMULATION OF THE HPA AXIS BY CRF IN NORMAL VOLUNTEERS AND PATIENTS WITH ADDICTIONS

J. H. Schluger, G. Perret, K. McClary, M. Gunduz, I. Disla, J. E. Myers, J. Daniels, A. Ho, and M. J. Kreek

The Laboratory on the Biology of the Addictive Disease, The Rockefeller University, New York, NY

Distinct stages of addictions to different substances of abuse are associated with alterations in stress responsivity, reflected by hypothalamic pituitary adrenal (HPA) axis activity. We explored whether these alterations may be related in part to changes in pituitary sensitivity to corticotropin releasing factor (CRF). In a controlled study conducted on the inpatient unit of the Rockefeller University Hospital GCRC, plasma ACTH and cortisol levels were measured after intravenous administration of h/rCRF in different doses to healthy volunteers without histories of drug or alcohol abuse and to patients with addictions. Nineteen normal volunteers (NV's) serving as their own controls received a placebo, 0.5 mg/kg CRF, and 2.0 or 4.0 mg/kg CRF on separate days. Each dose caused significant elevations in plasma ACTH ($p<0.00002$) and cortisol ($p<0.000001$) levels compared with placebo. While the 2.0 and 4.0 mg/kg doses caused greater increases than the 0.5 g/kg dose, there was no difference between them. Seven patients in methadone maintenance treatment, no longer abusing illicit opiates, yet dependent on cocaine (MMC's) were also studied. There were no significant differences in ACTH or cortisol levels measured after placebo administration in MMC compared with NV. However, ACTH levels were significantly higher in MMC after the 2 and 4 mg/kg doses of CRF compared with NV ($p<0.0002$), yet cortisol levels in MMC after all three doses were significantly lower than in NV ($p<0.02$). The results indicate the increased stress responsivity in defined stages and types of addiction, as reflected in HPA axis activity may be related in part to increased pituitary sensitivity to the effects of CRF.

ACKNOWLEDGMENTS: Supported in part by grants DA-P50-05130, DA00049, and M01-RR00102.

POSTER SESSION III

PRENATAL EXPOSURE TO NICOTINE IN RATS ENHANCES BEHAVIORAL SENSITIZATION TO NICOTINE IN ADULT OFFSPRING

G. S. Ward and R. T. Burkey

Emory and Henry College, Emory, VA

Time-release subdermal pellets which were designed to evenly deliver a total of either 25 or 0 mg of nicotine over the gestation period were implanted in pregnant female rats on gestational day 2. Following parturition, both surrogate and cross-fostering procedures were used to isolate the prenatal effects of nicotine. Around postnatal day 90 the activity testing phase began. Sixteen nicotine-exposed male rats and 16 control male rats that had served as saline controls in another study were used in the current study. To measure the development of sensitization to the motor activating effects of nicotine, a within-subjects repeated measures design was employed. For 9 consecutive days, each rat was placed in an activity chamber for a 20 min baseline period, then an injection of saline was administered and activity (distance traveled) was recorded for 20 min, finally an injection of nicotine (0.6 mg/kg) was administered and activity was recorded for an additional 40 min. Repeated measures analysis of variance (ANOVA) failed to indicate group differences in terms of baseline activity. Following the nicotine injections, a significant increase in activity was observed in both groups, and the magnitude of the nicotine effect increased over the test days for both groups. However, behavioral sensitization developed more rapidly in rats prenatally exposed to nicotine than in control rats, and while both groups reached a similar asymptotic level of nicotine-stimulated activity, the nicotine prenatally-exposed rats reached this asymptotic level 2 days sooner than control rats.

PRENATAL NICOTINE EXPOSURE IN RATS ATTENUATES BEHAVIORAL SENSITIZATION TO COCAINE IN ADULT OFFSPRING

R. T. Burkey and G. S. Ward

Department of Psychology, Emory and Henry College, Emory, VA

On gestational day 2, subdermal pellets designed to evenly deliver a total of either 25 or 0 mg of nicotine over the gestation period were implanted. Following parturition, surrogate and cross-fostering procedures were used to isolate the prenatal effects of nicotine in the offspring. Around postnatal day 70 the activity testing phase began. Thirty-six prenatal nicotine-exposed offspring (18 male and 18 female) and 36 control offspring (18 male and 18 female) were randomly assigned to one of 2 injection groups (10 mg/kg/ip cocaine or saline). Behavioral activity (distance traveled) was measured by 4 43X43X30cm infrared activity monitors (Med. Associates, Lafayette, IN). For 9 consecutive days, a 20 min activity baseline was recorded for each animal, then group appropriate injections were administered (10 mg/kg/ip cocaine or saline), followed by 40 min of activity monitoring. Analyses of the data (repeated-measures analysis of variance) failed to indicate an effect of prenatal nicotine exposure on activity levels either during the baseline period prior to injection, or following an injection of saline. However, prenatal nicotine exposure did significantly retard the development of behavioral sensitization to cocaine in both adult male and female rats. Additionally, the data revealed that independent of prenatal exposure condition, female rats showed enhanced behavioral sensitization to cocaine relative to their male counterparts.

THE PREGNANT EWE: A PARADIGM FOR STUDYING BIOMEDICAL SEQUELAE OF PERINATAL SUBSTANCE ABUSE

M. A. Plessinger and R. W. Wood

Department of Obstetrics and Gynecology, University of Rochester School of Medicine and Dentistry, Rochester, NY

Use of drugs during pregnancy continues to be a major problem which produces increased obstetrical, neonatal, and hospital costs. Adverse maternal and fetal effects of both licit and illicit drugs are often associated phenomena. i.e., a positive drug screen or patient history is correlated with adverse fetal outcome. Polydrug abuse in humans may obscure the effects of individual drugs, and raises questions concerning drug-drug interaction. Animal paradigms have been utilized to address some of these issues, as well as confirm several of the observed adverse effects of drug exposures in humans. However, these paradigms commonly tack relevant physiologic measures. The pregnant sheep and its fetus are well suited for chronic implantation of catheters and other implantable devices and have provided important information regarding physiologic responses and resultant sequelae of abused drugs in the fetus. In addition, the inllucnce of pregnancy upon maternal drug responses and drug distribution may also be examined to compare with the nonpregnant state. Thus, this animal paradigm provides opportunities to determine fetal effects of maternal drug use as welt as maternal effects of the hormonal milieu of pregnancy when compared to the nonpregnant state. Our research efforts are continuing to explore the effects of cocaine in the pregnant ewe.

ACKNOWLEDGMENTS: Supported by NIH-DA05080-08.

A PILOT STUDY OF SMOKING WITHDRAWAL AND URGES TO SMOKE IN A MONTH OF ABSTINENCE IN PREGNANCY

S. K. Richards, D. L. Haller, and T. Eissenberg

Departments of Internal Medicine and Psychiatry, Division of Substance Abuse Medicine, Medical College of Virginia of Virginia Commonwealth University, Richmond, VA

This pilot study investigated symptomatic experience of smoking withdrawal and urges to smoke, biophysical status, and nicotine use during the first month of a quit attempt by pregnant women admitted to the Center for Perinatal Addiction(CPA). Quit attempts were supported by cognitive-behavioral groups and an incentives program. Five women participated during their first month of residential treatment; three utilized the nicotine patch, two did not use the nicotine patch. All subjects reported complete abstinence (CO verified) across the 30 day period; however, smoking withdrawal and urges to smoke remained relatively stable. No adverse consequences (including birth outcomes) were attributed to patch use.

ACKNOWLEDGMENTS: Supported by CSAT grant #5 HSHAT100555-05 and SmithKline Beecham.

HAIR ANALYSIS TO MONITOR SUBSTANCE ABUSE DURING PREGNANCY

K. M. Höld, D. G. Wilkins, D. J. Crouch, M. L. Cheever, D. A. Savitz*, J. Thorpe* and D. E. Rollins

Center for Human Toxicology, Department of Pharmacology and Toxicology, University of Utah, Salt Lake City, UT; and University of North Carolina, Chapel Hill, NC

Maternal exposure to cocaine (COC) and /or nicotine (NIC) has the potential to adversely affect the developing fetus. Women participating in a study to identify risk factors for preterm rupture of membranes and preterm labor provided self-report of drug use, urine and hair specimens to identify those exposed to COC or NIC during pregnancy. Samples of urine and hair were collected at the end of pregnancy and screened by immunoassay. Positive hair samples were confirmed for COC and NIC and their metabolites by GC/MS. Of the initial 86 women studied, 1 reported the use of COC during pregnancy. Urine immunoassay identified 5 women (5.8%) as having used COC; 18 hair samples (20.9%) were positive for COC. Self-report identified 18 women (20.9%) who smoked cigarettes during pregnancy. Urine immunoassay identified 11 women (12.8%) who smoked during pregnancy; 30 hair samples (34.9%) were positive for NIC. These data indicate that hair analysis identifies more women as users of COC or NIC than does either self-report or urine analysis. Passive exposure to smoke containing either COC or NIC may partially explain the large number of positive hair samples.

ACKNOWLEDGMENTS: Supported by HD 28684 and NIDA grants DA09096 and DA07820.

RELATIONSHIPS AMONG DRUGS OF ABUSE, MATERNAL BLOOD CONCENTRATIONS OF LEAD (Pb^{+2}) AND INFANT BIRTHWEIGHT

W. L. West, E. M. Knight, C. H. Edwards, J. F. Diaz, G. Narula, L. Kessee, A. A. Johnson, U. J. O. Bailey, B. Spurlock, M. Manning, O. E. Westney, H. Laryea, S. Jones, and L. S. Westney

Center for Drug Abuse Research (CDAR), Departments of Nutritional Sciences, Human Development, Pharmacology, Obstetrics and Gynecology, Howard University, and DC General and Howard University Hospitals, Washington, DC

We examined the relationships among maternal blood concentrations of lead (Pb^{+2}) and their infant's birth weight as well as self-reports on the use of drugs of abuse via a questionnaire. The use of cocaine, PCP, and marijuana, were reported. Cocaine frequency was highest. In order to study the relationship between low birth weight (a binary variable) and lead levels (a continuous variable), we fitted a logistic regression model, adding drug use before pregnancy and prenatal care (Walk-ins versus Regulars) as covariates. This analysis was done using SPSS for windows version 7.5. Odds ratios were computed (95% CI). All data were derived from mothers who delivered live birth infants and had a delivery blood Pb^{+2} (concentration ranged from 5.2 µg/dl to 11.5 µg/dl. The normal birth weight was designated <2500 grams and low birth weight (LBW) <2500 grams. There were 42 cases from this subgroup included in the analyses. For the purpose of this report, only data on drug use before pregnancy will be used because guestionnaire response to usage in pregnancy was low. Thirty-two of these cases had a normal birth weight. Maternal blood Pb^{+2} concentrations for normal birth weight infants were 7.64±0.27 S.E.M.µg/dl and for LBW infants 8.8±0.50 S,E.M.µg/dl (P=0.04). Mothers with high levels of Pb^{+2} were 1.8 times more likely to have infants with LBW. Walk-ins at the clinic were ten times more likely to have LBW infants than Regular mothers. In these subgroups where all mothers had Pb^{+2} in the blood, drugs of abuse used before pregnancy did not show a significant difference. Therefore, it seems reasonable to suggest that these causative agents of disease (Pb^{+2} and drugs of abuse) are not always interactive even though many studies suggest that substances of abuse and Pb^{+2} each may impair functions in the central nervous system of a developing fetus.

FAMILIAL INFLUENCES ON NEONATAL OUTCOME

R. Pickens, D. Svikis, A. Gupman, L. Jamson, N. Haug, J. Lin, C. McCormick, P. Kuppusamy, and B. Dixon

NIDA-IRP, Johns Hopkins Medical School, Belair High School, and Auburn University

Birth outcome was examined in 218 pregnant drug-dependent women (81% African American, 19% Caucasian; mean age 28.5 yrs, education 10.9 yrs, EGA at admission 26.5 wks) who gave live birth to single infants while enrolled in a comprehensive drug abuse/prenatal treatment program. Current SCID DSM-IIIR diagnoses included 8% alcohol, 84% heroin, 71% cocaine, and 70% nicotine dependence. Based on race- and sex-specific Maryland norms, abnormal birth was found in 49% of infants (41% intrauterine growth retardation, 9% prematurity). Abnormal birth was related to lifetime duration proband regular alcohol ($p=.03$) and nicotine ($p=.03$) use, but not to amount of prenatal drug use. Abnormal birth was also related to infant gender ($p=.006$) and maternal age ($p=.05$) and EGA at admission ($p=.004$). Length of stay in treatment was inversely related to abnormal birth outcome ($p=.003$). Most probands (66%) had at least one biological parent with alcohol/drug dependence (FH-RDC criteria). Paternal and maternal substance dependence was associated with proband characteristics. Having a biological father with alcohol dependence significantly reduced risk of abnormal birth ($p=.02$). The protective effect remained significant even after proband's drug use and other characteristics related to birth outcome were controlled for. These results suggest birth outcome in pregnant drug-dependent women is determined not only by prenatal drug use but by other factors as well, including past history of drug use and familial history of substance dependence.

THE RELATIONAL PSYCHOTHERAPY MOTHERS' GROUP: A DEVELOPMENTALLY INFORMED INTERVENTION FOR METHADONE-MAINTAINED MOTHERS

N. E. Suchman and S. S. Luthar*

Yale University School of Medicine, New Haven, CT and *Teacher's College, Columbia University, New York, NY

Designed to address the risk factors and build upon the protective factors that influence addicted mothers' need for and response to treatment, the Relational Psychotherapy Mothers' Group (RPMG) integrates supportive, interpersonal, and insight-oriented approaches to group psychotherapy while maintaining a firm and consistent group structure. RPMG is a manualized, weekly, 1 1/2 hour intervention of 6 months' duration designed for methadone-maintained mothers as an adjunct to standard drug counseling (SDC). The preliminary efficacy of RPMG + SDC was tested in a pilot study with 61 methadone-maintained mothers randomly assigned either to RPMG + SDC or SDC alone. Standardized measures were administered at baseline, end-of-treatment, and a 6 month follow-up. In an analysis of covariance at the end of treatment, compared with mothers who received SDC alone, mothers who received RPMG + SDC demonstrated lower risk for maltreating their children, higher levels of communication and involvement with their children, and better psychosocial adjustment. Compared with children whose mothers received SDC alone, children whose mothers received RPMG + SDC demonstrated significantly better personal adjustment and fewer internalizing problems. In an analysis of covariance at the 6 month follow-up, in comparison with mothers who received SDC alone, mothers who received RPMG + SDC sustained their advantages in the maltreatment risk, involvement, and communication domains although the magnitude of differences was attenuated. Although not statistically significant, there were also notable effect sizes for sustained improvement in mothers' psychosocial adjustment. The maladjustment levels of children whose mothers received RPMG + SDC continued to improve such that, at the 6 month follow-up, they were at a signficant advantage over children whose mothers received SDC alone. In a random-effects regression model, a significant treatment x time interaction indicated that mothers receiving RPMG + SDS were less likely to USC opiates than mothers receiving SDC alone.

ACKNOWLEDGMENTS: Supported by NIDA grants P50-DA9241, R01-DA10726, and K21-DA00202.

IMPROVING RESIDENTIAL TREATMENT RETENTION AMONG DRUG DEPENDENT PREGNANT WOMEN

W. B. Kissin, D. S. Svikis, M. L. Stitzer, and N. A. Haug

The Johns Hopkins University School of Medicine, Baltimore, MD

Substance use during pregnancy is a major public health concern. The Center for Addiction and Pregnancy (CAP) effectively addresses the multiple needs of this population (Svikis et al., 1997), yet treatment retention remains an essential and continuous challenge. This study utilized an ABA design to assess the efficacy of a strategy for reducing the rate that patients leave residential treatment prematurely or against medical advice (AMA). The experimental "B" phase of the study involved introducing a patient advocate or liaison, who addressed patients' concerns in an effort to prevent premature dropout (AMA). Preliminary analyses from the initial baseline (Al) and intervention (B) phases were presented. Participants were 99 opiate- and/or cocaine-dependent pregnant women who were 82.7% African American with a mean age of 30.1 years and education of 10.9 years. Nurses rated each patient daily on her likelihood of completing residential treatment and other satisfaction-related variables. Patients enrolled during Phases Al and B were similar for demographic, drug, and psychiatric descriptors, and differed only in that more Phase Al than Phase B patients were Caucasian and heroin dependent. AMA rates were similar for Phases Al (19.1%) and B (17.3%), and patients left AMA after a mean of 1.8 days of treatment. AMAs and non-AMAs were similar for age, education, and psychiatric diagnoses. More AMAs received abstinence-based versus methadone maintenance therapy ($p<.01$), were Caucasian ($p<.05$), and had more previous drug treatment episodes ($p<.001$). Nurses rated AMAs as less likely to stay and more likely to mention wanting to leave AMA. There were trends for AMAs to report fewer alcohol and greater medical, employment, family/social, and drug problems on the ASI. These data suggest that patients' psychosocial variables and current assigned treatment intervention as well as nurses' observations may assist in identification of those at most risk for leaving AMA.

ACKNOWLEDGMENTS: Supported by NIDA grants P50 DA09258 and 5T32 DA07209.

TEMPORAL PATTERN OF DRUG TREATMENT ATTENDANCE

D. Svikis[1], R. Pickens[2], W. Schweitzer[1], N. Haug[1], and E. Johnson[3]

[1]John Hopkins University School of Medicine, Baltimore, MD; [2]National Institute on Drug Abuse, Intramural Research Program, Baltimore, MD; and [3]Henry Ford Center, Detroit, MI

In outpatient drug abuse treatment, outcome is positively related to length of stay and consistency of program attendance. Although a number of demographic and psychosocial factors have been associated with poor treatment attendance, little attention has been paid to temporal factors that may lead to relapse and treatment dropout. The present study examined the temporal pattern of treatment attendance in an intensive outpatient program for Medicaid-eligible, unemployed, pregnant and postpartum drug dependent women. Mean daily attendance in outpatient drug treatment was examined over a 29-month period (December, 1991, to April, 1994), comparing attendance during weeks 1, 2, 3, and 4 of each calendar month. Attendance was typically lowest on week 1 of each month, and increased systematically on weeks 2, 3, and 4. Using time series analysis, a significant reduction in program attendance was seen in week I relative to week 4 ($p<.001$) even after controlling for program growth and other confounding factors. Subsequently, an anonymous patient survey was conducted to assess reasons for patient treatment absence. For week 1, the most frequently reported reason for absence was drug use, which coincided with receipt of monthly welfare checks and food stamps. For week 3, major reasons for absence were physical illness, social services appointments and childcare issues. The clinical implications of providing substance abusing women with public assistance funds at a fixed time each month will be discussed.

ACKNOWLEDGMENT: Supported by Public Health Service grant P50 DA 09258 (Behavior Therapy Treatment Research Center).

LINKING PROCESS AND OUTCOME IN BEHAVIORAL TREATMENTS FOR COCAINE DEPENDENT PREGNANT WOMEN: A PRELIMINARY REPORT

M. V. Pantalon, J. M. Falcioni, J. Pakes, and R. Schottenfeld

Yale University School of Medicine and The APT Foundation, New Haven, CT

The Community Reinforcement Approach (CRA), a behavioral treatment, has shown promise for treating cocaine dependence. However, little attention has been given to the study of the process that account for change during CRA. The preliminary study investigated the relationship between processes that occur during CRA, and cocaine use. Two new process rating scales were used. The Mechanisms of Action Rating Scale (MARS) assess 5 content areas: 1) "Big Picture" Goals, 2) Functional Analyses of Behavior 3) Nondrug-Related Training & 5) Homework, while the Interpersonal variables Rating Scale (IVRS) measures: 3: 1) Empathy, 2) Responses to Resistance, and 3) Therapeutic Alliance. A trained rater, blind to outcome, used both scales to rate one early-stage CRA session videotape for each patient. Patients were 16 cocaine-dependent pregnant women who received CRA for 6 months. Six out of the 16 (37.5%) subjects achieved abstinence ($\geq$ 3 consecutive weeks of cocaine-negative urine toxicology tests) and the mean (SD) number of consecutive cocaine-negative weeks was 6.17 (3.76) for abstainers and 2.44 (3.72) for non-abstainers. Results indicated that 1) those who achieved abstinence had significantly higher Empathy, Response to Resistance, and total IVRS scores than those who did not achieve abstinence, and 2) "Big Picture" goals and nondrug-related activities were significantly correlated with the number of consecutive weeks of cocaine-negative urine toxicology tests (r=.67, r=.63, respectively, p<.01), as were therapeutic alliance and total IVRS scores (r =.58, r=.49, respectively, p<.05). These findings suggest that it is important to monitor both mechanistic and interpersonal processes during CRA, and that training clinicians to capitalize on processes most associated with change could potentially improve outcomes.

ACKNOWLEDGMENTS: Supported by NIDA grants DA09413 and DA06915

EFFECTIVENESS OF INTENSIVE CHILD CASE MANAGEMENT SERVICES FOR INFANTS OF DRUG DEPENDENT WOMEN

L. Jansson[1], D. Svikis[1], M. Adkins[2], P. Beilenson[2], C. Baugh[2], and S. Lester[2]

[1]Johns Hopkins University School of Medicine, Baltimore, MD and [2]State of Maryland Infants and Toddlers Program, Baltimore, MD

Children of drug dependent women are at increased risk for a variety of medical and psychosocial problems. Clinical data suggest that such children require more intensive case management services. The Reaching Families Early (RFE) program in Baltimore, MD provided drug-affected infants with child case management services from 0-3 years of age. The present study evaluated the impact of RFE services in this high-risk population. Mothers/Family members of 76 drug exposed infants born in 1994 were contacted 2 years later and asked to participate in a confidential survey. Subsequently, cases were divided into 2 groups: those who received 0-4 home visits (Low RFE group) and those who received 5+ home visits (High RFE). Groups were compared using t-tests and chi-squares. Mothers and infants in the 2 groups were demographically comparable, however, more male infants were found in the low versus high RFE groups (75 and 47%, respectively, p<.02). High RFE mothers were more likely to report drug treatment postpartum (83%) as compared to low RFE mothers (56%) (p<.03). Few high RFE mothers also reported recent drug use (33%) versus low RFE mothers (73%) (p<.002). Over two-thirds of high RFE mothers reported better parenting skills (67%) than low RFE mothers (31%) (p<.006). High RFE infants were more likely to be legal dependents of their biological mothers (81%) than low RFE infants (29%) (p<.0001). Although outcome data studies not involving random assignment must be interpreted with caution, study findings suggest that intensive child case management services were associated with decreased maternal drug use, increased enrollment in drug treatment, improved parenting abilities and a higher probability of mothers retaining legal custody of their infants.

OUTCOME OF INTENSIVE OUTPATIENT SUBSTANCE ABUSE TREATMENT FOR ADDICTED WOMEN

S. H. Schnoll, J. S. Knisely, E. Campbell, and K. S. Dawson

Medical College of Virginia of Virginia Commonwealth University, Richmond, VA

The purpose of the present study is to compare treatment outcome data of women who enrolled in one of two intensive outpatient treatment programs to women who refused treatment. Adult pregnant women or women with infants 6-mo of age or younger who met DSM-IV criteria for substance abuse or dependence were offered treatment at the Center for Perinatal Addiction. Based upon self-assignment, subjects either received treatment (5-18 mo) at the CPA (acceptors, n=48) or served as treatment refusers (rejecters, n=24). All subjects signed informed consent approved by the Committee on the Conduct of Human Research, Virginia Commonwealth University. Subjects were required to complete a battery of psychological instruments and several structured interviews including the ASI. Assessments were conducted at intake, discharge (or 5-mo post-intake for the rejecters), and 6, 12, 18, and 24-mo post-discharge. For each ASI domain (medical, employment, alcohol, drug, legal, family, and psychiatric), discharge and follow-up change scores from baseline were calculated. No significant group differences were observed regarding subject characteristics (age, race, marital status, primary substance of abuse). Most subjects in both groups were single, African American, and cocaine was the primary drug of choice. No group differences were found for any of the seven ASI composite scores at intake with the exception of legal problems (treatment group had higher scores, $p<.05$). Change scores from intake were also compared at discharge and each follow-up time point. In general, the treatment group displayed significant improvement in several areas throughout the follow-up period including medical ($p<.01$) employment ($p<.001$), drug($p<.001$), and legal ($p<.01$). Treatment rejecters demonstrated little change in any area.

ACKNOWLEDGMENT: Supported by NIDA grant DA06094.

INCREASED SENSITIVITY TO ALPRAZOLAM IN WOMEN WITH A PATERNAL HISTORY OF ALCOHOLISM

S. M. Evans and F. R. Levin

Columbia University and the New York State Psychiatric Institute, New York, NY

The present study compared the response to alprazolam and buspirone in women with a confirmed paternal history of alcoholism (FHP; N=14) to women without a family history of alcoholism (FHN; N=14). The two groups of women were matched on race, age and education; all women were infrequent alcohol users and had no current psychiatric disorders. The acute effects of placebo, alprazolam (0.25, 0.50, 0.75 mg) and buspirone (5, 10, 15 mg) were evaluated using a double-blind, placebo-controlled outpatient design. Drug effects were assessed using performance tasks, observer ratings of drug effect and subjective ratings of mood, drug strength and drug liking. Alprazolam impaired performance in a dose-related manner on several tasks including the Thorndike word memory task, the Digit Symbol Substitution Task (DSST) and Digit Recall for both groups of women. In contrast, buspirone had minimal effects on performance. Further, the highest dose of alprazolam impaired word memory, DSST and digit recall more in FHP women than in FHN women. Correspondingly, ratings of "Difficulty Concentrating" were higher in FHP women than in FHN women following alprazolam. However, alprazolam, produced similar dose-related increases in observer-rated drug strength for both groups of women. Lastly, there was no evidence of an increase in ratings of Drug Liking in either group following alprazolam, although FHP women liked buspirone more than FHN women. These findings suggest that women with a paternal history of alcoholism are more sensitive to the performance impairing effects of alprazolam.

ACKNOWLEDGMENT: Supported by NIDA grant DA-09114.

THE RELATIONSHIP BETWEEN PARENTAL HISTORY AND SUBSTANCE USE SEVERITY IN DRUG TREATMENT PATIENTS

S. J. Boyd,[1] B. W. Plemons,[1] R. P. Schwartz,[1] J. L. Johnson,[1] and R. W. Pickens [2]

[1]University of Maryland, Department of Psychiatry, Baltimore, MD and [2]National Institute on Drug Abuse, Baltimore, MD

This study explored the relationship between the history of parental problematic alcohol and drug use and their adult children's alcohol and drug use disorders. Subjects were 347 admissions to an outpatient substance abuse program. They were administered the Addiction Severity Index (ASI), Michigan Alcohol Screening Test (MAST), a substance use disorder diagnostic interview, and a family history questionnaire. A chi-square analysis revealed a positive relationship between the number of parents affected by alcohol and/or drug problems and the percentage of probands with co-existing alcohol and drug use disorders. This relationship was also found for probands with alcohol use disorders but not for those with only drug use. A one-way analysis of variance revealed that probands with two affected parents had significantly higher MAST, and ASI alcohol, drug family, and psychiatric composite scores than those with negative family history. This preliminary study indicates that the severity of a proband's substance use disorder may be influenced by parental substance use history.

SOCIAL ADJUSTMENT AMONG FAMILY MEMBERS AND SIGNIFICANT OTHERS OF DRUG ABUSERS

K. C. Kirby, M. L. Firely, D. S. Festinger, and D. B. Marlowe*

Temple University* and Allegheny University of the Health Sciences, Philadelphia, PA

Most of what we know about the effects of substance abuse on the family members and significant others (FSOs) of the user has been derived from studies on alcohol. We examined the social adjustment of 41 female partners and 24 mothers of drug abusers who responded to an advertisement offering help for people concerned about the drug use of a loved one. The purposes of the study were to: (1) compare the social adjustment of FSOs and the drug users; (2) see if social adjustment problems differed depending on the relationship of the FSO to the drug user; and (3) compare the FSOs' social adjustment to a community population. We assessed social adjustment using the Social Adjustment Scale - Self Report which examines functioning in seven role areas. These are work, social and leisure activities, extended family relationships, parental relationship, marital relationship, the family unit, and economic functioning. The community comparison data we used were provided by Weissman *et al.* (1978). We were unable to analyze data using MANOVA or other multivariate technique because SAS scores are not given in role areas that do not apply and the resulting empty cells are interpreted as missing data. Therefore, we conducted t-tests with Holm corrections. Results indicated that FSOs had significantly better social adjustment in most role areas when compared to the drug users. Partners of drug users had poorer adjustment than parents of drug users in the areas of marital and economic functioning. Finally, FSOs' social adjustment was significantly poorer than a community sample. The comparison to the community sample must be viewed cautiously because of considerable differences in the samples, but these results shed light on the effects of drug abuse on a segment of the population that has been largely ignored by addictions researchers. These findings suggest that we need further study to improve our understanding of the impact of drug abuse on family members and significant others.

REFERENCES: Available from senior author upon request.

ACKNOWLEDGMENT: Supported by NIDA grant DA-08907.

THE POTENTIAL FOR PHYSICAL CHILD ABUSE AMONG WOMEN MANDATED TO DRUG TREATMENT PROGRAMS IN NEW YORK CITY

G. P. Falkin and S. M. Strauss

National Development and Research Institutes, Inc., New York, NY

Substance abuse and domestic violence are highly intertwined. Research has shown that women who are victims of abuse tend to abuse drugs and alcohol, and that the use of these substances often precipitates violence within families, often directed toward children. This paper presents findings on the potential for child abuse in a large sample (N=550) of women who have been mandated to drug treatment in New York City. The women are interviewed at intake to drug treatment in four community-based and correctionsbased programs participating in project WORTH (Women's Options for Recovery, Treatment and Health), a NIDA-funded evaluation of treatment programs for women offenders. Using the Child Abuse Potential Inventory, the paper documents the degree to which women are at high risk for physically abusing their children. It also examines the relationship between this potential for abusing their children and a variety of characteristics of the women, including depression, gender role stereotyping, substance use, criminal activity, history of physical abuse, and motivation and readiness for drug treatment.

UNMET NEEDS OF SUBSTANCE ABUSING WOMEN IN THE CRIMINAL JUSTICE SYSTEM

M. Chan, A. Coutts, C. Ponath, and J. Guydish

Institute for Health Policy Studies, University of California, San Francisco, CA

Characteristics of substance abusing women entering a criminal justice treatment network (n=43) were compared with those of other women entering treatment in San Francisco (n=169). Comparisons were made on data collected at baseline, and included demographics, ASI composite scores, select ASI variables, BDI and BSI scores, and a measure of social support. Comparisons were also made of drug and alcohol use severity for the last 30 days of active use. Criminal justice women appeared younger (t=3.11, p<.002), and had a greater history of incarceration (chi sq=29.44, p<.001). More criminal justice women were currently on probation or parole (chi sq=67.16, p<.001), and more had been in a controlled environment in the 30 days prior to interview (chi sq=117.23, p<.001). Differences were also observed in drug of choice (chi sq=37.11 p<.001) and length of last voluntary abstinence (chi sq=12.76, p<.005). Criminal justice women were also more likely to have experienced emotional (chi sq=6.75, p<.009), physical (chi sq=6.62, p<.01), and sexual abuse (chi sq=8.85, p<.003). Analyses of the last 30 days of active use indicated that while alcohol use severity was lower for criminal justice women (t=7.45, p<.000), drug use severity was higher than that of women in the comparison group (t=2.65, p<.009). These preliminary results suggest that in addition to high levels of substance use severity, these women have legal, abuse, and possibly other needs that may not be addressed without specific interventions.

ACKNOWLEDGMENTS: Supported by CSAT grant 1UD8TI11215

HEALTH, DRUG USE, AND CRIMINAL JUSTICE DIFFERENCES AMONG INDIVIDUALS WITH INPATIENT AND OUTPATIENT TREATMENT HISTORIES

T. M. Godlaski, T. K. Logan, C. G. Leukefeld, M. Staton, and J. J. Clark

Center on Drug and Alcohol Research, University of Kentucky, Lexington, KY

This paper focuses on health, mental health, drug use, and criminal justice difference among individuals who either had previous inpatient treatment experience (n= 1,042) or previous outpatient treatment experience (n=544). Data were collected from males and females entering publicly subsidized substance abuse treatment facilities across the state of Kentucky between October, 1996 and October, 1997. Data for participants entering outpatient treatment were collected within the first three treatment sessions and data collected for participants entering inpatient treatment were collected within the first three days. Preliminary data indicate participants with inpatient treatment histories were 2 times more likely to be African-American, 6.6 times more likely to have attended AA/NA, 1.3 times less likely to have owned their own house, 1.4 times more likely to have been in the emergency room last year, 1.3 times less likely to have seen a doctor in the last year, 1.8 times more likely to report emotional abuse, 1.6 times more likely to have reported sexual abuse, 1.9 times more likely to have been arrested for property offenses in the past year, 1.3 times less likely to have been arrested for DUI in the past year, 2.6 times more likely to have ever used crack, and 3 times more likely to have used crack in the past year than those with outpatient treatment histories. Implications from this data arc that those with inpatient treatment may have more health care needs, mental health needs and have different criminal justice and drug use patterns.

PREDICTING THE PAROLE OUTCOME OF SUBSTANCE ABUSE OFFENDERS ON THE BASIS OF ADDICTION SEVERITY INDEX

*D. N. Nurco, T. E. Hanlan, and *K. E. O'Grady*

Department of Psychiatry, University of Maryland School of Medicine at Baltimore, MD and *Department of Psychology, University of Maryland, College Park, MD

This study involved male and female drug abuser parolees residing in Baltimore City who were assigned on release form incarceration, to routine parole procedures enhanced by weekly drug abuse counseling and urine monitoring. Of the 237 subjects referred for treatment, 222 were administered the Addiction Severity Index (ASI), according to the prescribed interview procedure, one month after their release from incarceration to allow for the required 30-day observation period in the community. Composite and severity scores for the ASI's major problem areas (medical, employment/support, alcohol, drug, legal, family/social, and psychiatric) covering the initial 30 days of parole were then examined with respect to their ability to predict treatment outcome during the year following release in terms of four areas of functioning: successful participation in treatment; the occurrence of major infractions. including parole violations arrests, and incarceration: drug use, and employment. Results of logistic regression analyses revealed the prominence of two problem areas in the prediction of outcome, employment and drug use. Those parolees with less severe problems in these areas during the first month of release from incarceration were more likely to expericnce more favorable outcome in terms of all four major areas of functioning during parole.

ACKNOWLEDGMENTS: This study was supported by Grant R18D06988 of NIDA and administered by Friends Research Institute, Inc., Baltimore, MD.

DEFINING THE RELATIONSHIP BETWEEN SEX AND DRUG USE

D. A. Calsyn[1,2], E. A. Wells[3,4], A. J. Saxon[1,2], and R. Jackson.[3,4]

[1]Veterans Affairs Puget Sound Health Care System, [2]Department of Psychiatry and Behavioral Sciences, University of Washington (UW), [3]Evergreen Treatment Services, and [4]UW School of Social Work, Seattle, WA

Despite an increase in research on the sexual behavior of injection drug users (IDU), little is known about the relationship between sexual behaviors and drug use. Eight male and 11 female heterosexual IDU in methadone maintenance were administered an open-ended interview regarding their beliefs and experiences concerning drugs and sex. For men the most common perceived positive effects of heroin and cocaine on sexual behavior were increased desire, delayed orgasm, decreased social and sexual inhibition. The negative effects of heroin, methadone and cocaine most frequently reported by men included decreased desire, erectile and orgasmic dysfunction. Women reported similar positive effects as men, and heroin made some unwanted sexual activities more tolerable. For women the negative effects of heroin, methadone and cocaine included decreased desire, decreased sensation and orgasmic dysfunction. Eight of the women spontaneously reported drugs had similar effects on their male partners as reported by the male interviewees. However, none of the men reported on the effects of drugs on the sexual behavior of their partners. For most subjects the positive effects of drugs on sexuality reported in the interview occurred more for them earlier in their lives and the negative effects were more prominent recently. Six men (75%) and 7 (64%) women reported being sexually active in the prior 6 months. Of these, 2 men (33%) and 2 women (29%) reported using drugs in conjunction with their most recent sexual event. All subjects who had not been sexually active in the prior six months reported using drugs in conjunction with their most recent sexual experience. Few sexual enhancements were reported for the most recent sexual event in which drugs were used. whereas sexual impairments were frequent. A structured interview was developed based on these findings and is now in pilot testing.

ACKNOWLEDGMENTS: Supported by UW Alcohol and Drug Abuse Institute and VA Medical Research Svc.

STRESS, DEPRESSION, AND DRUG USE AMONG OPIOID MAINTENANCE PATIENTS

C. A. Duva,[1] D. A. Wasserman,[1,2] and A. L. Stewart[1]

University of California[1] and Veterans Affairs Medical Center[2], San Francisco, CA

Although environmental stressors are widely believed to play a role in relapse to drug use, the specific nature of this relationship remains unclear. One reason for this may be that measures designed to assess environmental stressors have been developed with the general population. Due to the nature of drug addiction, addicts may encounter stressors that are different from those experienced by non-drug abusers. We are developing a measure of stressful events and chronic strains aimed specifically at identifying environmental stressors that are common among substance abusers. The measure comprises ten subscales that assess living conditions, crime and violence, transportation, drug treatment, general health, social services, finances, employment, relationships, and legal problems. It was administered to 250 opioid maintenance patients (52.8% M, 48.8% F; 52.8% Caucasian, 30.0% African-American, 10.0% Latino, 7.2% other). Subscale scores displayed satisfactory test-retest reliability (all ps < 0.001). Overall occurrence of stressful events was significantly correlated with heroin use in the last 30 days (r = .23, p < .001). Among the subscales, heroin use was most strongly correlated with stressors associated with drug treatment (r = .36, p < .001). Overall occurrence of stressful events was also correlated with scores on the Beck Depression Inventory (r = .41, p < .001). Relationships (r = .35, p < .001) and finances (r = .35. p < .001) were the domains most strongly correlated with depression. Major life events were less strongly related to drug use and depression than were stressful events and chronic strains. The present findings indicate that this new measure may be a useful tool for delineating the environmental stressors common to opioid maintenance patients and may be beneficial in determining the types of stressors that contribute to, and result from, continuing drug use.

COPING IN METHADONE MAINTAINED PATIENTS: ASSOCIATION WITH CONTINUED DRUG USE

L. A. Warburton, S. K. Avants, and A. Margolin

Department of Psychiatry, Yale University School of Medicine, New Haven, CT

Use of illicit drugs by opioid-dependent patients maintained on methadone undermines the benefits of methadone maintenance treatment. Because supplemental pharmacologic approaches have met with limited success, it is important to identify psychological mechanisms associated with drug use that could potentially contribute to the development of more effective treatments. Toward this end, the current study assessed coping and depression in 307 methadone-maintained patients, and found a reliance on avoidant coping strategies, most notably by depressed patients. Patients who achieved abstinence following a 12-week coping skills training intervention decreased the use of avoidant coping strategies. Patients who relied on emotional discharge were more likely to drop out of treatment prematurely.

ACKNOWLEDGMENTS: Supported by NIDA grants DA08754, DA00277 and DA10851 (SKA).

INFLUENCE OF SOCIAL ANXIETY ON RESPONSE TO TWO INTENSITIES OF METHADONE MAINTENANCE TREATMENT

S. K. Avants, A. Margolin, T. R. Kosten, B. J. Rounsaville, and R. S. Schottenfeld

Department of Psychiatry, Yale University, New Haven, CT

Drug treatment programs are faced with the pressing need to match patients to the appropriate level of adjunctive psychosocial services in order to provide treatment cost-effectively. Clinical intuition and previous research suggests that substance abusers, especially those with psychiatric comorbidity, should be provided with an increased level of care. However, there may be patients with psychiatric symptoms for whom more intensive psychosocial services would actually be counter-therapeutic and not cost-effective. The current study tested the hypothesis that socially anxious methadone patients would achieve less benefit from an intensive day treatment program than from a less socially demanding, and less costly, intervention. Social anxiety was assessed in 307 methadone-maintained patients using the Social Anxiety and Distress Scale prior to randomization either to an intensive, 25-hour per week, Day Treatment Program or to a 2-hour weekly coping skills training group. Both interventions were manual-guided and were 12 weeks in duration. Results supported the hypothesis. Socially anxious patients were drug free for more weeks during treatment, were more likely to be abstinent at treatment completion, and had greater reductions in HIV risk behaviors if they received the lower intensity intervention, which was provided at one-third the cost of the DTP.

ACKNOWLEDGMENTS: Supported by NIDA grants DA08754, DA00277 and DA00122

STANDARDIZING DESCRIPTIONS OF OPIATE WITHDRAWAL CURVES: NEW VITAL STATISTICS

M. Law, J. Melichar, J. Myles, and D. Nutt

Psychopharmacology Unit, Division of Psychiatry, University of Bristol, School of Medical Sciences, University Walk, Bristol, UK

Opiate withdrawal studies rarely publish actual withdrawal curves, and as the quality of data presented is very variable they are very difficult to compare. Previous workers have compared curves by roughly defining the "total withdrawal distress" as the area under the curve (AUC) from time-zero to when the curve declined to 50% of its peak value (Himmelsbach 1941a), or the AUC for a specified number of days (Himmelsbach 1941b). A new method is proposed using comparisons of curves at end-points where both the gradient and severity of withdrawal are equal, as AUC after these points will be of the same size if they reflect identical underlying processes. We therefore propose 3 defining parameters: 1) Total withdrawal distress (TW) = AUC; 2) Peak withdrawal distress (PW) = height of curve at peak; 3) Average daily withdrawal distress (AW) = TW divided by the number of days it takes for the withdrawal (to compare withdrawal curves of different lengths). By this method results can be easily compared, are easy to understand and apply to clinical practice. The table below illustrates the potential of this method based on the results of classic open studies, where abrupt morphine withdrawal is taken as 100%. (Bup = buprenorphine):

Withdrawal Type	PW	TW (peak day)	AW	Study Reference
Abrupt Morphine	100%	100% (2)	100%	Refs below, Kolb & Himmelsbach 1938
14-day Morphine	60%	148% (15)	54%	Mayors Committee 1930
7-day Morphine	71%	138% (9)	60%	
Abrupt Methadone	59%	58% (9)	132%	Isbell *et al.* 1947
Abrupt Bup	≈ 44%	≈ 88% (14)	≈ 36%	Jasinski *et al.* 1978

RECENT RE-EVALUATION OF OUTCOME OF TWO METHADONE MAINTENANCE TREATMENT PROGRAMS IN NEW YORK

I. M. Disla[1], J. E Myers[1], J. Kreuter[1], D. Melia[2], L. Borg[12], E. Khuri[2], A. Wells[2] and M. J. Kreek[1]

The Rockefeller University' and The New York Hospital - Cornell University Medical Center[2], New York, NY

The purity of illicit heroin has markedly increased in New York City, from 7-30% in the past up to >70% over the last 2 years. Methadone maintenance, an effective treatment for heroin addiction, has been under study at The Laboratory of the Biology of Addictive Diseases at The Rockefeller University, which has been affiliated with the NYH-CUMC's methadone programs: the Adolescent Development Program (ADP) and the Adult Clinic (AC) since their inception in 1969 and 1972, respectively. Both clinics offer a comprehensive range of services. In this study, prospectively collected (January 1, 1997 through March 31, 1997) urine toxicology findings, methadone doses, and time in treatment for all patients in both clinics were analyzed. The relationship between time in treatment and urine positive for illicit opiate use was determined. Urine specimens collected randomly at time of medication were analyzed for illicit opiate use. At the ADP (n=118) the number of patients with 22 illicit opiate positive urine specimens decreases from 60%, for patients in treatment for 3-6 months (n=10), to 10%, for patients in treatment for ≥5 years (n=32). At the AC (n=215) the number of patients with ≥2 illicit opiate positive urine toxicology specimens decreases from 47%, for patients in treatment for 3-6 months (n=17), to 2% for patients in treatment for ≥5 years (n=83). At the ADP the overall dose range was from 25-125 mg, with a median dose of 92.5 mg and an average dose of 86.5 mg, while at the AC there was a range of 1-120 mg, a median dose of 80 mg and a mean dose of 75.3 mg. Over the last 3.5 years it was found that 38%-41% of the patients dropped out during the first year. In conclusion, as in the past, use of appropriate methadone doses, coupled with comprehensive services yields a decrease in heroin use.

ACKNOWELDGMENT: Supported by NIDA DA-050-05130 and DA-K05-00049.

A BRIEF MEASURE OF PERCEIVED HEROIN AVAILABILITY: PSYCHOMETRIC CHARACTERISTICS AND ASSOCIATIONS WITH DRUG USE

D. A. Wasserman[1,2], A. L. Stewart[1], and C. A. Duva[1]

University of California[1] and Veterans Affairs Medical Center[2], San Francisco, CA

The day-to-day environments of drug abuse patients may influence the likelihood of continued drug use. An important environmental variable to explore is drug availability. We report on the psychometric evaluation of a brief, multidimensional self-report instrument, the Heroin Availability Inventory. The instrument was completed by 250 patients at three opioid-maintenance (methadone/ LAAM) treatment programs. Patients were 59.2% male; 52.8% white, 30.0% black, 10.0% Latino, and 7.2% other. Preliminary analyses suggested that a subset of 16 items from the larger inventory had good distributions and a clear factor structure and formed an internally consistent (alpha = .83) general availability scale with six subscales: ease of heroin acquisition, proximity to heroin dealing, heroin cost, heroin quality, contact with heroin users, and willingness to steal to obtain heroin. Total availability scores were significantly related to days since last heroin use (r = -.34), heroin use in the last 30 days (r = .26), and time in treatment (r = -.27). Further, five of the six subscales were significantly related to days since last heroin use (rs -.13 to -.44), four to heroin use in the last 30 days (rs .20 to .42), and five to time in treatment (rs -.15 to -.20). Heroin availability differed by gender and treatment program. Responses did not seem affected by socially desirable responding or psychological distress. A revision of the instrument is being validated with a new sample (N = 120) and will be available upon study completion.

METHADONE DOSE AND RECENT HEROIN USE IN METHADONE MAINTENANCE TREATMENT

R. Stohler, S. Petiljean, and D. Ladewig

Department of Psychiatry, University of Basel, Switzerland

The relationship between methadone dose and recent heroin use was examined in methadone maintained patients by a cross-sectional survey. Subjects were questioned with a standardized questionnaire. Responders (n=775) and non-responders differed regarding two baseline variables (age and years in treatment). 54% of the responders had been in treatment-for 2 or more years (3.2±3.02 yrs), mean age was 30.1±6.4 yrs, male 67%. Mean dose of methadone was 64±38 mg/day and ranged widely from 3 to 210 mg/d. 68% reported heroin use during the last 30 days prior to the interview. The association between low methadone dose (<70 mg/d) and more frequent heroin use was not confused (Chi-Sq = 1.05, p>0.5). Furthermore patients in treatment for less than 2 years on low-dose methadone had no higher levels of heroin use than those on high doses (Chi-Sq = 1.35, p>0.5). Patients in treatment for more than 2 years showed a tendency to use more heroin if maintained on high methadone doses (Chi-Sq = 4,8, p=0.09). These data do not support the use of high-dose methadone to control heroin use.

PREDICTORS OF CONTINUED USE OF HEROIN VS. COCAINE IN POLYDRUG USERS ENTERING TREATMENT

D. H. Epstein, A. Umbricht, A. DeJesus, and K. L. Preston

National Institute on Drug Abuse, Intramural Research Program, Baltimore, MD

During the baseline phase of a treatment study for cocaine-using opiate-dependent patients, we observed that patients continued using both opiates and cocaine, but that different patients used each drug to different degrees. We hypothesized that the frequency of use for each drug might reflect a preference for that drug as psychiatric self-medication, and that the use of each drug would therefore be associated with a distinct set of psychiatric symptoms. Data were analyzed retrospectively from the records of 146 patients during the study baseline (5 weeks of methadone maintenance plus weekly counseling). Predictors were taken from questionnaires and interviews administered at intake, and from measures of craving for each drug (self-rated thrice weekly). The two dependent variables were: 1) percentage of opiate-positive urines during baseline, and 2) percentage of cocaine-positive urines during baseline. For each dependent variable, predictors were eliminated in two phases: univariate analyses (ANOVAs or Pearson correlations) followed by multiple linear regression with backward elimination. Results showed that for each drug (opiates and cocaine), the strongest predictor of continued use was self-reported craving for that drug, although that relationship was stronger for cocaine than for opiates. Other predictors of continued use differed by drug, but did not clearly support a self-medication hypothesis, because, unexpectedly, continued use of either drug was associated with better psychiatric and interpersonal functioning.

ENHANCED METHADONE TREATMENT FOR COCAINE-USING METHADONE PATIENTS

L. Handelsman, S. Magura, A. Rosenblum, S. Acevedo, R. Greenberg, J. O'Day, B. Fallon, S. Bovaird, and E. Friedman***

NDRI, New York, NY; *Mount Sinai Medical Center, New York, NY; and **Beth Israel Medical Center, New York, NY

Objectives: To describe a manual-driven 12-month enhanced treatment intervention for cocaine-using methadone patients and to present case examples of patients exposed to this treatment. The enhanced intervention, based on Richard Rawson's MATRIX model (1991) is a cognitive-behavior based treatment for dually-addicted enrollees into methadone maintenance. One of the methadone programs is predominantly for offenders released from jail. In addition to treating heroin and cocaine, treatment objectives include an emphasis on establishing active participation and retention in the program and increasing self-care in terms of hygiene, grooming, physical and mental health. The enhanced treatment consists of several components in addition to standard methadone program services (a stabilized methadone dose and methadone counseling). Structured individual and group sessions (5 x per week) are used to identify drug use patterns and triggers and to build coping responses. The model also utilizes a treatment reinforcement intervention as developed by Iguichi *et al.* (1997); therapist and patients collaboratively develop realistic treatment goals, break them down into weekly achievable tasks, and set up a reward structure for task completion. Patients also attend monthly group leisure activities and outings in the community. A less intensive second phase of treatment, four months after entering treatment, integrates these components into twice weekly groups which are run by regular methadone counseling staff who have been trained in this model and receive ongoing clinical supervision.

ACKNOWLEDGMENT: Supported by NIDA grant RO1 DA06959.

URINE MONITORING AND STAFF CLINICAL EVALUATION IN METHADONE MAINTENANCE

*L. Gourarier**, J. Fellous*, B. Bonan*, and W. Lowenstein***

***Pharmaceutical Services, **Monte-Cristo Center, Hôpital Laënnec, Paris and ***Laboratory of Biostatistic, Hôpital Necker-Enfants Malades, Paris**

The Monte-Cristo Center at Laennec Hospital in Paris, France has provided methadone treatment to heroin addicted patients since October, 1994. The present study evaluates the importance of systematic urine sampling in addition to clinical evaluation among the heroin-addicted patients under methadone treatment at the Center. The absence of statistical agreement between subjective analysis of drug addiction, by physician and patient, and objective analysis through urine samples emphasizes the complementary nature of the two types of data collected. When reliably performed that is, in absence of disciplinary response likely to alter results, urinary monitoring could enable physicians to anticipate initial clinical improvement in the early stages of treatment. Evidence points to positive biological findings relative at the sixth month of treatment (M6), while clinical evaluations made at the same stage remained relatively pessimistic. In addition, close observation of urine samples could be of great predictive value if further studies could confirm that relapse in drug using appears first in urine sample analyses before being diagnosed through clinical exams.

FOUR YEARS PROSPECTIVE STUDY OF ISRAELI REPLICATION MODEL AGONIST TREATMENT PROGRAM: EXTENSION OF EARLIER STUDY

M. O. Adelson,[,**], R. Hayward, G. Bodner, M. Gelkopf,[*] A. Bleich[*], and M. J. Kreek[**]*

***The Dr. Miriam and Sheldon G. Adelson Clinic for Drug Abuse Treatment and Research: Sourasky Medical Center, Tel Aviv, Israel and **Laboratory of Biology of Additive Diseases The Rockefeller University, New York, NY**

We have hypothesized that we can replicate an effective U.S.A. model clinic for opiate addiction in another country. with a similar success, in spite of major geographical, linguistic and cultural differences. Four years ago, we established a new outpatient model methadone maintenance and research clinic for 120-150 patients affiliated with a major university hospital in Tel Aviv, Israel. Since the establishment of the clinic in July 1993, prospective data on demographic and other factors relating to addiction and treatment were collected. The clinic uses adequate doses of methadone pharmacotherapy in conjunction with appropriate medical and behavioral treatment. A total of 212 patients with opiate addiction were admitted to clinic and followed from July 1993 until July 1997. The main outcome measures were the overall retention and one year retention rate for all patients admitted since July 1993, and the prevalence of patients with no evidence of illicit opiate use, after one and one and a half years in treatment. We have found that the overall retention in treatment, irrespective of time in treatment, is 67.9%. The one-year retention rate for all patients admitted since the clinic was opened in July 1993 is 72.5%. The current one year retention rate is 81.5%. After one year in treatment, 58.8% (n=131) of our patients had no further evidence of illicit use of opiates in urine, and after one and a half years of treatment 71.2% (n=104) had no evidence of illicit opiates use. We have succeeded in replicating a model clinic from the U.S.A. to Israel, as shown by the high retention rate and the significant reduction in the use of illicit opiates in spite of the geographical, linguistic and cultural differences between the countries.

LONG-TERM METHADONE IN OPIOID DEPENDENCE: A SYSTEMATIC REVIEW

M. Farré, A. Mas, V. Moreno[1], M. Torrens, and J. Camí[2]

Department of Pharmacology, Institut Municipal d'Investigació Mèdica. Universitat Autònoma, [1]Institut Català d'Oncologia and [2]Universitat Pompeu Fabra, Barcelona, Spain

Methadone (M) is considered the standard treatment of opioid dependence in long-term and maintenance programs. Other drugs has been proposed as alternatives to M (e.g. Buprenorphine [B] or LAAM). The objective of this study was: 1) to test the evidence of the efficacy of M in long-term programs, and 2) to compare the results of M with other opioids. We searched MEDLINE (from 1966 to 1997, keywords: M [all fields] and randomized controlled trial [publication type], date of search: 11-26-1997) for published articles of M efficacy in opioid dependence. Articles were selected according the following criteria: randomized controlled double-blind clinical trials, long-term efficacy (from 13 to 40 weeks). Outcomes were treatment retention and urine samples positive for opioids. Only eleven articles of the search fulfil the above mentioned criteria. Summary odds ratios (OR) and 95% confidence interval were calculated in RevMan 3.0 software with the Mantel-Haenszel method. We tested for heterogeneity using a (^{2} test. In the retention analysis, M was more effective than other drugs (all together, OR 1.84, [1.55-2.19]). Higher doses of M ((50 mg/day) were superior than lower doses (OR 2.09 [1.69-2.581). When compared to B, both drugs produced similar results, being B slightly better at low M dose, and M better at higher dose (OR 0.86 [0.57-1.31] and 1.36 [0.98-1.88] respectively). M produced higher retention rate than LAAM (OR 1.96 [1.41-2.72]). No significant differences were found between treatments in urinary opioids. The results suggest that methadone is more effective than other opioids in the long-term management of opioid dependence.

ACKNOWLEDGMENT: Supported by grant CIRIT 1997SGR00077.

LOFEXIDINE: ITS USE IBYDRUG DEPENDENCY UNITS IN THE UNITED KINGDOM

J. S. Akhurst and K Davies

Britannia Pharmaceuticals Limited, Redhill, Surrey, England

Background: The alpha, adrenergic agonist, lofexidine (Britlofex®), has been available in the United Kingdom since 1992. It offers a rapid, non-opioid alternative to methadone for inpatient and community opioid detoxifications. **Aims:** To identify current usage and safety of lofexidine. **Design:** A telephone survey of 121 drug dependency units in the UK, indicated that 105 (87%) were using lofexidine. A sample of 39 units, randomly selected, completed a questionnaire for each patient who had recently embarked on a lofexidine detoxification. **Results:** 1074 questionnaires were completed. Nearly two thirds of patients (62.5%) attempted an outpatient detoxification, with the remainder attempting an inpatient detoxification with lofexidine. Overall 617 patients (60.4%) successfully completed the detoxification, with nearly 60% of outpatient detoxifications successful. Patients started on a mean dose of 0.8mg/day (median 0.6mg/day) of lofexidine. Those completing the detoxification titrated to a mean dose of 2.2mg/day (median 1.6mg/day) and detoxified in a mean duration of 10 days (median 10 days). Employed patients, those withdrawing from opioids other than heroin and those taking diazepam or naltrexone with lofexidine were more likely to complete the detoxification. However the success rate was, nevertheless, greater than 50% for those withdrawing from heroin and for unemployed patients. The starting dose of lofexidine, duration of opioid dependency and number of previous detoxification attempts appeared not to influence outcome. Adverse events were recorded in 351 detoxifications (32.7%), although many are most likely attributable to the underlying withdrawal syndrome. The most frequently recorded were dry mouth (5.3%), dizziness (8.5%), hypotension (7.5%), bradycardia (3.9%) and sedation (6.6%). **Conclusion:** This retrospective, observational survey has provided useful information on the safety and current usage of lofexidine in the UK. It has identified different treatment methods, given an insight into the characteristics of those patients most likely to succeed with a lofexidine detoxification, and quantified the adverse events.

LAAM: FOUR YEARS, FOUR HUNDRED PATIENTS LATER

P. Casadonte, E. O'Donnell, N. Lynch, and J. P. Rotrosen

Department of Veterans Affairs New York, Department of Psychiatry, New York University Medical School, NIDA/VA Medications Development Research Unit

Beginning October 1994 LAAM has been offered for maintenance treatment at the NYVA. Since April 1995, LAAM has been used for all new parients entering treatment to minimize methadone diversion. Four hundred and two patients have been inducted on LAAM. We reviewed retention since 1994. current patient satisfaction and random urine drug screens for opiate/cocaine use in 20 LAAM and 20 methadone patients. Induction closes are rapidly titrated upward until the patient is comfortable. Patients' most common complaint is constipation. Majority of patients receive 3 doses/week. although 15 % receive LAAM twice a week. Eighty percent of patients remain in treatment longer than 6 months. A patient satisfaction survey of 131 respondents on LAAM, previously treated with methadone indicated that 66% prefer LAAM. Individuals who are employed and functional prefer the reduced clinic visits on LAAM. Patients who prefer LAAM have fewer median years of addiction. are younger, more rapidly stabilized, lower incidence of psychiatric disorder. Review of 20 randomly selected urine drug screens indicates occasional opiate use in both groups, 23 % LAAM, 22% methadone. LAAM patients arc newer to treatment. the last methadone patient having been admitted in 1995. LAAM is a safe and effective alternative to methadone treatment and although is more expensive milligram per milligram than methadone, when other costs-staff time. etc. are considered, we believe that LAAM presents its own costs savings. The fact that LAAM has significantly reduced diversion and requires fewer visits presents a distinct advantage over methadone. Further studies remain to be done on treatment matching of LAAM and methadone patients.

ACCEPTANCE AND EFFECTIVENESS OF Lα-ACETYL-METHADOL (LAAM) IN METHADONE PATIENTS WHO HAVE NOT YET ACHIEVED HEROIN ABSTINENCE

L. Borg[1,2] , A. Ho[1], A. Wells[2], I. M. Disla[1], J. E. Myers[1], H. Joseph[3], P. Appel[3], D. Moody[4], A. Spanbauer[4], and M. J. Kreek[1]

Rockefeller University, NY, NY[1]; Cornell University Medical Center, New York, NY[2]; Office of Substance Abuse Services New York, NY[3]; and Center for Human Toxicology, University of Utah, Salt Lake City, UT[4]

LAAM, a long-acting congener of methadone, has been FDA-approved since 1993 as a maintenance. thrice-weekly administered pharmacotherapy for the treatment of heroin addiction. Many studies have shown that heroin-addicted subjects have disruption of the normal hypothalamic-pituitary-adrenal (HPA) axis, with normalization during effective methadone maintenance treatment (MMT). To date, there have been limited studies of the neuroendocrine status of patients treated with LAAM. Patients (9M, 3F; mean age = 39.9±1.6 yrs) in MMT for >6 months (range 11-81, mean=28 mo) on >60 mg of methadone (mean dose=96, range=60-120 mg, mean trough methadone plasma levels =341.0±45.5 mg) who continued to abuse illicit opioids (>3 positive urine toxicology results for opioids within past two months), were transferred to LAAM treatment, at dosages (as per manufacturer's guidelines) aiming for 1.2x the pre-LAAM methadone dosages. Plasma ACTH and cortisol levels were measured prior to the initiation of LAAM and were repeated, along with serum prolactin levels and plasma levels of LAAM and its active metabolites, after 6-8 weeks of LAAM treatment on each day of LAAM dosing (M-W-F). Supervised weekly urine toxicology specimens were obtained. For diverse reasons, all 12 patients preferred LAAM, although 4 patients did not complete the study due to noncompliance or by their request, and were returned to MMT. Of the 8 remaining patients, only one had stopped illicit opiate use by end of study. ACTH, cortisol and prolactin levels did not vary by LAAM dosing day, however norLAAM levels varied significantly. ACTH levels were significantly increased on LAAM vs. methadone. This study suggests that "problem patient" (defined as MMT patients using heroin despite effective treatment) acceptance of LAAM treatment is high, with moderate compliance. Illicit opiate use continued in most subjects despite adequate LAAM and previously adequate methadone dosages. LAAM patients were not in steady state since, in addition to the variation in norLAAM levels, overall ACTH levels on LAAM were significantly > methadone.

ACKNOWLEDGMENTS: Supported by NIDA DA-P50-05130, DA-K05-00049, RO1DA1-0100, and OASAS-NY.

PATIENT SATISFACTION WITH ORLAAM IN AN INNER CITY METHADONE TREATMENT PROGRAM

M. Chu, L. S. Brown, R. Sage, B. J. Primn, and J. E. Rawls*

Addiction Research and Treatment Corporation, Brooklyn, NY

Levomethadyl acetate hydrochloride (Orlaam) is the last pharmacotherapeutic agent approved for the treatment of opioid dependence. However, very little is known about its efficacy and limitations in clinical settings, partly because of the hesitancy of treatment providers and patients. **Objectives:** The purpose of this presentation is to evaluate outcomes of enrollment of opioid dependent patients on Orlaam. **Methods:** At this writing, 46 patients from three different New York City clinics began Orlaam therapy from February through September of 1997. The mean age of these patients is 35.5 years. There are 10 African Americans and 34 Latino patients among these enrollees; 23.9% were female. All had a history of methadone treatment. Patients provided urine toxicological specimens at least every two weeks. Patients also completed an Orlaam satisfaction survey at various periods during Orlaam enrollment. **Results:** While the evaluation is ongoing, preliminary information is available. Twenty-four patients discontinued Orlaam after an average of 37 days on this therapy. Seventeen of these 24 converted to methadone therapy; the other seven left treatment. Patients who remained on Orlaam therapy were less likely to test positive for heroin (P=0.037). Analysis of the patient satisfaction surveys will be presented. **Conclusion:** Preliminary analysis suggests that there were significant differences between those patients who remained on Orlaam and those who discontinued. Given the paucity of chemotherapeutic agents for treatment of opioid treatment, more information is needed to determine the usefulness of Orlaam. The public health significance is especially critical in view of role of untreated drug abusers in the prevalence of HIV/AIDS. Results of further analyses will be presented.

COMPARISON OF ACUTE PHYSICAL DEPENDENCE DURATION IN HUMANS AFTER SINGLE DOSES OF LAAM OR METHADONE

T. Eissenberg, M. L. Stitzer, G. E. Bigelow, A. R. Buchhalter*, and S. L. Walsh*

Johns Hopkins University School of Medicine, Baltimore, MD and *Department of Psychology, Virginia Commonwealth University, Richmond, VA

Acute physical dependence can occur after single dose opioid agonist exposure, as revealed by naloxone precipitated withdrawal. Levo-alpha acetylmethadol (LAAM) and methadone (METH) are μ-opioid agonists used as opioid dependence treatments. The acute physical dependence engendered after a single LAAM dose has not been investigated systematically in humans. LAAM's long half-life and active metabolites may contribute to long-lived acute physical dependence. This study compared the magnitude and duration of the acute physical dependence engendered by single-dose LAAM versus METH exposure. Five non-dependent opioid-experienced volunteers received once weekly doses of placebo, LAAM or METH (15, 30, or 60 mg/70 kg p.o. of each drug). Volunteers then received naloxone (1.0 mg/70 kg i.m.) 24, 72, or 144 hr after dosing in 3.5-hr sessions. Subject-rated, observer-rated, and physiological measures were assessed regularly in each session. For both LAAM and METH, acute precipitated withdrawal magnitude was positively related to pretreatment dose. For both agonists acute precipitated withdrawal effects were observed up to 6 days after 60 mg/70 kg treatment, though these effects were more reliable for LAAM than for methadone. These results indicate that acute physical dependence persists for longer than has been previously reported. They also suggest that LAAM's physical dependence may be longer-lived than METH's.

ACKNOWLEDGMENTS: Supported by USPHS grants P50-DA05273, RO1-DA04011, R29-DA11082, and T32-DA07209.

AN OPEN-LABEL PILOT SAFETY STUDY OF LOFEXIDINE FOR THE TREATMENT OF OPIATE WITHDRAWAL

E. Yu[1], B. H. Herman[2], P. J. Fudala[1], A. Montgomery[2], C. N. Chiang[2], R. Walsh[2], K. Kampman[1], V. Dhopesh[1], J. Cornish[1], F. J. Vocci[2], P. Bridge[2], and C. P. O'Brien'

[1]University of Pennsylvania, Department of Psychiatry and the Department of Veterans Affairs Medical Center, Philadelphia, PA and [2]NIH, National Institute On Drug Abuse, Medications Development Division, Rockville, MD

Preliminary data have indicated that lofexidine, an alpha-2 adrenergic receptor agonist, may be effective for the clinical management of the opiate withdrawal syndrome while producing less hypotension than clonidine. The present 20-day inpatient study is being conducted to assess the relative safety of lofexidine and to obtain information related to its potential efficacy. Opiate-dependent individuals are stabilized on morphine subcutaneously (25 mg four times daily) for 8 days. On day 9, morphine is discontinued, and lofexidine is administered daily through day 18. No medication is administered on days 19 and 20. Nine subjects have taken lofexidine in the 1.6 mg/day dosage group. Three of these subjects have completed the protocol; five dropped out secondary to opiate withdrawal symptoms and one for personal reasons. Two subjects experienced transient orthostatic hypotension that quickly resolved upon sitting. Of these two, one was secondary to dehydration from diabetes mellitus, type II. Nine subjects have taken lofexidine in the 2.4 mg/day group. Five of these subjects have completed the protocol and four dropped out secondary to opiate withdrawal symptoms. Five subjects in this group exhibited transient orthostatic hypotension. Of these five, four reported vertigo that quickly resolved upon sitting. Three subjects have taken lofexidine and completed the 4.0 mg/day group and all three experienced transient orthostatic hypotension. Of these three, two reported vertigo that quickly resolved upon sitting. None of the subjects at any dose level experienced syncope, symptomatic bradycardia, or persistent hypotcnsion. No serious adverse medical events have been observed.
ACKNOWLEDGMENTS: Supported by Britannia Pharmaceutical Limited and an interagency agreement (YO1-DA30011) between the NIDA and the Philadelphia Veterans Affairs Medical Centers.

OUTCOMES FOR OPIOID ADDICTS TREATED IN A 30-DAY AMBULATORY DETOXIFICATION PROGRAM

B. Poddig, U. Malkerneker, and F. Vozak

Edward Hines, Jr. VA Hospital, Hines, IL

The purpose of this study was to examine the outcome of veterans treated in an ambulatory detoxification program. Patients were admitted to the program and received initial doses of methadone in the 20-30 mg range. During the first week of treatment, the dose of methadone was adjusted in an attempt to stabilize the patient. A gradual taper of methadone that occurred over three weeks followed this period. In addition to the pharmacological treatment, patients were required to participate in an ambulatory detoxification group thrice weekly. Throughout their treatment patients were monitored for level of opioid craving assessment of confidence in ability to resist drug use (DTCQ), self-report of drug use, and were subjected to random urine drug testing. A sample of 167 records of veterans enrolled in this program were analyzed and subjects were classified into two groups: completers (C), n= 79 and noncompleters (NC). n=85. There were no significant differences in age (45 vs. 44). years of heroin use (17.5 vs. 18.8) or previous treatment with methadone (57% vs. 62%) between groups. C group had a two-fold increase in length of treatment compared to NC group (27 days vs. 14) and attended 70% of groups. Both groups reported significant decreases in level of craving for opioids compared to baseline. Group C had significant improvements in confidence level for drug avoidance for the majority of profiles measured in the DTCQ. Sixty-eight percent of C group continued treatment compared to 5 % of NC group. Urine toxicology results confirmed a significant decrease in opioid use in the C group (97 % positive at baseline vs. 54% at discharge). Use of other illicit substances decreased in the C group (60% vs. 41%) during the course of treatment compared to an increase in illicit drug use (56% vs. 71%) for the NC group. In light of these findings, authors conclude that an ambulatory detoxification program should be considered as a viable treatment option for opioid addicts.

DETAILED FREE SELF-HELP INFORMATION FOR CLIENTS DETOXIFYING FROM OPIATES: "THE SAMURAI APPROACH"

J. Myles, F. Law, M. Dean, I. Sherwood, H. Cottee, G. Monahan, and A. Hewitt

Bristol Specialist Drug Service, Frenchay Healthcare NHS Trust, Blackberry Hill Hospital, Manor Road, Fishponds, Bristol, UK

Introduction and Justification: No detailed self-help booklets currently exist for opiate detoxification. Providing detailed guidance and information is important to detoxifying opiate addicts for a number of reasons: **1)** It is more likely to result in appropriate behavior change (Gatherer *et al.* 1979); **2)** It may help treatment resistant clients who have unrealistic expectations about the detox (e.g. high detoxification fear); 3) It may help in particularly difficult detoxes (e.g. methadone, high dose, prolonged usage); 4) It is generally thought that psychological factors have a major impact on the severity of withdrawal symptoms (Senay *et al.* 1977, Cohen *et al.* 1983), and indeed providing information in a brief (15-30 mins) interview reduced both the peak and total severity of withdrawal by one-third (Green and Gossop, 1988). **Details of Approached Used:** To avoid the difficulty of assimilating detailed information, the strategy utilized involved use of a synopsis style with bullet points, illustrations by cartoons of all major points, and a Samurai warrior analogy (Marlatt, 1985) in order to promote the cognitive strategies of mastery and self-control (Beck *et al.* 1993). The client prepares for the detox as a warrior who prepares for a battle. Self-discipline, learning self-defense skills, planning the campaign carefully, and repairing the fortifications (life-style factors) are all important. Withdrawal symptoms are seen as the external enemy, complacency as the enemy within, and social support as the allies. Acute opioid withdrawal is a pitched battle lasting 5-10 days, protracted withdrawal the subsequent guerrilla warfare lasting 3-6 months. Drugs (e.g. clonidine, lofexidine) are physical warfare, naltrexone is body armour, psychological self-techniques are internal propaganda, and myths about withdrawal are enemy propaganda.

REINFORCING THERAPEUTIC BEHAVIORS: PRELIMINARY RESULTS FROM A TWO-SITE DETOXIFICATION STUDY

A. R. Morral, M. Y. Iguchi, K. C. Kirby[1], R. J. Lamb[2], and S. P. Weinstein[3]

[1]RAND, Santa Monica, CA; Temple University, [2]Allegheny University of the Health Sciences and [3]Thomas Jefferson University, Philadelphia, PA

Reinforcing either abstinence or behavioral progress toward treatment plan goals can produce increased abstinence rates among clients in drug treatment. We examine if these contingency management strategies can also improve detoxification treatment (DT) success rates and naltrexone maintenance (NMT) compliance. In this 2 x 2 experimental design, we randomly assign 168 subjects at two sites (Phila. and L.A.) who are receiving a 20-week DT and 12 week NMT aftercare program, to one of four counseling interventions: vouchers for abstinence, vouchers for completing treatment plan tasks, vouchers for abstinence and completing treatment plan tasks (Combined), or a no voucher control. Findings from the first 45 subjects suggest the long-term detox might attract those who are unwilling or unable to enter methadone maintenance treatment. The detox is achieving high retention rates (89% of planned program days successfully completed), and large reductions in drug use and other problem behaviors. No significant group effects are detectable yet, but no subject has dropped out of the Combined condition during detoxification, and it is yielding especially good urinalysis outcomes.

ACKNOWLEDGMENT: Supported by NIDA RO1 DA10778

VOUCHER-BASED REINFORCEMENT OF OPIATE ABSTINENCE DURING METHADONE DETOXIFICATION

E. Robles, K. Silverman, E. C. Strain, G. E. Bigelow, and M. L. Stitzer

Johns Hopkins University School of Medicine

This ongoing study is evaluating voucher-based reinforcement of opiate abstinence during a methadone detoxification. After a 4-week methadone maintenance baseline, patients are randomly assigned to an abstinence reinforcement or control group. Reinforcement patients receive a 22-week intervention in which they can earn vouchers for providing opiate-free urines before, during and after a methadone detoxification. Patients can earn vouchers three times per week under a schedule of escalating reinforcement for sustained abstinence (maximum earnings of $2,232). Controls receive noncontingent vouchers (i.e., independent of urinalysis results). Methadone doses are maintained during the first 6 weeks of the voucher intervention (maintenance phase), and are gradually reduced to 0 mg during the following 10 weeks (detoxification phase). Forty nine patients have been enrolled in the study. We report outcomes for 26 abstinence reinforcement and 22 controls who have completed the detoxification. During the reported 20 weeks no differential attrition has occurred, and more than 86% of the patients in both groups were maintained in treatment until the end of the detoxification phase. Repeated measures ANOVAs with Group and Phase (baseline, maintenance, detoxification) as factors showed a significant Group effect on the percent of opiate-free samples ($F = 11.0$, $p = 0.002$). Tukey's posthoc tests showed no significant differences during baseline or maintenance phases; during the detoxification phase, abstinence reinforcement patients provided more ($p \leq 0.01$) opiate-free (89% vs. 66%) urines than controls. During the detoxification phase, significantly more ($F = 4.86$, $p < 0.001$) cocaine-free samples were submitted by the opiate abstinence reinforcement group than by the control group (60% vs. 30%). Patients in the abstinence reinforcement group sustained longer (13.79 vs. 8.12 weeks) intervals of continuous abstinence from opiates than controls ($t = -3.37$, $p = 0.002$). These preliminary results suggest that voucher reinforcement can retain patients in treatment, and prevent relapse to opiates and cocaine during a methadone detoxification.

ACKNOWLEDGMENTS: Supported by NIDA grants P50 DA09258 and T32 DA07209.

CONTINGENCY BASED COMMUNITY REINFORCEMENT THERAPY FOR OPIATE AND COCAINE ABUSERS

K. Gruber, M. L. Stitzer, and M. A. Chutuape

Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD

We have developed a new outpatient drug-free treatment, called Contingency Based Community Reinforcement Therapy (CCRT), tailored to the needs of opiate abusers residing in an impoverished inner city environment. Our treatment is conceptually based on the Community Reinforcement Approach (CRA), whose primary goal is to facilitate behavioral lifestyle changes that will help clients achieve and maintain abstinence from drugs. In addition, a contingency-based monetary incentive program is woven into the therapy process in order to directly support CRA interventions. Fifty-one subjects exiting a 3-day detoxification unit were randomly assigned to either standard referral aftercare (Control; N=24) or CCRT (N=27). Results showed that 63% of the CCRT patients versus 17% of the control group were enrolled in treatment by the end of week four ($p<.001$). In addition, 59% of CCRT patients reported abstinence for heroin at one month verified through urine analysis versus only 17% of the control group ($p < .01$). Employment, which was a goal of therapy, increased from 0% to 33% in the CCRT group and from 0% to 8% in the control group ($p<0.05$). Finally, on a checklist measure, CCRT members reported significantly more behavioral changes consistent with a healthier drug-free lifestyle than did Controls ($p<0.01$). These results support beneficial effects of this aftercare treatment for opiate abusers that utilizes financially supported CRA techniques. This suggests that further controlled evaluation is warranted.

ACKNOWLEDGMENT: Supported by NIDA grant DA10192.

IMPULSIVITY, PAYMENT PREFERENCE AND OUTCOME MEASURES OF POLYDRUG DEPENDENT VBRT PARTICIPANTS

M. P. Reilly, J. Roll, K. Downey, and C. R. Schuster

Wayne State University School of Medicine, Department of Psychiatry and Behavioral Neurosciences, Clinical Research Division on Substance Abuse

Polydrug-dependent adults, enrolled in a voucher-based reinforcement therapy (VBRT) program that provided vouchers exchangeable for goods and services contingent upon abstinence from illicit drug use, were asked to choose between receiving different hypothetical amounts of money and different hypothetical amounts of voucher using a modified multiple choice procedure (MCP). They were also asked to complete the Barratt Impulsivity Scale (BIS) questionnaire. The goal was to relate payment preferences for money and voucher and to the BIS impulsivity scores and also to VBRT treatment outcome measures. Because most VBRT programs involve delayed reinforcement (there is a delay between voucher receipt and exchange), impulsive participants that heavily discount delayed rewards may be less susceptible to the VBRT contingencies and thus have poorer treatment outcomes. It was hypothesized that the participants that reported preferences of money over voucher would have higher BIS scores and have poorer treatment outcomes than participants that reported preferences for vouchers. There were significant correlations between BIS subset scores and time to first abstinence and total number of abstinences. The results indicate that impulsivity was directly related to treatment outcome. There were also correlations between the Drug composite score on the Addiction Severity Index and the BIS scores providing external validity to the BIS scores. The results have implications for voucher-based therapies to the extent that BIS scores and payment preferences predict the reinforcing efficacy of the vouchers used in VBRT programs.

ACKNOWLEDGMENTS: Supported by NIDA grants 1 RO1 DA 10239-01 and 5 T32 DA 07267-04.

A TECHNOLOGY TRANSFER CASE STUDY: VIRGINIA'S SUBSTANCE ABUSE TREATMENT OUTCOME EVALUATION MODEL

K. Ingersoll, C. Wagner, P. Horvatich, N. Baturka, and D. McCall***

Virginia Commonwealth University, Richmond, VA; *University of Virginia, Charlottesville, VA; and **Virginia Department of Mental Health, Mental Retardation, and Substance Abuse Services, Richmond, VA

Researchers are concerned that the substance abuse treatment field often fails to adopt effective, validated, research-based treatments into practice. The Virginia Addiction Technology Transfer Center (VATTC) is one of 11 CSAT centers that aims to improve the quality of substance abuse treatment by transferring research technologies systematically to the treatment field. VATTC's collaboration with the state's Department of Mental Health, Mental Retardation, and Substance Abuse Services to develop the motivational group intervention arm of Virginia's Substance Abuse Treatment Outcome Evaluation (SATOE) model is a case example of technology transfer in action. VATTC efforts have focused on the intervention and evaluation arms of the model, and have included technical assistance, consultation, and education, participation in a Workgroup to refine the model, evaluations of the field's readiness to adopt empirically-based practices, development of a treatment manual, implementation of complementary clinical training, development of a listserv, piloting several methods of training practioners, and developing a technology transfer plan. Two needs assessments of the public sector substance abuse treatment field revealed that although most agencies wanted to implement motivational services, they were unprepared and wanted further staff training. The strategic plan for dissemination of the motivational group innovation evolved over time from a top-down, expert authority training strategy to a customized, tailored training package in collaboration with diverse stakeholders that evaluated and dealt with individual resistance related to the introduction of "taboo" subjects, system resistance related to organizational structures, spontaneous diffusion of some elements of the model, and the need for a high degree of interpersonal contact.

ACKNOWLEDGMENT: Supported by CSAT U98TI00837.

DIHYDROETORPHINE (DHE) ALL BUT ABOLISHES PHYSICAL DEPENDENCE ON MORPHINE IN RHESUS MONKEYS

M. D. Aceto, L. S. Harris, and E. R. Bowman

Department of Pharmacology and Toxicology, Medical College of Virginia of Virginia Commonwealth University, Richmond, VA

We reported that DHE, a potent opioid analgesic, possessed a very low physical dependence capacity in rhesus monkeys (Aceto et al. NIDA Monograph, 1997). In the present preliminary study, DHE was substituted for morphine in 3 maximally dependent monkeys for 7 days. At a dose of 0.00006 mg/kg, s.c., 4 x day, it substituted completely for morphine during the entire period. Thereupon, the monkeys were placed in abrupt withdrawal and 15 hr after DHE was withdrawn, very few abstinence signs were observed. The DHE dose regimen was resumed and a day later, the monkeys were challenged with naloxone (NAL) at 0.05 mg/kg, s.c., a dose that would have otherwise precipitated a full-blown withdrawal syndrome in monkeys dependent on morphine. Few withdrawal signs were noted. The dose of NAL was doubled and again the number of abstinence signs was insignificant. Additionally. at the end of the experiment, the usual dose regimen of morphine (3.0 mg/kg. s.c., every 6 hr.) was resumed. Repeated scratching was observed. These results suggest that DHE may alter the expression of tolerance to and physical dependence on morphine. Although physical dependence is no longer considered a necessary condition for drug addiction, for human opioid addicts withdrawal is so distressful that opioids are used to stop withdrawal effects (Kleber, cited in Altman et al., 1996). Finally, DHE may be useful, clinically, in the pharmacotherapy of pain and opioid dependence.

ACKNOWLEDGMENTS: Supported by NIDA Contracts DA 5-8059 and DA 5-8060.

EFFECTS OF ACUTE ALPRAZOLAM, AMPHETAMINE, AND CODEINE ADMINISTRATION ON REFLECTIVE PROCESSING

R. C. Taylor, S. J. Heishman, H. J. Weingartner, J. E. Henningfield, A. C. Ross, and J. M. Lutz*

NIDA, Intramural Research Program, Baltimore, MD and *NIAAA, Bethesda, MD

We have previously found that drug abusers, not under the influence of any drug, demonstrated a selective failure in reflective processing (ie., increased intrusion errors on a test of delayed recall). We hypothesized that this inability to inhibit inappropriate responses would be worsened by an acute drug challenge. Thus, we administered *d*-amphetamine (0, 12.5, and 25 mg), alprazolam (0, 1, and 2 mg), and codeine (0, 12.5, and 25 mg) to separate groups of subjects (n = 12 each group). Subjects received each drug dose twice in random order, and test sessions were conducted at least 72 hr apart. At predrug baseline and two postdrug times (1 and 3 hr for alprazolam and codeine; 2 and 4 hr for *d*-amphetamine), subjects were presented a list of 12 categorically-related words, 6 of which were repeated twice. After 15 min of intervening tests, subjects were asked to recall the words in any order. Different word lists were used at each time and dose. The results indicate that alprazolam decreased working memory and the number of words recalled. d-Amphetamine produced a trend toward decreased working memory, decreased explicit memory, and increased intrusion errors. Codeine had no effect on any of the measures. The similar effect pattern of alprazolam and d-amphetamine suggests that these deficits are not due to drug-induced sedation.

ACKNOWLEDGMENT: Supported by NIDA Intramural Research Program.

NALBUPHINE HYDROCHLORIDE (NUBAIN®) DEPENDENCE IN ANABOLIC STEROID USERS

J. D. Wines, Jr. [1], A. Gruber[2], H. G. Pope, Jr.[2] , and S. E. Lukas[1]

[1]Behavioral Psychopharmacology Research Laboratory and [2]Biological Psychiatry Laboratory, McLean Hospital/Harvard Medical School, Belmont, MA

Nalbuphine hydrochloride, a nonscheduled opioid agonist/antagonist analgesic, is approved for the treatment of pain. Recently, nalbuphine dependence was reported in 3 anabolic steroid users in Britain; we have now encountered 11 cases of nalbuphine abuse or dependence among American athletes. At least 8 subjects were dependent on nalbuphine. Nine subjects began using nalbuphine for pain from weightlifting injuries, but several also took it as an "anticatabolic" agent. One subject initially took it to get "high." Seven subjects were asked about tolerance and withdrawal with nalbuphine; all acknowledged these symptoms. Eight subjects, who had never used drugs intravenously before, reported using nalbuphine via the i.v. route. Additional morbidity related to nalbuphine use included inpatient detoxification from nalbuphine (3), progression to other opioids (3) severe abscesses (1), endocarditis (1), and passive suicidal ideation (1). The subjects' histories also were remarkable for a high prevalence of alcohol and illicit drug abuse/dependence. All subjects reported anabolic-androgenic steroid use, and most had misused numerous other "ergogenic" (performance-enhancing) drugs. Psychiatric comorbidity was frequent, with 7 subjects reporting other Axis I disorders such as major depression (4) and body dysmorphic disorder (4). Virtually all subjects described widespread nalbuphine use in the gymnasiums they frequented. These observations, together with the many recent nalbuphine-related articles in the lay press, suggest that nalbuphine may represent a new drug of abuse among athletes especially those using anabolic steroids, and its scheduling status may need to be re-evaluated.

ACKNOWLEDGMENTS: Supported by grants DA10055, DA03994 and DA00343

THE EFFECTS AND PATTERNS OF USE OF GAMM-HYDROXYBUTYRIC ACID (GHB)

K. A. Miotto, J. Darakjian, W., and R. A. Rawson

University of California, Los Angeles, Department of Psychiatry and Biobehavioral Sciences

There has been an increasing report of toxicity and lethality associated with CHB use, especially when combined with other drugs of abuse. The present investigation was designed to assess the effects and patterns of use for GHB. A brief survey consisting of demographic and psychiatric information and a questionnaire about the participants' experience using GHB was administered. Data from this pilot study (30 males, 9 females) was gathered; 72% were Caucasian descent and 72% were employed. Majority of participants had no current or past psychiatric problems. Results from this study indicated that GHB users generally endorse multiple drug use, among the most commonly used drugs are: Marijuana and ecstasy. Participants reported increased feelings of subjective effects such as, tranquility, happiness, euphoria, relaxation, increased sexuality, pleasant drowsiness, optimism, placidity, well-being and intensity of orgasm. Sixty-nine percent reported that they would either relax/sleep or have sex after GHB use. Thirty-two out of 33 (97%) reported that they would not drive after using GHB because of decreased coordination. Twenty-one (54%) participants reported using GHB on a weekly basis. Twenty-seven (70%) reported using 2 or more times/day. Sixty-six percent (n=26) of individuals using GHB reported loss of consciousness at least once. Three (8%) reported of having seizures and were evaluated at an emergency room. Thirty-one percent of regular users reported developing a tolerance. This data provides a foundation for continued research to develop treatment interventions for this emerging drug problem.

FLUOXETINE VERSUS PLACEBO FOR THE CRAVING OF DEPRESSED ALCOHOLICS

J. R. Cornelius, I. M. Salloum, M. D. Cornelius, J. G. Ehler, and P. J. Jarrett

University of Pittsburgh School of Medicine, Pittsburgh, PA

To date, no studies have been published concerning whether fluoxctinc decreases the alcohol craving or the substance craving of depressed alcoholics. However, our previous work has demonstrated efficacy for fluoxetine in decreasing their drinking and depression (Cornelius *et al.,* 1997). In this report, we focus on the craving of 51 alcoholics with major depression, many of whom also abused other substances, in a 12-week, double-blind, placebo-controlled, parallel group trial (AA09127). Twenty-two of these patients also abused cannabis, and 17 also abused cocaine. Weekly ratings of symptoms were conducted. Craving was rated on a scale from 0 (none) to I (mild). 2 (moderate). and 3 (severe). Alcohol craving decreased more in the fluoxetine group than the placebo group. but this difference was not statistically significant. However, craving for other substances decreased in the fluoxetine group, but increased in the placebo group, which resulted in a significant difference between treatment groups (x^2 = 7.2, df= 2. p = 0.03). There was also a significant group-time effect on marijuana use shown on repeated measures anova (F=3.61: df=2, 19; p=0.036). with the fluoxetine group showing a significantly greater improvement than the placebo group. These findings suggest that fluoxetine decreases the drug craving and the cannabis use of depressed alcoholics.

THE SUBJECTIVE EXPERIENCE OF CRAVING: MULTI-DRUG CONFIRMATION OF A GENERAL FACTOR STRUCTURE

E. P. Merikle and D. B. Marlowe***

***Addiction Research Center, Department of Psychiatry, University of Pennsylvania, and **Institute for Addictive Disorders and Department of Psychiatry, Allegheny University of the Health Sciences, Philadelphia, PA**

Clients abusing a variety of substances (alcohol (N=122]; cocaine [N=50]; heroin [N=20], and nicotine [127]) completed a self-report measure of craving, the General Craving Scale (GCS, Merikle, 1997), that assesses six dimensions (specificity, strength. positive outcomes, behavioral intention, physical symptoms, and affect) associated with the subjective experience of craving. A multi-group confirmatory factor analysis was conducted to test the invariance of a general factor structure of craving (i.e. six dimensions loading on a single craving factor) across these four substances. The factor loadings of the six dimensions on a general craving factor were constrained to be equal across substances. This model fit the data well according to practical fit criteria (NNF=.92 and CFI=.93). Thus, the dimensionality of the subjective experience of craving is consistent across drugs of abuse. However, Lagrange Multiplier tests of the adequacy of these constraints indicated that the factors loading of the positive outcomes and the strength dimensions were not equivalent across substances. Thus, the importance of the different dimensions to the subjective experience of craving varies across substances.

ACKNOWLEDGMENTS: Supported by NIDA grants R01-DA-10113 and R01-DA-08885

PREVALENCE OF ANGER DISORDERS IN A SAMPLE OF SUBSTANCE ABUSERS

R. M. Awalt, P. M. Reilly, M. S. Shopshire, and H. W. Clark

University of California, San Francisco and Department of Veterans Affairs Medical Center, San Francisco, CA

Anger disorders have been correlated with substance abuse and psychiatric severity. We studied the prevalence of anger disorders in two samples of substance abusers. Participants in Study 1 (N=560) were enrolled in treatment studies at the San Francisco Treatment Research Center and completed the hostility subscale of the Symptom Checklist 90-R (SCL-90-R; Derogatis, 1983). Participants in both studies were interviewed using the Addiction Severity Index (ASI; McLellan, Luborsky, O'Brien, and Woody, 1980). In Study 2, we assessed anger disorders with the State-Trait Anger Expression Inventory (STAXI, Spielberger, 1988) in a sample of 94 patients at the San Francisco VA Medical Center. Results showed that 38% of individuals entered treatment with symptoms consistent with an anger disorder compared with non-clinical samples. Of patients who were alcohol- or alcohol and cocaine dependent, 44% had anger disorders based on trait-anger and addiction severity scores. Although individuals with anger disorders did not show higher levels of psychiatric severity than those without anger disorders, the mean anger expression score of the STAXI was 29.4 (SD=10.6); a percentile rank of 91, which correlates with psychiatric severity (r=. 19, p,.05) and family conflict (r=.31, p,.05). When angry, substance abusers tend to display their anger outwardly rather than control their anger.

ACKNOWLEDGMENT: Supported by NIDA grant P50DA09253

DRUG DEPENDENCE AMONG INPATIENTS AT A REGIONAL TRAUMA CENTER

C. A. Soderstrom, D. A. Gorelick, N. J. Carriero*, G. S. Smith#, P. C. Dischinger, D. R. McDuff, J. R. Hebel, T. J. Kerns, S. M. Ho, and K. M. Reid*

University of Maryland at Baltimore, *NIH/NIDA Intramural Research Program, and #Johns Hopkins University, Baltimore, MD

We evaluated the prevalence of drug dependence in an unselected series of 1,118 adult patients admitted from the injury scene to a regional trauma center (mean age 37.4 years, 72.1% male, 56.3% white, 27.5% married, 57.3% employed, 67.7% high school graduates, 51.6% smoke cigarettes, 24.1% currently alcohol dependent). All subjects received the substance use disorders section of the Structured Clinical Interview for DSM-IIIR and the 4-question CAGE drug questionnaire (modified from the CAGE for alcohol); 64% also had urine drug screening. 349 (31.2%) patients had lifetime drug dependence, 209 (18.7%) on > 1 drug (commonest combination cocaine + opiates + cannabis = 48 [4.3%]). 198 (17.7%) patients had current (past 6 months) drug dependence. Lifetime/current prevalence rates for drug dependence (abuse) were sedative-hypnotics--l.5%/0.7% (0.2%/0%), cannabis--14.8%/10% (3.3%/0.6%), cocaine 16.4%/11.3% (1.4%/0.5%), other stimulants-- 1.9%/0.6% (0.1%/0%), opiates--13.9%/9.9% (0.1%/0%), hallucinogens2.3%/0.6% (0%/0%), other drugs--0.9%/0.5% (0.2%/-0%). Patients with current drug dependence were significantly younger, less educated, poorer, and more likely to be African-American, unmarried, unemployed, smoke cigarettes, and have current alcohol dependence than patients without current drug dependence. Among those who had urine drug testing, 42.4% of those with cannabis dependence tested positive for cannabis, 69.1% with cocaine dependence tested positive for cocaine, and 65.7% with opiate dependence tested positive for opiates. Giving ≥ one "yes" answer on the drug CAGE had 83.3% accuracy (91.4% sensitivity, 81.6% specificity) in identifying patients with drug dependence. These findings suggest a significant prevalence of drug dependence among trauma center inpatients, much of which would be missed by urine drug testing, and that the drug CAGE is a useful screen in this population.

ACKNOWLEDGMENT: Supported by NIH grant RO1 AA09050.

THE IMPACT OF ALCOHOL, TOBACCO, AND DRUG USE ON EMERGENCY ROOM UTILIZATION

S. M. Boles, P. B. Johnson, K. McVeigh, H. Richardson, L. Goldfrank, and H. D. Kleber

The National Center on Addiction and Substance Abuse at Columbia University, New York, NY and Bellevue Hospital Center, New York, NY

There is growing recognition that substance use may be implicated in emergency room visits and overcrowding. Consequently, researchers have begun to explore the impact of substance use on emergency room utilization. The main purpose of this study was to determine the volume and nature of substance-related visits in an urban hospital emergency department. One thousand three hundred and forty-seven patients presenting to the emergency department were questioned about their reasons for the visit and their use of alcohol, tobacco, and prescription and illicit drugs. The results indicated that almost 20% of the visits were clearly related to patient substance use. Alcohol use was related to 11% of the visits, tobacco to 6%, crack/cocaine to 6%, heroin to 3%, and marijuana to 2%. Daily drinkers had significantly more emergency room visits in the past year than all other alcohol use categories. Substance use was more frequently related to visits for chronic than for acute medical conditions regardless of the substance involved. These results reveal a clear relationship between substance use and the nature and frequency of emergency room utilization.

A COMPARISON OF IMPAIRED HEALTH-CARE PROFESSIONALS WHO CAN VS CANNOT PRESCRIBE CONTROLLED SUBSTANCES

J. S. Knisely, S. H. Schnoll, and E. Campbell

Medical College of Virginia of Virginia Commonwealth University, Richmond, VA

Most of the existing literature regarding substance abuse by health-care professionals has focused upon physicians. State monitoring programs are currently making services available to a variety of professionals including pharmacists, respiratory therapists, nurses, and others. The present study compared substance abuse patterns and relapse rates of those impaired health-care professionals who can prescribe controlled substances to those who cannot prescribe controlled substances. Four geographically distinct state monitoring programs participated in the study. All participants active in the programs as of November 1995 and all new admissions after October 31, 1995 signed program contracts approved by each state's institutional review board (n=1533). A comprehensive intake interview was conducted that included a chemical use history, psychosocial history, psychiatric history, and medical history. All relapses that occurred while enrolled in the monitoring program were quantitatively and qualitatively assessed. The prescribing group consisted primarily of MDs (78%), DOs (9%), and DDSs (5%). The most frequent types of professionals in the comparison group were pharmacists (36%), respiratory therapists (22%), physician assistants (9%), and nurses (8%). These groups were significantly different regarding gender ($p<.001$), age ($p<.0001$), race ($p<.05$), and marital status ($p<.001$). Prescribers were more likely to be male, older, and married. Both groups were approximately 90% Caucasian; however, more prescribers were Asian and non-prescribers African American. There was also a significant difference between the groups regarding primary drug of choice ($p<003$). Alcohol abuse was more frequent for prescribers and cocaine abuse was more frequent for non-prescribers. No between-group differences were observed in either number of relapse episodes prior to admission or episodes while active in the monitoring program. These unexpected findings suggest that accessability may not be a contributing factor to relapse.

ACKNOWLEDGMENT: Supported by Ortho-McNeil Pharmaceuticals.

WINICK'S MODEL EXPLAINS SUBSTANCE USE IN NURSES

A. M. Trinkoff, Q. Zhou, C. L. Storr, and K. L. Soeken

University of Maryland School of Nursing, Baltimore, MD

The American Nurses Association estimates 6-8% of nurses have a drug or alcohol problem. Nurses handle and administer most medications given to hospitalized patients, giving them unique access to many controlled substances. In addition, nurses endure social roles and job characteristics thought to promote psychological distress and substance use. The utility of a model proposed by Winick (1974) which asserts that groups with access to substances, that have freedom from negative proscriptions and experience role strain have an increased likelihood of drug dependence, was assessed in this study to explain substance use among a probability sample of employed registered nurses who participated in an anonymous mailed survey (n=3600). A structural equation model fitting access (measured in three dimensions: perceived availability, handling of medications, pharmacological knowledge), freedom from negative proscriptions (internal: religiosity; external: social network), role strain (job demands: time pressure, physical and cognitive demands; depressive symptoms) and the frequency of past year marijuana, cocaine, prescription-type drug, and heavy alcohol use was tested. Nurses were more likely to use substances as access to substances increased ($p<0.001$), as their social network contained more drug users, and as religiosity decreased ($p<0.001$). Role strain was also related to substance use. Depressive symptoms were directly related to decreased substance use ($p<0.01$), while job demands were indirectly related to substance use through depressive symptoms. The model has utility in explaining nurse's substance use, with results serving as a basis for developing longitudinal studies. These can clarify the temporal relationships and to identify predictors of substance use and substance use problems among nurses.

ACKNOWLEDGMENT: Supported by NIDA grant R01 DA07434.

JOB STRAIN AND NON-MEDICAL DRUG USE

C. L. Storr, J. C. Anthony, and A. M. Trinkoff

University of Maryland and Johns Hopkins University, Baltimore, MD

The "Demand-Control" formulation of job strain, initially used in research on cardiovascular health, has been extended to mental health and behavioral outcomes such as drug dependence. In theory, a high strain and health challenging work environment is one with high levels of demand and low levels of control. In contrast, low strain or more salubrious jobs have low demands and high control. Working within this conceptual framework, this study estimates the association between job strain and non-medical drug use. A nationally representative sample of registered nurses participated in an anonymous mailed survey (response rate=78%). A total of 2,375 full-time nurses served as the sample for these analyses. Using logistic regression models, nurses in high strain jobs were 1.5 times more likely to be a recent non-medical drug user as compared to nurses in low strain jobs. These associations persisted even with statistical control over potentially confounding factors, such as being female and age. Notwithstanding some study limitations, these results suggest the demand-control model might be useful in shaping work environments that are associated with adverse behavioral outcomes. Access to psychotherapeutic medicines might not be the only factor that places a nurse at increased risk for non-medical drug use. In addition to personal characteristics, such as age and gender, the psychosocial work environment also might influence whether nurses use non-medical drugs.

ACKNOWLEDGMENT: Supported NIDA grant R01 DA07434.

COMPARISON OF SUBSTANCE USE DIAGNOSES USING DSM-III-R VERSUS DSM-IV IN OUTPATIENT DRUG ABUSERS

V. L. King, R. K. Brooner, M. S. Kidorf, and K. B. Stoller

The Johns Hopkins University School of Medicine, Baltimore, MD

This study compared the DSM-III-R and DSM-IV for deriving lifetime diagnostic rates for substance abuse and dependence for opioids, cocaine, alcohol, cannabis, sedatives, hallucinogens, and stimulants. The substance use disorder sections of the Structured Clinical Interview for DSM-III-R and DSM-IV (SCID) were combined into one interview and given in a single session to 349 consecutive new admissions to a large substance abuse treatment and research program. The interview was conducted 1 to 3 weeks following admission. Interviewers were systematically trained to 100% reliability using a two-stage training paradigm. Periodic co-ratings were obtained for each interviewer over the course of the study to maintain excellent reliability. Analyses for each drug class were restricted to patients who reported use of the substance. The overall findings show a consistent pattern. Virtually all patients were dependent on opioids (98%) using either nosology system. For most other drug classes (cocaine, sedatives, hallucinogens, stimulants), DSM-IV dependence rates were slightly lower and abuse rates were slightly higher ($\leq$ 4%) than those derived from the DSM-III-R. The rate for cannabis abuse was 10% higher in DSM-IV and for cannabis dependence was 9% lower in DSM-IV compared to DSM-III-R. There were statistically significant differences between systems for rates of cannabis abuse and dependence, alcohol abuse and dependence, and sedative abuse ($p \leq .001$). Most of these differences were accounted for by change of diagnosis from dependence in DSM-III-R to abuse in DSM-IV, and from no diagnosis in DSM-III-R to abuse in DSM-IV. Kappa values for agreement between systems were in the good to excellent range for all abuse and dependence diagnoses except for cannabis abuse, which was in the fair range. Overall, in this population of chronic drug abusers. the magnitude of changes from abuse to dependence was modest with the exception of cannabis use disorder.

CLUSTER TYPOLOGY OF PERCEIVED TREATMENT-ENTRY PRESSURES AMONG SUBSTANCE ABUSERS: A MULTI-SITE ANALYSIS

D. B. Marlowe, E. P. Merikle, D. S. Festinger, and J. J. Platt

Institute for Addictive Disorders and Department of Psychiatry, Allegheny University of the Health Sciences, Philadelphia, PA

We evaluated perceived pressures to enter drug abuse treatment among 393 clients in methadone maintenance (n = 99, 25%). detoxification (n = 71, 18%) intensive outpatient (n = 67, 17%), cocaine outpatient (n = 61, 16%). dual diagnosis inpatient (n = 60, 15%) psychiatric inpatient (n = 22, 6%), and pregnant women's addiction (n = 13, 3%) programs. Subjects were interviewed within 10 days of intake using the Survey of Treatment-Entry Pressures (STEP; Marlowe, *et al.,* 1996). Cluster analysis of the STEP data using Ward's Method yielded a stable five-cluster solution across programs, Wilk's lamba = .02, $F(60, 1462) = 40.10$, $p < .0001$. Clients in Cluster 1 (n = 98) reported being predominantly influenced by medical and psychological problems to enter treatment. Clients in Cluster 2 (n = 165) reported being mostly influenced by financial problems to seek treatment. Clients in Cluster 3 (n = 42) reported experiencing numerous coercive pressures to enter treatment stemming from various sources. Clients in Cluster 4 (n = 65) reported being mostly influenced by family pressures to enter treatment. Finally, clients in Cluster 5 (n = 23) reported being influenced by legal problems to enter treatment. Importantly, cluster membership was significantly predictive of tenure and outcome in treatment. Clients in Clusters 3 and 4 remained in treatment the longest and provide the most drug-negative urine samples; however, primary therapists rated clients in Clusters 2 and 4 as being most compliant with program rules and regulations. These data confirm that a standardized assessment of perceived treatment-entry pressures has important prognostic utility for treatment response.

REFERENCES: Marlowe, D. B.; Kirby, K. C.; Bonieskie, L. M.; Glass, D. J.: Dodds, L. D.; Husband, S. D.; Platt, J. J.; and Festinger, D. S. (1996). Assessment of coercive and noncoercive pressures to enter drug abuse treatment. Drug Alc Depend 42: 77-84.

ACKNOWLEDGMENTS: Supported by NIDA grants R01-DA-10113 and R18-DA-06986.

DIFFERENCES AMONG OUT-OF-TREATMENT INJECTORS WHO USE STIMULANTS ONLY, OPIATES ONLY OR BOTH

D. S. John, C. F. Kwiatkowski, and R. E. Booth

University of Colorado School of Medicine, Denver, CO

This study investigated the differences in drug/alcohol use, psychological symptoms, substance abuse treatment entry, and changes in motivation for drug cessation among out-of-treatment injection drug users in Denver who used stimulants only, opiates only, or both. Results indicated that stimulant only users scored higher on alcohol use. Stimulant only users and those who used both scored higher than opiate only users on four symptom dimensions from the SCL-90: hostility, paranoid ideation, psychoticism, and interpersonal sensitivity. When stimulant only users were asked if they would enter treatment if it were free, 70% answered yes. However, when offered free treatment, none of the stimulant only users entered as compared to 55% of the opiate only users and 53% of those who use both. We measured stage of change regarding motivation toward quitting drug use at baseline and again at a two month follow-up interview. Stimulant only users were more likely to regress (30%) in stages of change than the other two groups. Treatment facilities need to take these differences into account in order to better serve the stimulant using population.

ACKNOWLEDGMENT: Supported by NIDA grant DA09832-03

DETERMINANTS FOR PATIENTS LEAVING A HOSPITAL DETOXIFICATION UNIT AGAINST MEDICAL ADVICE (AMA)

S. H. Armenian, M. A. Chutuape, and M. L. Stitzer

Department of Psychiatry, Johns Hopkins University School of Medicine, Baltimore, MD

This study identifies factors associated with patients leaving a 3-day hospital detoxification unit Against Medical Advice (AMA). In AMA discharge, the patient leaves despite discussion with staff who attempt to address the presenting problem precipitating premature termination and despite potential future consequences (e.g. re-admission denials). Medical records of 424 patients who were admitted for opiate and/or alcohol withdrawal were reviewed. After exclusion criteria were applied, the study sample consisted of 71 AMA and 231 non AMA cases (overall AMA rate = 23.5%). Variables examined were: demographics, reported history of drug use, urine toxicology at admission, medication received during the detoxification, and admission day. Data were analyzed using a case-control design. Four variables were found to be significant predictors in logistic regression, which was used to adjust for potential confounding variables. Those who left AMA were younger than the non AMA sample (mean age = 33.4 versus 39.7 years) and reported a shorter history of cocaine use (mean = 2.7 versus 5.2 years). Two program factors were also significant. Patients admitted on Fridays (n=81; AMA rate = 32%) were more likely to leave AMA than those admitted on Mon, Tues or Thurs (n=221; AMA rate = 20%); adjusted OR Fri vs all other days = 2.0. Patients receiving clonidine only as detox medication for opiate withdrawal (n=134; AMA rate = 34%) were more likely to leave AMA as compared to those receiving Valium for alcohol withdrawal (n=89; AMA rate = 12%) or both medications (n=79; AMA rate = 18%); adjusted OR clonidine vs other meds = 2.5. These findings provide information that can help clinicians to identify those who are most at risk for leaving AMA and to examine program policies and procedures that might be altered to improve retention rates. For example, clonidine may be a less effective detox medication for opiate withdrawal compared to other options. Also, special programming may be needed over weekends to reduce attrition. Reductions in premature attrition could improve patients' physical and mental health outcomes and increase cost-effectiveness of treatment resources.

ACKNOWLEDGMENT: Supported by NIDA grant R01-DA10192.

CLIENTS' PERCEIVED NEED FOR TREATMENT AND ITS IMPACT ON OUTCOME

Q. Shen, J. Merrill, and A. T. McLellan

Treatment Research Institute at University of Pennsylvania

Based on the concept of the stages of change, and using two waves of clinical survey data (N = 696) collected using the ASI (Addiction Severity Index) and TSR (Treatment Service Review), this paper examines the relationship between patients' motivation for substance abuse treatment, participation during treatment, and post treatment improvements in the areas measured by the ASI (alcohol, drug, medical, employment, psychiatric, family, legal). We answer the following questions: Do motivated and nonmotivated patients differ with respect to treatment outcomes? What factors are associated with clients' motivation for treatment? In the study, motivation is measured by responses to ASI questions dealing with patients' perceptions of "how bothered they are" by their substance problems and "how important treatment is" for their problems. Our data show that clients' motivation makes a substantial difference in treatment participation and in posttreatment outcomes. "Motivated" patients also used significantly more treatment services, and/or used them for longer periods. While treatment is important, these data are consistent with other findings from the "stage of change" literature suggesting the importance of increasing patients' readiness for treatment in order to achieve better treatment effects.

EFFECTS OF READINESS FOR DRUG ABUSE TREATMENT ON CLIENT RETENTION AND ASSESSMENT OF PROCESS

G. W. Joe, D. D. Simpson, and K. M. Broome

Institute of Behavioral Research, Texas Christian University, Fort Worth, TX

The relationship of treatment readiness (TR)—as defined by the importance of treatment to recovery and the willingness to do what is required to change—to critical lengths of stay in treatment and to process indicators was investigated in three major treatment modalities using data from the national Drug Abuse Treatment Outcome Study (DATOS), The TR scale, an 8-item reliable scale, represented the third stage of Simpson and Joe's (1993) "stages of readiness" treatment motivation model. "Critical" retention periods were 90 days in 18 long-term residential (LTR, N = 2265) and 16 outpatient drug-free (ODF, N = 1791) programs and 360 days in outpatient methadone (OMT. N = 981) programs. From hierarchical linear model analyses, treatment readiness was found to be the most notable predictor of retention rates in LTR and OMT programs, compared to a variety of client background characteristics. Additional analyses confirmed that higher treatment readiness was significantly related to early therapeutic engagement indicators in each of the three modalities. These indicators included rapport with counselor, therapeutic engagement, and confidence with the treatment in months 1 and 3 of treatment. The generalizability of this relationship extends evidence for the importance of intrinsic motivation as a key predictor of outcome and the need to determine the client's stage of motivational change at the time of treatment entry.

ACKNOWLEDGEMENT: Supported by NIDA grant U01-DA10374.

DIFFERENTIAL EARLY RELAPSE BETWEEN DAY AND RESIDENTIAL DRUG TREATMENT CLIENTS

B. Tajima, M. Chan, A. Coutts, and J. Guydish

Institute for Health Policy Studies, University of California, San Francisco, CA

Clients entering a drug abuse treatment agency were randomly assigned to either day (n=114) or residential treatment (n=147), and were interviewed at baseline, and reinterviewed at 6, 12, and 18 months. Follow-up rates were 83% at 6 months, 82% at 12 months, and 79% at 18 months. Previous analyses showed few differences between groups on outcomes including ASI severity scores, and measures of psychological symptoms. In this study we compared the two groups using two definitions of self-reported relapse: a) use at least 3 times per week for at least 4 weeks, and b) any drug/alcohol use in the past 6 months. While 235 persons were interviewed at 6 months, relapse defined as any drug use was asked only of 156 persons. Below is the proportion reporting relapse by each definition at each time point.

Use	6 months		12 months		18 months	
	Day	Res	Day	Res	Day	Res
3x/week for 4 weeks	17%	18%	24%	25%	27%	25%
Any use	61%	41%	53%	54%	45%	50%

No differences between groups were observed at any time point using the more stringent definition of relapse. However, using the broader definition, day treatment clients reported greater relapse than residential treatment clients at 6 months (chi sq=5.82, $p<.02$). This difference was not significant at 12 and 18 months. Our results suggest that while long-term relapse rates do not differ between modalities, residential treatment may be more protective against drug use in early recovery.

ACKNOWLEDGMENTS: Supported by NIDA grant # R18 DA06979.

APPLICATION OF A NOVEL QUANTITATIVE MODEL TO THE STUDY OF POST-TREATMENT RELAPSE TO DRUG USE

L. A. Marsch and W. K. Bickel

Departments of Psychiatry and Psychology, University of Vermont, Burlington, VT

The most influential theoretical model of relapse to drug use post-treatment, the Marlatt 2-stage model of relapse, posits that *initial* drug use after a period of abstinence and *continued* drug use result from distinct processes. Initial use is due to the interaction between exposure to high-risk situations and preparedness to cope with such situations; whereas, continued use is dependent upon the cognitive-affective reaction to the initial lapse. Despite the intuitive appeal of this model, no quantitative support of the 2-stage process of relapse has as of yet been provided. The present study reviews and reanalyzes the relapse literature using a modified version of a non-linear regression equation (used to quantify demand curves in behavioral economic studies-Hursh *et al.,* 1988) to quantify relapse data within a novel quantitative framework. In this analysis, the equation was applied to 13 studies (and 35 relapse curves) of alcohol, marijuana, smoking, heroin, cocaine and polydrug use, in order to describe the relationship between time (based on number of days to first use) and % abstinence. Results indicate that all abstinence curves were positively decelerating in shape (congruent with previous behavioral economic analyses of drug and non-drug maintained behavior), the percent of variance accounted for (R^2) by the model's fitted parameters ranged from 0.70 to 0.99, and measures of the elasticity of the abstinence curves paralleled results from traditional analyses of the effectiveness of various treatment interventions (e.g., both higher D-max values, identifying delayed shifts from inelasticity to elasticity in post-treatment abstinence, and lower mean elasticity values were associated with more effective interventions). In addition, the standardized mean elasticity of abstinence measures (z-scores) enable the comparison of post-treatment relapse results both within and between drug classes. Finally, the Hursh model provides quantitative support (e.g., D-max values) for Marlatt's qualitative model of relapse

NEUROBIOLOGY AND DRUG ABUSE TREATMENT: CONCEPTUAL AND METHODOLOGICAL ISSUES

A. M. Horton, Jr.

National Institute on Drug Abuse, Bethesda, MD

Research studies are needed that will document change following psychosocial and/or pharmacological treatment of drug abusers. It may be expected that these changes will vary depending upon the specific drug or drugs of abuse, the type of drug abuse treatment delivered and extent of past usage. Neurobiological evaluation might be seen as including multiple modalities or categories of assessment. Primary means of assessing mental activity may be described having a focus on structural aspects, electrical activity, chemical means, or behavioral measures. Research studies should use multiple neurobiological modalities to assess the effects of various types of treatment interventions (e.g., pharmacological, behavioral, psychological, social, somatic), for a specific drug or drugs of abuse (e.g., marijuana, cocaine, opiates, hallucinogens, inhalants, sedative-hypnotics, etc.), on measurable changes in the central nervous system to determine the underlying neurobiological substrates responsible for treatment efficacy. Treatment modalities to be assessed include methadone maintenance. detoxification, drug-free outpatient, therapeutic community, and short-term residential/inpatient programs.

DEVELOPMENT OF A SERVICE DELIVERY UNIT QUESTIONNAIRE FOR THE DRUG EVALUATION NETWORK STUDY

L. S. Gifford, D. Carise, and A. T. McLellan

Treatment Research Institute at University of Pennsylvania, Philadelphia, PA

Substance abuse treatment programs can differ greatly in terms of their demographics, orientation, and services delivered. The Drug Evaluation Network System (DENS) is a nationwide electronic tracking system that provides standardized, timely information on patients entering into substance abuse treatment. Data are collected from four modalities of public and private treatment: inpatient, traditional outpatient, intensive outpatient and methadone. In addition, data are available from the entire population of Veterans Administration medical centers. Creating an effective and efficient instrument to categorize treatment programs for outcome evaluation. internal examination. or patient tracking, has presented an interesting challenge. We are not aware of an operational definition of a treatment "program" and there is no universally accepted instrument that describes these fundamental units of treatment delivery. Thus, the authors have developed a questionnaire based on aspects of treatment programs including IRS status and affiliation, capacity, intensity, and length of the program, types of treatment, patient demographics, staff demographics, activities and services offered, and source of payment. This presentation will discuss the rationale and difficulties in constructing a brief yet comprehensive tool to describe and compare substance abuse treatment providers. The instrument and data from 38 "service delivery units" will be presented.

PROTEIN ENGINEERING OF COCAINE DETOXICATION CATALYSTS: TOWARDS A THERAPEUTIC AGENT

J. R. Cashman, C. Berkman, Z. Radic, I. Tsigelny*, and P. Taylor**

Human BioMolecular Research Institute, Seattle, WA and *University of California, San Diego, CA

In the United States, abuse of naturally occurring (-)-cocaine is implicated in more medical complications and emergency room deaths than any other chemical agent. The drug addicting and pathopharmacological effects of cocaine abuse are likely due to the residence time and amount of exposure to cocaine. The major route of cocaine detoxication in humans is enzymatic hydrolysis, however, human butyrylcholinesterase only sluggishly hydrolyzes (-)-cocaine. Interestingly, (+)-cocaine is efficiently hydrolyzed by human butyrylcholinesterase. To probe the molecular architecture of this phenomena, phosphonothiolates corresponding to the transition state analogs of both (-)- and (+)-cocaine hydrolysis were synthesized and tested as inhibitors of mouse acetylcholinesterase. In addition, the (*R*)- and (*S*)-diastereomers (about phosphorous) for each (-)- and (+)- cocaine diastereomer were separated and also tested as inhibitors of mouse acetylcholinesterase. On the basis of detailed enzyme kinetic measurements, molecular modeling and thermodynamic calculations, the absolute configuration of the putative enzyme-inhibitor complexes were mapped for each of the four diastereomers. From these results, selected amino acid changes were introduced by site-directed mutagenesis of the wild type enzyme and the engineered enzyme was examined for (+)- and (-)-cocaine hydrolysis. Rational protein engineering of cholinesterases may provide a highly active cocaine detoxication catalyst that may be useful to prevent cocaine abuse.

ACKNOWLEDGMENTS: Supported in part by NIDA grants DA-08531 and DA-00269.

EVALUATION OF THE PSYCHOMOTOR STIMULANT EFFECTS OF POTENTIAL MEDICATIONS FOR COCAINE ABUSERS

B. E. Garrett, F. I. Carroll, and M. J. Kuhar*

Yerkes Regional Primate Research Center, Emory University, Atlanta, GA and *Research Triangle Institute, Research Triangle Park, NC

This study examined the psychomotor stimulant effects of several novel phenyltropane cocaine analogs that are currently being evaluated as potential substitute medications for treating cocaine abuse. Cocaine abuse is one the nation's largest public health epidemics. Therefore, finding a medication for treating cocaine abuse is essential. An ideal medication for treating cocaine abuse would substitute for cocaine as methadone does for heroin abuse and nicotine for smoking cessation. It would also enter the brain slowly and have a long duration of action. Using the locomotor activity procedure, the locomotor stimulant effects of two groups of analogs were evaluated and compared to the stimulant effects of cocaine. Analogs in Group 1 were several fold more potent than cocaine for the dopamine transporter (DAT) relative to the other monoamine transporters, and analogs in Group 2 had similar affinities to cocaine at all three monoamine transporter sites (nonselective). Findings from this study indicate that some the cocaine analogs are longer in duration than cocaine. However, the affinity for the DAT does not predict locomotor activity efficacy of these compounds.

ACKNOWLEDGMENT: Supported by OND6069.

THE NMDA ANTAGONIST, MEMANTINE, POTENTIATES SOME SUBJECTIVE EFFECTS OF COCAINE IN HUMANS

E. D. Collins, A. S. Ward, D. M. McDowell, R. W. Foltin, and M. W. Fischman

New York State Psychiatric Institute and College of Physicians and Surgeons of Columbia University, New York, NY

Eight male frequent cocaine smokers participated in a 44- to 47- day inpatient and outpatient study to assess the effects of the noncompetitive N-methyl-D-aspartate (NMDA) antagonist, memantine, on cocaine self-administration, subjective effects, and psychomotor performance. Participants were maintained on memantine, 20 mg daily, and placebo. for 7 to 10 days prior to laboratory testing, using a double-blind crossover design. Under each medication condition, participants smoked each of four doses of cocaine base (0, 12, 25, and 50 mg), and were subsequently given five opportunities, fourteen minutes apart, to self-administer that dose of cocaine or receive a merchandise voucher ($5.00). Each cocaine dose was tested twice under each medication condition, and the order of medication condition and cocaine dose was systematically varied. Vital signs were recorded every two minutes, and subjective effects were assessed at baseline and after each cocaine or voucher delivery. In addition, psychomotor perfomance was assessed before and after each self-administration session. Memantine maintenance was not associated with changes in psychomotor performance or the number of cocaine doses chosen each session. Memantine maintenance was, however, associated with significant increases in some subjective effects of cocaine: ratings of "good drug effect," "high," "potency," "quality," and street value were all greater under memantine compared with placebo. These data suggest that NMDA antagonists may have limited usefulness as treatment medications for cocaine abuse.

ACKNOWLEDGMENTS: Supported by NIDA grants DA-10755 and DA-00317.

PHARMACOKINETIC DISPOSITION OF IBOGAINE AFTER ORAL ADMINISTRATION TO HUMAN SUBJECTS

J. Pablo, R. Tyndale, S. Obach, W. L. Hearn, and D. C. Mash

Department Neurology, University of Miami School of Medicine, Miami, FL; Department Pharmacology, University of Toronto, Toronto, Ontario; Drug Metabolism, Pfizer, Groton, CT; and Miami-Dade Medical Examiner Department, Miami, FL

Ibogaine, a drug used to treat opiate and cocaine dependence, undergoes significant first-pass metabolism after oral dosing to *O*-desmethyl ibogaine (noribogaine). The metabolite appears to have increased therapeutic activity compared to the parent drug. Blood concentration-time effect profiles of ibogaine and noribogaine were obtained for individual subjects. The results demonstrate a multimodal frequency distribution of the logarithm of the subjects' (N=27) parent to metabolite ratios (noribogaine AUC/ibogaine AUC) derived from analysis of samples taken between zero to 24 hours post oral ibogaine. These distributions suggest the existence of three groups: poor metabolizers, intermediate metabolizers, and extensive metabolizers. *In vitro* studies have identified two cytochrome P-450 (CYP) isozymes involved in ibogaine metabolism: CYP2D6 and CYP3A4. The results demonstrate that the majority of ibogaine biotransformation proceeds via CYP2D6, including the *O*-demethylation of ibogaine to noribogaine. The results of CYP2D6 genotyping assays of these subjects demonstrated the existence of three groups (wt/wt, wt/null allele, and null allele/null allele). Taken together, these data suggest that the individual variability in the conversion of ibogaine to noribogaine may be due to pharmacogenetic polymorphism of CYP2D6, and that the resulting differences in the levels of the metabolite between individuals may be a determinant in the resulting efficacy of treatment.

ACKNOWLEDGEMENT: Supported by the Addiction Research Fund.

IBOGAINE: CLINICAL OBSERVATIONS OF SAFETY AFTER SINGLE ORAL DOSE ADMINISTRATIONS

D. C. Mash, K. Allen-Ferdinand, M. Mayor, C. A. Kovera, J. F. Ayafor, I. C. Williams, and F. R. Ervin

University Miami Medical School, Miami, FL; Healing Visions Institute for Addiction Recovery, Ltd, St. Kitts, WI; University Dschang, Republic of Cameroon, and McGill University, Montreal, Canada

Ibogaine, a naturally occurring indole alkaloid derived from the roots of *Tabemanthe iboga,* is currently under investigation as a therapeutic agent for drug dependence. We report here preliminary observations on the safety of single oral dose administrations of ibogaine to cocaine and heroin dependent subjects. Baseline screening included a medical evaluation, physical examination, ECG, blood chemistries, and hematological work-up, as well as psychiatric and chemical dependency evaluations. Subjects (N = 39; 32 M, 7F) were assigned to one of four fixed-dose treatments under open label conditions: 500 mg, 600 mg, 800 mg and 1000 mg ibogaine. Adverse effects were assessed by clinician side-effect ratings and open-ended query. No significant adverse events were seen under these study conditions. The most frequent side effects observed were nausea and mild tremor at early time points after drug administration. White blood cell count, neurotrophil levels, sodium or potassium levels were in the normal range. No significant changes from baseline were seen for ALT, AST, alkaline phosphatase (ALP), and GGT. Six patients had some significant bradycardic heart rate response as compared to their base line heart rate. Only one of these episodes was associated with significant hypotension, which may have represented a transient vasovagal response. Intensive monitoring demonstrated that no electrocardiographic abnormalities were produced or exaggerated following ibogaine administration. These preliminary results demonstrate that single doses of ibogaine were well tolerated in drug-dependent subjects, and that there were no significant problems with safety.

DECREASED DRUG CRAVING DURING INPATIENT DETOXIFICATION WITH IBOGAINE

C. A. Kovera, M. B. Kovera, E. G. Sirgleton, F. R. Ervin, I. C. Williams, and D. C. Mash

University Miami Medical School, Miami, FL; Florida International Universtiy, Miami, FL; Johns Hopkins University of Baltimore, MD; McGill University, Canada; and Healing Visions Institute, Ltd, WI

Previous observations of ibogaine's effects have indicated that it may be useful for reducing drug craving for a significant period. The present study involved administration of a single psychoactive dose of ibogaine in a clinical setting to treatment-seeking patients having a chemical dependency on opiates or cocaine. Patients underwent Structured Clinical Interviews for assignment of Axis I and Axis II diagnoses, with admission and follow-up measures of life area impairment given by summary scores from the Addiction Severity Index. Patients reported three times on aspects of craving by completing "at-the-moment" craving questionnaires for heroin (HCQ-29-NOW) or cocaine (CCQ-NOW and MCCS), as well as their health symptoms and mood via the SCL90-R, BDI, and POMS. Craving data were analyzed according to the category scales specified by Tiffany and Singleton, 1993. Significant reductions in craving were found within 48 hours following ibogaine treatment, as indicated by decreased mean scores in all five category scales for the HCQ-29-NOW, and in 3 or the 5 category scales for the CCQ-NOW. The significant reductions were maintained for both groups upon discharge assessment, seven to nine days later. There was greater intersubject variability in cocaine craving ratings according to the MCCS, but the data showed near-zero frequency and duration of craving episodes upon discharge. Significant reductions in negative or withdrawal type health symptoms, as well as improvements in mood and energy/vigor were consistently found across all SCL-90R scales, POMS scales, and the BDI score, both shortly after ibogaine and again at discharge. Significantly reduced craving and continued positive health status were reported again at one month post-discharge, giving preliminary evidence of a significant and lasting benefit of ibogaine pharmacotherapy.

DIVALPROEX IN THE TREATMENT OF COCAINE DEPENDENCE

H. Myrick, S. Henderson, and K. T. Brady

Center for Alcohol and Drug Programs, Department of Psychiatry, Medical University of South Carolina

The current project was designed to evaluate the use of a loading dose of divalproex (DVPX) to modify relapse to cocaine use in an 8 week open-label clinical trial in patients who met DSM-IV criteria for a diagnosis of cocaine dependence. The dose of DVPX used was 20 mg/kg in t.i.d. dosing. Subjects were assessed weekly with follow-up assessments done at 12 weeks. The primary dependent variable, relapse to cocaine use, was determined by self-report as well as urine drug screening. Other dependent variables (e.g., side effect checklists, analog rating scales, psychological assessments) were assessed for secondary analyses, as well. Preliminary data on 11 patients in this ongoing trial indicate the amount of money spent weekly on cocaine decreased from $323/week during the 30 days prior to study entry to $35/week during the first 4 weeks of the study. Likewise, the number of days cocaine was used decreased from 13.5 times during the month prior to study to 1.8 times during the first 4 weeks of the study. Baseline rating of craving and percent of time craved decreased from 69 and 62% to 20 and 19% respectively by week 4. The medication and dosing strategy were well tolerated. This preliminary study indicates that DVPX loading is well tolerated and may be efficacious in the treatment of cocaine dependence. A placebo-controlled trial would be of interest.

A DOUBLE-BLIND, PLACEBO CONTROLLED CLINICAL TRIAL OF NALTREXONE AS A TREATMENT FOR COCAINE DEPENDENCE

E. Somoza, J. Carter, H. Upadhyaya, J. Mezinskis, J. Lutz, T. Geracioti, R. J. Goldsmith, S. Dyrenforth, G. Doan, J. Harrer, and J. Baker

Cincinnati VA/UC NIDA MDRU, VA Medical Center, Cincinnati, OH

The purpose of this study was to evaluate naltrexone as a treatment for cocaine dependence. The subjects were 45 patients who volunteered for the study while inpatients in a 28 day, substance abuse treatment program. Subjects were enrolled in the study during their first week of inpatient treatment. On day 10 of their inpatient stay, they were randomized to naltrexone (23 subjects) or placebo (22 subjects). After discharge from inpatient treatment on day 28, subjects were followed as outpatients bi-weekly for an additional three months. The outcome measures included: self-reported drug use, urine drug screens, subjective cocaine craving, the Brief Symptom Inventory (BSI), and subject retention rates. Subjects in both the naltrexone and the placebo groups showed a drop in cocaine craving over the course of their inpatient stay. On day 28 subjects in the naltrexone group reported significantly ($p < .05$) lower craving than the placebo group. However, the results are equivocal because the difference appeared due to an unexpected rebound in craving for the placebo group, rather than a continued reduction in craving for the naltrexone group. In addition, on day 28, the BSI mean Hostility score was significantly lower ($p < .05$) for the naltrexone group than for the placebo group. Outpatient care was marked by high attrition rates. After three months of follow-up, only six subjects in the naltrexone group and seven subjects in the placebo group remained active in the study. Statistical comparisons between the two groups are therefore not meaningful. Suggestions for increasing retention rates for subjects in a study of cocaine dependence were discussed.

ACKNOWLEDGMENTS: Supported in part by a grant from the DuPont Pharmaceuticals Company and by a NIDA Inter-Agency Agreement # 1 YO1 DA 50038-00.

A NIDA SPONSORED COCAINE RAPID EFFICACY SCREENING TRIAL (CREST) OF GABAPENTIN, LAMOTRIGINE AND RESERPINE

S. P. Berger, T. Winhusen, J. Goldsmith, J. Harrer, C. Himmler, J. Mezinskis, P. Bridge, D. Leiderman, A. Montgomery, and E. Somoza

Cincinnati VA/UC/ NIDA MDRU: VA Medical Center, Cincinnati, OH

Considerable progress in preclinical research has provided a basis for hypothesis driven clinical trials in cocaine dependence. A greater mechanistic understanding of both cocaine and many clinically approved medications has led to the identification of many promising medications for the treatment of cocaine dependence. For this reason NIDA has developed a CREST (Clinical Rapid Evaluation Screening Trial) protocol to provide a needed incremental medication screening step between preclinical research and full blown expensive Phase III pivotal trials. While patients receive manual based psychotherapy, three medications are screened compared to unmatched placebo in an eight-week, 60-subject, four cell design trial. Other important features of the CREST protocol include collecting baseline measurements over a two week period and analyzing primary outcome measures (quantitative urine toxicology and clinical global improvement scales) in terms of a composite score of overall individual patient improvement. The three medications being evaluated in this trial include reserpine, gabapentin and lamotrigine. Reserpine is being screened because of its well-known preclinical ability to functionally antagonize cocaine (by depleting neurochemicals elevated by cocaine). Gabapentin and lamotrigine are hypothesized to interfere with glutamatergic cocaine sensitization/kindling mechanisms relevant to addiction. Preliminary results from the ongoing CREST trial are presented below.

ACKNOWLEDGMENT: Supported by NIDA Y01 DA 50038-00.

USING RIBOFLAVIN TO ASSESS THE VALIDITY OF SELF-REPORTED MEDICATION COMPLIANCE IN A DOUBLE-BLIND PHARMACOTHERAPY TRIAL

J. M. Schmitz, S. L. Sayre, A. L. Stotts, C. Davis, H. M. Rhoades, and J. Grabowski

Substance Abuse Research Center, University of Texas - Houston

Compliance with medication regimens is a key determinant of treatment outcome. The extent to which research subjects fail to take their study medication as prescribed may render conclusions invalid. Indirect methods to assess compliance include reports of pill-taking by subjects. A more direct method involves the use of a riboflavin tracer with UV light detection. We have been examining the agreement between two measures of medication compliance; self report (SR) and urinary riboflavin (UR), in participants from a double-blind, placebo-controlled medication trial for cocaine dependence. To date, 25 subjects have received either naltrexone (50mg) or placebo over a 12-week period as an adjunct to psychotherapy. All capsules contain 25 mg of riboflavin. Subjects provide urine specimens twice weekly, at which time self-reported pill-taking data is collected by the therapist. Riboflavin detection is based on judgements of fluorescence percentage ≥ 10 using a UV lighting device. The mean percentage of agreements between SR-compliance and UR-compliance was high, at 66.6%. Of the 173 observations that were SR-compliant, the majority (88%) were also UR-compliant. Conversely, of the 181 observations that were UR-compliant, the majority (84%) were also SR-compliant. The correlation between percent SR-compliant and UR- compliant was in the expected positive direction (r=0.364) and approached statistical significance (p=0.10). The relationship between percent SR- and UR-compliant appears consistent across the two study medication conditions. Discrepancies between UR and SR were found in 22.9% of the observations and may be due to various factors, such as time of pill ingestion and/or urine specimen collection, poor recall, dietary influences. Given the serious problem of noncompliance in clinical trials, UR monitoring is recommended as a relatively effective, unobtrusive, and low-cost method of determining whether an adequate evaluation of the medication conditions has been achieved.

ACKNOWLEDGMENT: Supported by NIDA grant DA-09262-02.

BASELINE MEASURES AS PREDICTORS OF OUTCOMES IN COCAINE PHARMACOTHERAPY TRIAL: ONE FOR THE FDA?

W. Ling[1,2,3], S. Shoptaw[1,2], A. Huber[1,2], and R. A. Rawson,[1,2,3]

[1]L.A. Addiction Treatment Research Center, [2]Long Beach VA MDRU, [3]UCLA School of Medicine, Department of Psychiatry and Biobehavioral Sciences, Los Angeles, CA

A recent FDA advisory panel suggested that cocaine use patterns during a baseline observation period relative to the pattern of use during treatment may be useful to measure each patient's treatment effects. In response, several planned ongoing pharmacotherapy trials have adopted strategies to measure patient performance and to define study outcomes. The specifics include screening potential patients based on their baseline drug use, enrolling into controlled clinical trials only those who exceed a certain level of use at baseline. Primary outcome responses are defined according to several drug use parameters during treatment relative to baseline, then are used for classifying patients into complete and incomplete responders as measures of treatment success, Using data from our recently completed double-blind, placebo-controlled amantadine study, we classified our 69 cocaine dependent patients into baseline use groups: (1) "light" users (i.e., 2 or fewer cocaine positive urine samples during screen); or (2) "heavy" (i.e., 3 or more cocaine positive urine samples during screen). The study design featured a 2-week non-medication baseline screening period followed by 16 weeks of medication treatment. We counted the number of urine samples detecting cocaine metabolite during baseline and correlated these to the number of samples documenting absence of cocaine metabolite during treatment (the Treatment Effectiveness Score) by treatment condition crossed with baseline use group. Findings indicated baseline performance correlated significantly with the TES (Kruskal-Wallis=11.59, df=3, $p<.01$), but "light" and "heavy" users did not respond differentially to the medication. Our inability to detect differential treatment responses for "light" and "heavy" cocaine user groups is likely due to insufficient power. While our data indicate that baseline drug use clearly correlates with drug use during treatment, it is uncertain that it predicts treatment response or that such response, if present is related to the assigned treatment. The effects of excluding patients from clinical trials based on baseline drug use remains unclear.

SENSITIZATION OF OPERANT BEHAVIOR TO ORAL COCAINE, BUT NOT CAFFEINE, WITH CUMULATIVE AND REPEATED DOSING REGIMENS

E. Lobarinas, C. E. Lau, and J. L. Falk

Department of Psychology, Rutgers University, New Brunswick Campus, Piscataway, NJ

Eight rats were reinforced by food-pellet delivery on a DRL 45-sec schedule in 190-min daily sessions. Each session was composed of five, 35min subsessions, with each subsession preceded by a three-min time-out (TO) period. For selected sessions, first a cumulative dose-effect relation for cocaine was determined by administering an ascending cocaine dose by oral gavage during each of the five TO periods, Three such cycles were given, separated by 7-10 sessions. Later, four such cycles were given using a repetitive 10 mg/kg cocaine p.o. dose in place of the cumulative-dose sequence. Within a cocaine cycle, short (<45 sec) interresponse time (IRT) rates progressively increased with doses, and reinforced response rates correspondingly decreased. As cycles were repeated, both rate changes became progressively more marked, indicating the development of sensitization to cocaine's effect. Upon later exposure to 5 mg/kg cocaine cycles, none of these rate changes occurred and performances were equivalent to those occurring under saline cycles. For oral 10 mg/kg caffeine dose cycles, within-cycle increases in short IRT rates and decreases in reinforcement rate also occurred, but, unlike cocaine, no development of sensitization across caffeine-session cycles occurred.

ACKNOWLEDGMENTS: Supported by NIDA grants R37, DA03117, R01 DA050305, and Research Scientist Award (to JLF) K05 DA00142.

REGULATION OF COCAINE SENSITIZATION BY THE MEDIAL PREFRONTAL CORTEX

B. A. Sorg, B. M. Prasad, and T. Hochstatter

Program in Neuroscience, Dept. VCAPP, Washington State University, Pullman, WA

Cocaine-induced increases in extracellular dopamine levels in the nucleus accumbens are augmented after repeated daily cocaine. However, our recent studies indicate that the response of extracellular dopamine levels in the medial prefrontal cortex (mPFC) is attenuated. The role of mPFC dopamine tolerance in the expression of sensitized locomotor behavior was further examined by injection of d-amphetamine sulfate (AMPH) into the prelimbic mPFC prior to cocaine challenge in cocaine-sensitized rats. Male Sprague-Dawley rats were non-handled (naive) or given five daily injections of either saline (1 mL/kg, ip) or cocaine (15 mg/kg, ip). Seven to 12 days later, rats were given direct microinjection of either saline or a range of AMPH doses into the mPFC. Within 3-5 minutes, all rats were challenged with an ip injection of either saline or cocaine. Amphetamine microinjection into the mPFC did not significantly affect locomotor behavior produced by an ip saline challenge in any of the three treatment groups. In cocaine-challenged rats, AMPH produced a strong trend toward decreased locomotor responding to cocaine challenge in naive rats while no effect of AMPH was evident in daily saline pretreated rats. Daily cocaine pretreated rats demonstrated sensitization, and this enhanced behavioral response to cocaine challenge was blocked by a low dose of AMPH (0.175 μg/side) in the mPFC, an effect which disappeared in animals administered higher AMPH doses. The results suggest that in cocaine-sensitized rats, the previously reported diminished mPFC dopamine responsiveness to cocaine challenge may contribute to behavioral sensitization. These findings indicate a decrease in mPFC-mediated control over locomotor behavior in the sensitized rat, and may have implications for cortical control of drug-seeking and drug-taking behavior in humans.

ACKNOWLEDGMENT: Supported by NIDA grant R29 08212.

COCAINE ABSTINENCE IN THE RAT: A QUANTITATIVE MODEL

D. H. Malin, W. D. Moon, O. B. Wilson[1], E. T. Moy, R. E. Jennings, D. M. Moy, V. Phillips and R. L. Watner[2]

University of Houston-Clear Lake, Houston, TX; [1]Baylor College of Medicine, Houston, TX and [2]Uniersity of Texas Health Science Center, Houston TX

Cocaine abusers often display an abstinence syndrome involving various signs and symptoms of anxiety and depression. The object of this study was to develop a rat model of cocaine abstinence syndrome based on quantitation of spontaneously emitted behaviors following termination of drug exposure (analogous to common methods of assessing morphine abstinence). Groups of 8 male S-D rats were infused s.c. for 7 days via Alzet 2MLl osmotic minipump with saline alone or with 40 or 60 mg/kg/day cocaine HCl. Pumps were then removed under halothane anesthesia and rats were observed under "blind" conditions at 12, 24, 36 and 48 hours post-removal. Each 15 minute observation employed a standard checklist for counting instances of abstinence signs including ptosis, chews, teeth chatters, gasps, writhes, seminal ejaculations, head shakes and scratches. The high dose group displayed consistently more signs than the low dose group, which, in turn, displayed consistently more signs than the saline group. Two-way ANOVA of overall signs, cumulated across all categories, revealed a significant effect of infusion rate, $p<.01$, but no significant effect of trial and no significant interaction effect. There was a significant, $p<.01$, positive linear trend of signs (averaged over the 4 trials) as a function of cocaine infusion rate. Twelve rats were observed further; differences between the three groups had virtually disappeared at 156 hours of withdrawal. A second experiment tested the ability of cocaine to reverse the abstinence signs. Eight rats previously infused with 60 mg/kg/day cocaine were observed at 35 hours of withdrawal and injected s.c. either with saline or 3 mg/kg cocaine five minutes prior to being observed again at 37 hours. Signs decreased by 4.9% after saline injections, but by 83.3% after cocaine injections. This difference was significant, $p<.01$. In summary, this rapid and simple model quantitated cocaine abstinence syndrome in a dose-related and drug-reversible manner.

BEHAVIORAL STEREOTYPY AND LOCOMOTOR ACTIVITY DURING CHRONIC "BINGE" PATTERN COCAINE ADMINISTRATION AND EARLY WITHDRAWAL IN RATS

S. D. Schlussman, A. Ho, Y. Zhou, A. E. Curtis, and M. J. Kreek

The Laboratory of the Biology of Addictive Disease, The Rockefeller University, New York, NY

We have previously demonstrated that administration of cocaine in a "binge" pattern to Fischer rats results in significantly elevated levels of horizontal locomotor activity and that this activity shows sensitization during the course of chronic administration. Also we have found that increased locomotor behavior persists during the early stages of withdrawal, suggesting a phenomenon of conditioning or expectancy. The present study extends these earlier studies by examining behavioral stcreotypy as well as locomotor activity in the same animals during both chronic (14 day) "binge" cocaine administration and withdrawal from this regimen. "Binge" pattern cocaine administration resulted in behavioral stereotypy and this behavioral stereotypy was significantly incrensed compared to controls on all days of injections. Neither tolerance nor sensitization with respect to stereotypy was observed. On the first day of withdrawal, the expression of behavioral stereotypy was significantly less than the last day of cocaine injections, but still significantly higher in cocaine treated animals than in controls. By the third day of withdrawal, behavioral measures of stereotypy were not significantly different from controls. In contrast to stereotypy, the animals did exhibit sensitization during chronic "binge" pattern cocaine administration in respect to locomotor activity. As with stereotypy, locomotor activity was significantly lower during withdrawal compared to treatment days but significantly higher in cocaine treated animals compared to saline controls during the first 2 days of withdrawal, confirming our previous findings. These results demonstrate the expression of behavioral stereotypy as well as increased locomotor activity in the same animals during. and also transiently following, chronic cocaine administration.

ACKNOWLEDGMENTS: Supported by DA P05005130 and DA K05 00049 (MJK).

PREPULSE INHIBITION OF ACOUSTIC STARTLE WAS NOT ALTERED IN COCAINE-WITHDRAWN RATS

T. R. Efferen, J. Rotrosen, and J. U. Adams

New York NIDA/VA MDRU, NYU and VA Medical Centers, New York, NY

Chronic cocaine administration has been shown to induce long term alterations in dopaminergic function. including both neurochemical and behavioral changes. The present study used prepulse inhibition (PPI) of the acoustic startle reflex to assess the effects of withdrawal from chronic cocaine in rats. PPI of acoustic startle is a sensorimotor gating task in which a startle response to an auditory stimulus is reduced when the stimulus is preceded by a subthreshold pulse (prepulse). Administration of dopamine agonists disrupts PPI, an effect which can be reversed by dopaminergic antagonists, such as haloperidol. Male Sprague-Dawley rats received either saline (n=8) or cocaine (n=8, 30.0 mg/kg, ip) daily for 14 days. Acoustic startle and PPI were measured prior to, and at 3 and 14 days withdrawal from, the chronic cocaine regimen. No significant differences in startle amplitudes or PPI were observed between cocaine treated rats and saline treated controls. Apomorphine (0.1, 0.3. and 1.0 mg/kg, sc) induced disruption of PPI was measured prior to, and at 4 and 15 days withdrawal from, the chronic cocaine regimen. Again, no significant main effects were seen between the saline- and cocaine-treated groups. These negative results were somewhat surprising on three counts. 1) The cocaine regimen used has been shown to induce changes in DA function in rats; 2) PPI of startle is sensitive to alterations in DA neurotransmission (both pharmacological and pathological); 3) In a parallel clinical study (see E. Duncan *et al.,* this meeting). altered startle responses were observed in withdrawn cocaine addicts.

EFFECTS OF CHRONIC COCAINE USE ON ACOUSTIC STARTLE IN HUMANS

E. J. Duncan, T. R. Efferen, S. Szyilagy, S. Chakravorty, P. D. Butler, S. Gonzenbach, D. Vanderburg, J. U. Adams, and J. Rotrosen

New York NIDA/VA MDRU, NYU and VA Medical Centers, NY, NY

Chronic cocaine use has been shown to produce long-lasting neurochemical alterations which persist after the acute withdrawal period. This study assessed the effects of chronic cocaine use on the acoustic startle response and sensorimotor gating using a task known as prepulse inhibition (PPI) of startle. PPI of startle is a paradigm in which a startle response to an auditory stimulus is reduced when that stimulus is preceded by a lower intensity, subthreshold pulse (prepulse). Nine male normals (avg. age = 41.6) and 15 male cocaine addicts (avg. age = 43.2) were tested, the latter after a period of heavy cocaine use ranging from 4-27 years (mean= 16.7 years). At the time of testing, cocaine users had been cocaine free for 4 days to six months, the average being approximately 8 days. All subjects had a hearing test and psychiatric evaluation to exclude DSM IV Axis 1 pathology other than substance related diagnoses. Cocaine addicts had significantly lower startle amplitudes (ANOVA $F= 7.4$; $df=1,22$; $p<0.0123$) than normal controls. There were trends towards increased PPI in the cocaine addicts under certain stimulatory conditions, however, there were no significant main effects. These results indicate that chronic cocaine use produces impairment of the startle response which persists after the acute withdrawal period. In these subjects, sensorimotor gating remained intact. We propose that these findings are related to long term changes in the dopaminergic system resulting from chronic cocaine use.

ACKNOWLEDGMENT: Supported by NIDA/VA MDR.

BEHAVIORAL EFFECTS OF PCP AND MK-801 ARE POTENTLY INCREASED BY DESIPRAMINE

K. A. Trujillo, K. Warmoth, J. Van Treijen, C. Lanning, and A. B. Chinn

Psychology Program, California State University, San Marcos, CA

Antidepressants have been reported to increase the locomotor stimulant effects of the NMDA receptor antagonist MK-801. Although it is suspected that these effects are related to NMDA receptor blockade, no NMDA receptor antagonists other than MK-801 have yet been examined. The present study explored whether phencyclidine (PCP), a non-competitive NMDA receptor antagonist and well-known drug of abuse, would produce a similar interaction with the antidepressant desipramine (DES). Adult, male Sprague-Dawley rats (6-8/group) received PCP (3.0 or 6.0 mg/kg), MK-801 (0.1 or 0.3 mg/kg), DES (5.0 mg/kg), or combinations of PCP+DES or MK-801+DES. Locomotor effects were assessed in a photocell apparatus, and motor incoordination quantified by a rating scale over a 3 hour period. DES, by itself, produced a mild and non-significant decrease in locomotion. PCP and MK-801 produced dose-dependent increases in locomotion and incoordination, with mild non-significant effects at the lower doses, and potent increases at the higher doses. The onset of the behavioral effects of PCP was more rapid and the time course shorter than that of MK-801. Paradoxically, when administered in combination, DES potently increased the effects of both PCP and MK-801, including both locomotion and motor incoordination. The results suggest that the effects of PCP and related drugs may be dramatically increased in the presence of antidepressants, and that caution should be used when considering use of these drugs in combination. In addition, the results suggest that NMDA receptors may be involved in the actions of antidepressants.

ACKNOWLEDGMENTS: Supported by the National Alliance for Research on Schizophrenia and Depression (NARSAD) and by CSU San Marcos.

EFFECTS OF REPEATED PCP ADMINISTRATION ON RECEPTOR BINDING AND NMDA RECEPTOR SUBUNIT GENE EXPRESSION

R. N. Pechnick

Department of Pharmacology, LSU Medical Center, New Orleans, LA

The acute administration of phencyclidine (PCP) affects behavior as well as alters neuroendocrine function and body temperature in the rat. However. these responses to PCP change after the repeated administration of drug; tolerance develops to some effects (ataxia and activation of the hypothalamic-pituitary-adrenal axis), whereas sensitization is observed with other responses (locomotor activity and hyperthermia). Although PCP interacts with a number of neurotransmitter systems, the binding site within the NMDA receptor channel is a prirnary target site, and many of the effects of PCP are thought to be mediated via interactions with central glutamatergic systems. The NMDA receptor is a heteromeric receptor, comprised of NR1 and NR2 subunits that arise from two gene families. The purpose of the present study was to determine whether the repeated administration of PCP affects PCP receptor density and/or NMDA receptor NR1, NR2A, NR2B or NR2C subunit gene expression. Rats were treated with daily injections of PCP (5.0 mg/kg/s.c.) for 14 days. On Day 15 cerebral cortical tissue was obtained, and PCP receptor density was determined using saturation binding experiments with tritiated dizolcipine (MK-801), and NR1, NR2A. NR2B and NR2C mRNA levels were rneasured using ribonuclease protection assays. The repeated administration of PCP affected neither PCP receptor density nor NMDA subunit gene expression. These results suggest that the changes in response to PCP that occur after repeated administration take place downstream from interactions with NMDA receptors, involve other target sites for PCP, or are localized to specific regions within the brain.

ACKNOWLEDGMENT: Supported by NIDA grunt DA-04113.

THE DISCRIMINATIVE STIMULUS PROPERTIES OF DEXTROMETHORPHAN IN DARK AGOUTI RATS

W. L. Sun and W. D. Wessinger

Department of Pharmacology and Toxicology, University of Arkansas for Medical Sciences, Little Rock, AR

Dextromethorphan is metabolized to an active metabolite, dextrorphan, by CYP2D6 in humans or CYP2D1 in rats. These two drugs share many pharmacological effects. Both drugs have been shown to bind to the NMDA receptor channel with different affinities (dextrorphan has about 8 times higher affinity than dextromethorphan). It is unclear whether the discriminative stimulus properties of dextromethorphan are produced by dextromethorphan or dextrorphan. In the current study, female dark Agouti rats (n = 6), which genetically lack the activity of CYP2D1, were trained to discriminate dextromethorphan (i.p., 18 mg/kg) from saline in a 2-lever operant chamber under a fixed ratio 15 schedule of food reinforcement. The drugs that completely substituted for the training drug ($\geq$ 85% drug-appropriate responding) are listed in order of potency: dizocilpine > phencyclidine > dextromethorphan > dextrorphan. Fluoxetine and *dl*-cyclazocine produced about 70% drug appropriate-responding. The sigma ligands, caramiphen, *d*-pentazocine, did not substitute for the training drug. Neither did morphine, pentobarbitat or cocaine. These results suggest that dextromethorphan produces its discriminative stimulus effects by blocking the NMDA receptor channel and not via actions on sigma receptors or mu receptors.

ACKNOWLEDGMENT: Supported in part by NIDA grant R01-DA10358.

RITANSERIN ANTAGONIZES THE EFFECTS OF DOI ON THE ACQUISITION AND PERFORMANCE OF RESPONSE SEQUENCES IN MONKEYS

P. J. Winsauer and J. M. Moerschbaecher

Department of Pharmacology, LSU Medical Center, New Orleans, LA

Many of the effects of hallucinogenic drugs are thought to be mediated by 5-HT_{2A} receptors, but this premise has not been extensively examined in regard to the effects of these drugs on learning. Therefore, in the present study, a 5-HT_{2A} receptor agonist (DOI; 2,5-dimethoxy-4-iodoamphetamine) and a 5-HT_{2A} receptor antagonist (ritanserin) were administered both alone and in combination to 4 rhesus monkeys responding under a multiple schedule with repeated acquisition and performance components. In the acquisition component, subjects learned a different 5-response sequence each session. In the performance component, the 5-response sequence was the same each session. Responding in both components was maintained by food presentation under a second-order fixed-ratio (FR) schedule. Errors in either component produced a 5-sec timeout but did not reset the sequence. Sessions began in the acquisition component, which then alternated with the performance component after 15 reinforcers or 20 min, whichever occurred first. Sessions terminated after 120 reinforcers or 80 min, whichever occurred first. When increasing doses of DOI (0.018-0.56 mg/kg) were administered 30 min prior to the start of the session, dose-dependent decreases in overall response rate occurred in both components. However, decreases in response rate occurred in the acquisition component at doses that had little or no effect on response rate in the performance component. Accuracy of responding was also affected by DOI, but increases in percent errors generally did not occur until substantial decreases in response rate were obtained. A 0.32 mg/kg dose of ritanserin administered 40 min prior to the start of the session antagonized the disruptive effects of DOI, shifting the DOI dose-effect curve 1/2-3/4 log unit to the right. Taken together, these data indicate that learning is more sensitive than performance to disruption by hallucinogenic drugs such as DOI, and that these disruptive effects are mediated by 5-HT_{2A} receptors.

ACKNOWLEDGMENT: Supported by DA04775.

MECHANISM OF TOLERANCE DEVELOPMENT TO DOI: DOWN-REGULATION OF 5-HT_{2A} RECEPTOR AFTER CHRONIC TREATMENT

R. L. Smith, E. Sanders-Bush, and R. J. Barrett

John F. Kennedy Center and Department of Psychiatry and Pharmacology, Vanderbilt University and VA Medical Center, Nashville, TN

The present study was conducted to determine first, if tolerance develops to the discriminative stimulus (DS) effects of the hallucinogen, 2.5 dimethoxy-4-iodo-amphetamine (DOI) and second, the mechanism mediating tolerance. Rats were trained to discriminate 0.75 mg/kg DOI from saline on a VI-30" schedule of reinforcement with a 15" TO. To ascertain the respective roles of the 5-HT_{2A} and 5-HT_{2C} receptors, rats were tested for their ability to discriminate DOI following pretreatment with either SB 206533, a 5-$HT_{2B/C}$ antagonist, or MDL 100907, a selective 5-HT_{2A} receptor antagonist. The results indicate that the DS effects of DOI are largely mediated by the 5-HT_{2A} receptor. To determine if tolerance develops to DS effects of DOI, rats were assigned to one of 4 groups (n=10). Prior to chronic treatment, two groups were tested for choice behavior following 0.38 mg/kg DOI. One group from each pre-test condition was injected with either saline or DOI (1 mg/kg) for 8 days. 24 hr later the pre-test was replicated. Animals receiving chronic DOI and tested on 0.38 mg/kg DOI showed a 60% decrease in DOI lever responding (from 100 to 40%) while animals receiving chronic saline and tested on 0.38 mg/kg DOI were not different. Using receptor autoradiography, changes in receptor density for both 5-HT_{2A} and 5-HT_{2C} receptors were measured in rats that had received identical treatment conditions as above. Significant changes in binding were observed in 5-HT_{2A} receptors but not 5-HT_{2C}. These results suggest that behavioral tolerance to DOI reflects neuroadaptive changes in 5-HT_{2A} receptors.

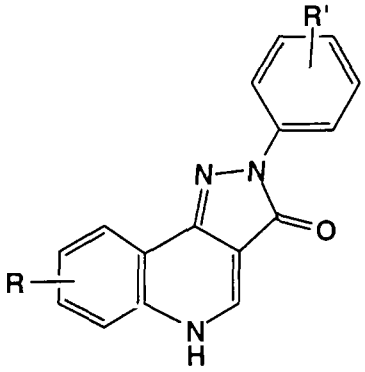
ACKNOWLEDGMENT: Supported by NIDA grant 05181.

EXPLORATION OF REGIONS L_2 AND L_{D1} OF PHARMACOPHORE/RECEPTOR MODELS FOR BABAA/BZR SUBTYPES

J. M. Cook, Q. Huang, C. Ma, X. He, and S. Yu

Department of Chemistry, University of Wisconsin-Milwaukee, Milwaukee, WI

Based on the affinities of over 450 BzR ligands at 5 distinct recombinant $GABA_A$ receptor isoforms [$\alpha x\beta 3\gamma 2$ (x=1, 2, 3, 5, or 6)], pharmacophore/receptor models for 5 BzR subtypes are proposed. In probing for more selective ligands toward BzR subtypes, a number of rigidly substituted pyraoloquinolonones (CGS series) have been synthesized to explore the L2 region of the pharmacophore/receptor model. The synthesis as well as the biological activity of these ligands will be reported.



GENETIC VARIATIONS IN FLUNITRAZEPAM EFFECTS

E. M. Sellers, U. E. Busto, T. Kilicarslan, K. Reed, N. Y. Li, and R. F. Tyndale

Departments of Pharmacology, Medicine and Psychiatry and Centre for Research in Women's Health, University of Toronto; Addiction and Mental Health Services Corporation, Toronto, Canada

Flunitrazepam is an abused benzodiazepine that has achieved notoriety in the United States for being associated with "date rape". The drug can produce sedation and memory loss. Two individuals, genetically deficient in the drug metabolizing cytochrome P450 (CYP) enzyme CYP2C19 (CYP2C19*2/*2), showed more sedation, "spacey feeling" and psychomotor impairment than a CYP2C19*1/*1 (extensive metabolizer). CYP2C19*2/*2 plasma flunitrazepam concentrations were higher than in CYP2C19*1/*1. CYP2C19 is polymorphically expressed and metabolizes diazepam, omeprazole [OMP] and S-mephenytoin. Immunochemical, mass spectrometric and cDNA expressed microsomes were used to identify the CYPs that mediate OMP metabolism. 5-hydroxyomeprazole (5-OH-OMP) and OMP sulphone are formed by CYP2C19 and CYP3A respectively. Flunitrazepam competitively inhibits the formation of 5-OH-OMP in CYP2C19 (Ki 40 μM) and OMP sulphone in CYP3A4 (Ki 225 μM) expressed and human liver microsomes. OMP (5, 10, 20 μM) inhibited flunitrazepam (80 μM) metabolism to desmethyl-flunitrazepam. S-mephenytoin (100 μM) inhibited diazepam (20 μM) and flunitrazepam (20 μM) N-demethylation by 28 ± 8% and 34 ± 9% respectively. Flunitrazepam metabolism and clinical effects appear to be influenced by the CYP2C19 polymorphism *in vitro* and *in vivo.* Individuals who are genetically missing this enzyme (e.g. 15% of Chinese) should be more sensitive to flunitrazepam. The risk of abuse may also be higher.

ACKNOWLEDGMENT: Supported in part by NIDA grant DA06889.

TRIAZOLAM AND ZOLPIDEM: A COMPARISON OF EFFECTS ON HUMAN MEMORY AND COGNITIVE PERFORMANCE

M. Z. Mintzer and R. R. Griffiths

Johns Hopkins University School of Medicine, Baltimore, MD

Zolpidem (ZOL) is an imidazopyridine hypnotic with preferential binding affinity for the ω1 benzodiazepine receptor subtype. The present double-blind, crossover study evaluated the acute effects of orally administered ZOL (5, 10, and 20 mg/70 kg) relative to those of the benzodiazepine hypnotic triazolam (TRZ; .125, .25, and .50 mg/70 kg) on specific memory and cognitive functions in 18 healthy volunteers. Drug effects on memory for target (i.e., focal) information and contextual information (i.e., peripheral details surrounding a target stimulus' presentation) were evaluated using a source monitoring paradigm, and drug effects on selective attention mechanisms were evaluated using a negative priming paradigm. TRZ and ZOL produced strikingly similar dose-related effects on memory for target information across a comparable range of dose levels. Both TRZ and ZOL impaired subjects' ability to remember whether a word stimulus had been presented to them on the computer screen or whether they had been asked to generate the stimulus based on an antonym cue (memory for the origin of a stimulus, which is one type of contextual information). The results suggested that only TRZ impaired memory for spatial contextual information. Although both TRZ and ZOL increased overall reaction time in the negative priming task, only TRZ increased the magnitude of negative priming relative to placebo. The observed differences between TRZ and ZOL in memory performance and in selective attention mechanisms may be related to ZOL's somewhat unique pharmacological profile.

ACKNOWLEDGMENT: Supported by NIDA grant DA03889.

EFFECTS OF THIAMINE ON VERBAL WORKING MEMORY AND P300 AMPLITUDE

L. Costa and L. O. Bauer

Department of Psychiatry, University of Connecticut Health Center, Farmington, CT

Previous research has shown beneficial effects of thiamine versus placebo on event-related electroencephalographic potentials (P300 amplitude) and working memory task performance in abstinent cocaine dependent subjects. In the present study, the effects of 5 g of thiamine versus 5 g of a lactose placebo were examined in 16 healthy individuals using similar measures. Subjects orally ingested thiamine and a placebo on two consecutive days. Double blind procedures were followed. One and a half hours after ingesting the capsules, subjects completed Sternberg's (1975) memory scanning task and the "*n*-back" task, a version of the continuous performance test. Compared to placebo, thiamine was found to increase P300 amplitude for both tasks and to decrease reaction time during the "*n*-back" task. The P300 amplitude increase was most reliable under more difficult task conditions. These findings warrant the further examination of the relation between thiamine and neurocognitive functioning in healthy individuals, substance abusers, and patients with cognitive impairment (e.g., AIDS-dementia, Alzheimer's disease).

ACKNOWLEDGMENTS: Supported by NIDA grants P50-AA03510, M01RR06192, and T32AA07290.

EFFECTS OF SCHEDULES OF REINFORCEMENT AND DRUGS OF ABUSE ON SHORT-TERM MEMORY PERFORMANCE

C. A. Dayer, D. Wright, C. Moore, and G. R. Wenger

Department of Pharmacology and Toxicology, University of Arkansas for Medical Sciences, Little Rock, AR

To determine the role of the schedule of reinforcement and the effects of drugs of abuse on short-term memory, 6 pigeons were trained to respond under a matching-to-sample paradigm in which correct matches were reinforced under either a FR1, FR5 or FI300 schedule of reinforcement. Under control conditions, percent matching accuracy and rate of responding were slightly higher under the FR1 schedule than under the FR5 and FI300 schedules. The effect of pentobarbital (0.3-13 mg/kg) on overall percent matching accuracy was similar under all three schedules. Under the FR5 schedule, but not the FRI or FI300 schedules, pentobarbital increased rates of responding following doses of 5.6 and 10 mg/kg while 13 mg/kg decreased responding under the FR1 and FI300 schedules. Diazepam (0.03-10 mg/kg) produced larger decreases in matching accuracy under the FR1 schedule compared to the FRS and FI300. Diazepam increased the rate of responding under the FR5 schedule at a moderate dose (1 mg/kg) and decreased the rate of responding under all three schedules at higher doses. In contrast, the effects of phencyclidine and d-amphetamine were similar across all three schedules. These results suggest that the schedule of reinforcement can influence the effects of drugs of abuse on memory function, but the influence of the schedule is not consistent for all drugs.

ACKNOWLEDGMENT: Supported by NIDA grant DA05815.

NO SEX DIFFERENCES IN THE REINFORCING EFFECTS OF THREE SEDATIVE-HYPNOTICS USING LH-SELF STIMULATION

J. A. Stratmann and R. M. Craft

Department of Psychology, Washington State University, Pullman, WA

A growing interest in women's health issues has spurred research on sex differences in drug effects. Animal models of various drugs' analgesic, locomotor-activating, discriminative and reinforcing effects have revealed sex differences in the magnitude and/or time course of these effects following some opioids and psychostimulants. A self-stimulation paradigm was used to examine sex differences in the reinforcing effects of three sedative-hypnotics: chlordiazepoxide (1.0–10 mg/kg, s.c.), pentobarbital (0.56–5.6 mg/kg, i.p.) and ethanol (0.032 – 0.56 g/kg, i.p.). A bipolar electrode was implanted into the lateral hypothalamus (LH) of 10 male and 10 female Sprague Dawley rats. There was no significant sex difference in the current that produced high rates of responding (149.5 ± 5.6 vs. 138.0 ± 6.5 μA). Rats responded for 100, 80, 60 and 40% of this current on a VI 3-sec schedule of reinforcement. and these currents did not produce significantly different response rates in males and females following saline administration (0.78 ± 0.11 vs. 0.58 ± 0.05 responses/sec, n.s. Chlordiazepoxide and pentobarbital increased responding for stimulation, but there was no sex difference in the magnitude of this reinforcing effect. Ethanol increased response rates to approximately 200% of saline rates, but only in eight rats. Thus, across all subjects, ethanol did not produce significant increases in response rate. None of the drugs significantly increased responding during timeout periods (extinction); that is, no drug produced non-specific increases in motor behavior. Thus, these data did not reveal any significant sex differences in the reinforcing effects of three sedative-hypnotics using LH-self stimulation.

EFFECTS OF COGNITIVE BEHAVIOR THERAPY FOR ANXIETY ON ALPRAZOLAM SELF-MEDICATION BEHAVIOR

J. D. Roache, L. M. Oswald, M. A. Stanley, D. R. Creson, and N. N. Shah

Substance Abuse Research Center, University of Texas - Houston HSC

Twenty-five M,F patients with generalized anxiety or panic disorder were allowed to self-administer color-coded alprazolam (0.5 mg) and placebo capsules using a double-blind outpatient choice-preference procedure. Computerized medication bottles recorded the date and time of patients' capsule use in the outpatient environment. Self-medication behavior was assessed for one week of placebo, one week of alprazolam, and one week of concurrent access to both placebo and alprazolam using standard choice-test methodology. Patients were random block assigned to either a cognitive-behavioral therapy (CBT) or control group balancing the two groups on demographic and anxiety variables. After an initial 3-wk choice trial, the CBT group received education, relaxation, and cognitive therapy to reduce anxiety while the Control group only was assessed for anxiety levels. After 10 weeks of CBT or Control treatment, a replicate but independent 3-wk choice trial (with new capsule colors) was employed to redetermine patterns of medication use. The results showed that anxiety decreased over time, equally for both groups; the only differential treatment effect was an improvement in the quality of life for the CBT group. Alprazolam was preferred over placebo by most patients, but measures of preference, frequency, and amount of drug use decreased over time in both groups; there was no differential tendency to use less medication in the CBT group. These results do not support the hypothesis that psychotherapy for anxiety should be expected to reduce patient tendencies to self-medicate. However, conclusions are limited by the minimal anxiolytic effects demonstrated in the CBT group and the non-specific time-related decreases in both anxiety and medication use in both groups.

ACKNOWLEDGMENT: Supported by NIDA grant DA-08220-04

ROLE OF ANXIETY IN ALPRAZOLAM SELF-ADMINISTRATION

L. M. Oswald, J. D. Roache, and H. M. Rhoades

Substance Abuse Research Center, University of Texas Houston Health Science Center

Twenty-seven M, F patients seeking treatment for generalized anxiety or panic disorder participated in a 6-wk outpatient study in which alprazolam (0.5mg) and placebo were available for self-medication "as needed." Medications were dispensed in color-coded capsules under double-blind conditions at weekly clinic visits. Initial drug sampling involved one week of each drug/color combination. Drug condition and order of presentation were counterbalanced across subjects. During weeks 3-6, patients received both medication colors and were free to choose whichever they preferred at any time. Measures of drug use included alprazolam preference ratio (Alz/total), % of days that capsules were self-administered, and- number of capsules consumed. Alprazolam was self-administered conservatively, but clearly preferred over placebo by the majority of subjects. We previously reported that over 70% of the variance in alprazolam preference and over 50% of the variance in frequency of medication use could be accounted for by patients' intake characteristics, such as aggression, locus of control, and extroversion. Unexpectedly, state measures of intake anxiety were not among the measures that correlated with either preference or frequency of use, leaving the relationship between self-medication and anxiety somewhat ambiguous. Subsequent analyses have shown that measures of anxiety obtained *after* patients began the study did correlate significantly with their medication use. Patients with greater anxiety used anxiolytic medication more frequently than patients with less anxiety. They also experienced greater anxiety reduction. Inclusion of anxiety measures increased the power of the regression model previously developed to predict frequency of use. Finally, drug liking scores were found to correlate with alprazolam preference, but these measures did not add anything to the overall predictive power of the regression models.

ACKNOWLEDGMENT: Supported by NIDA grant DA-08224-04.

ASSESSING SUBJECTIVE EFFECTS OF NITROUS OXIDE IN DENTAL PATIENTS

D. J. Janiszewski, L. Graham, and J. P. Zacny

Department of Anesthesia and Critical Care, The University of Chicago, Chicago, IL

A number of laboratory studies have characterized the mood-altering effects of nitrous oxide in volunteers. The present study investigated whether the mood-altering effects of N_2O in patients resemble the mood effects that have been observed in laboratory volunteers. and if anxiety modulates the subjective effects of N_2O in dental patients. Twenty-nine dental patients (15 females and 14 males) aged 18 and over participated. Dental anxiety, as measured by the Corah Dental Anxiety Scale (DAS), was assessed prior to N_2O inhalation. Mood. as measured by VAS ratings. was assessed before. during. and after N_2O exposure. Concentrations of N_2O ranged from 25 to 50% (M=40.0±8.3%) and duration of N_2O inhalation ranged from 30 to 120 min (M=53.7±19.5). High-DAS patients (N=8) gave higher baseline VAS ratings of "anxious" and "feel bad" than did Low DAS patients (N=8), and reported marked decreases in these ratings during inhalation. Despite these differences between High-DAS and Low-DAS patients, anxiety level did not affect the increased ratings of "floating." "high." "having pleasant thoughts," and "tingling" that both groups reported during inhalation of N_2O, suggesting that anxiety level does not modulate N_2O's effects on these variables. Increased ratings of these adjectives are consistent with results from laboratory studies. The results indicate that some similarities in subjective effects of N_2O exist among research volunteers and dental patients. In addition. studies with dental patients provide a means for determining the degree to which anxiety modulates the subjective effects of N_2O, something that could not be done realistically in the laboratory.

ACKNOWLEDGMENT: Supported by NIDA grant DA-08391.

TIME COURSE OF THE ETHANOL-LIKE DISCRIMINATIVE STIMULUS EFFECTS OF ABUSED INHALANTS IN MICE

M. E. Tokarz, S. E. Bowen, and R. L. Balster

Department of Pharmacology and Toxicology, Medical College of Virginia of Virginia Commonwealth University, Richmond, VA

We have previously demonstrated that abused solvents have behavioral and pharmacological effects that are similar to those of abused depressant drugs such as barbiturates and ethanol. Drug discrimination procedures have been used previously in our laboratories to access the perception of several of these inhalant effects in laboratory animals. In an attempt to further clarify these effects, the present experiment was designed to evaluate the time course of the discriminative stimulus effects of toluene and 1,1,1-trichloroethane (TCE). Male albino mice were trained to discriminate between i.p. injections of ethanol (ETOH; 1.25 g/kg) and saline in a two-lever operant task in which responding was under the control of a fixed-ratio 20 schedule. After 20-min inhalation exposures to toluene (500-6000 ppm) and TCE (1,000-12,000 ppm) stimulus generalization was examined at 0, 5, 10, 20, and 40 min post-exposure. Concentration-related increases in ETOH-lever responding were observed for toluene at 0, 5, and 10 min post exposure with ETOH-lever responding still occurring at several concentrations 20-min post exposure. Response rates which had been decreased at several concentrations immediately following inhalant exposure were found to be elevated up to 20 min post exposure. TCE had a similar time course for discriminative stimulus and response rate effects, but toluene was more potent.

ACKNOWLEDGMENTS: Supported by NIDA grant DA-03112 and DA-05670.

KNOWLEDGE, ATTITUDES, BELIEFS, AND BEHAVIOR ABOUT THE CONSUMPTION OF ALCOHOL DURING PREGNANCY

J. P. Gossage, and P. A. May

University of New Mexico Center on Alcoholism, Substance Abuse, and Addictions, Albuquerque, NM

Researchers at the University of New Mexico are engaged in accurately determining the prevalence and epidemiologic characteristics of Fetal Alcohol Syndrome (FAS) among all ethnic groups in New Mexico through an aggressive, population-based education, referral, and screening network. FAS is completely preventable. One method of changing the behavior of women who drink during their pregnancy is to increase their knowledge and alter their attitudes and beliefs about the use of alcohol and how it can injure the fetus. As part of our research, five questions were included in the 1994 cycle of the statewide Behavioral Risk Factors Surveillance Survey (BRFSS) to expand our understanding about what knowledge, attitudes, and beliefs New Mexicans have concerning alcohol consumption during pregnancy. Analyses for this presentation focused on women in the sample who were in their childbearing years, ages 15-44. The data revealed that knowledge was mixed. While a majority of women (89%) had heard of FAS, only 44% of the women knew that alcohol can affect the fetus during all months of the pregnancy. While 81% of the women knew that abstinence was best during pregnancy, only 46% knew that any and all alcoholic beverages could be equally harmful to the fetus. Lastly, and very importantly, among the women in the overall sample, a surprisingly large number of women (67%) had not been counseled by their physician or some other health care provider about the risk of drinking alcohol during pregnancy; this included 27% of those women in their childbearing years. These data point to the need to broaden FAS prevention messages via techniques endorsed by the Institute of Medicine: universal, selective, and indicated.

A SOUTHWEST TRIBE IS SUCCESSFUL IN REDUCING FETAL ALCOHOL SYNDROME

L. L. Ballinger, P. A. May, J. P. Gossage, and M. M. Harris

University of New Mexico Ctr on Alcoholism, Substance Abuse, and Addictions, Albuquerque, NM

Researchers at the University of New Mexico were among the first to explore the occurrence of Fetal Alcohol Syndrome (FAS) among American Indians. An FAS epidemiological study was completed in this Pueblo Indian community in New Mexico in the late 1970s and early 1980s. The prevalence rate of FAS in that community at that time was 4.1 children with FAS per 1,000. Following that research, the community was involved in the National Indian FAS prevention project from 1983-85 and has subsequently embarked on a series of self-initiated FAS prevention programs which were tailored to the community's culture. This community was included in a second FAS epidemiological research project from 1992-1997. In this second study, the prevalence rate of FAS in that same community ranged from 1.8 to 1.96 children per 1,000 (the rate varies according to whether population estimates from the Indian Health Service Unit or the U.S. census are used). To achieve this result, the tribe utilized various prevention techniques which have subsequently been endorsed by the Institute of Medicine; these techniques are called universal, selective, and indicated. Tribal officials attribute their success to four major factors. 1) They used a community development, empowerment, and organization model to recruit informal leaders who had a variety of skills. 2) Educational efforts were used to get information out, refine information and messages, and then target specific workers, populations, and service organizations. 3) Funding (several small grants totaling less than $30,000) helped some, but most efforts were those of the daily task force initiative members, much of it volunteer work integrated into their professional and personal lives. 4) Strong leadership was vital.

LOW-COST CONTINGENCY MANAGEMENT FOR TREATMENT OF ALCOHOL DEPENDENCE

N. M. Petry, B. Martin, J. Cooney and H. Kranzler

Department of Psychiatry, University of CT School of Medicine, Farmington, CT

This study evaluated the efficacy of a low-cost contingency management procedure. Forty-two alcohol-dependent outpatients were randomly assigned to 8 weeks of standard treatment or standard treatment plus contingency management. Those in the enhanced condition earned the chance to draw from a bowl and win prizes ranging from $1 to $100 for every negative breathalyzer sample submitted and for completing steps related to their treatment goals. Eighty-five percent of subjects assigned to the contingent condition completed the 8-week treatment. compared with 21% assigned to standard treatment. Twenty-One percent of subjects in the contingent group relapsed to heavy drinking in the treatment period. which averaged $200 per subject, may be a low-cost alternative to the voucher system.

PARTICIPATION OF NON-DRUG ABUSERS IN OPIOID STUDIES AND SUBSEQUENT REPORTED DRUG USE

K. Kirulis and J. P. Zacny

Department of Anesthesia and Critical Care, The University of Chicago, Chicago, IL

There is evidence that opioid and cocaine abusers participating in clinical pharmacology research involving the administration of opioids and cocaine do not subsequently increase the use of these or other abused drugs outside of the laboratory setting (Bigelow *et al.,* 1995; NIDA Res. Monograph Series 153, p. 354). We sought to determine if these results could be systematically replicated in non-drug abusing volunteers. Over the past four years we have had over 100 non-drug abusing volunteers in 14 studies involving the administration of opioids. The opioids studied included morphine, meperidine, fentanyl, buprenorphine, and mixed agonists-antagonists. At the end of our studies, subjects are debriefed, which involves informing them about the purpose of the study and what drug(s) and dosages they received. Thirty days or later after their study participation, we contact them by telephone and ask them several questions regarding their drug use in the last 30 days. Of the 138 volunteers who have been debriefed in opioid studies and then contacted by phone, no volunteers reported seeking out the opioid(s) they had been exposed to in the study. 118 volunteers reported no change in their frequency of use of other recreational drugs (e.g., alcohol or marijuana), while 6 and 14 volunteers reported increases and decreases, respectively. This survey study provides evidence that the risk of non-drug abusing healthy volunteers adversely changing their drug use habits as a result of participating in laboratory-based opioid studies is minimal. Further, these results along with the results reported by Bigelow et al. (1995) may be useful to both investigators and Institutional Review Boards when dealing with safety and ethical issues regarding the laboratory exposure of drugs of abuse to human volunteers.

ACKNOWLEDGMENT: Supported by NIDA grant DA-08573.

NALTREXONE FOR REDUCING ALCOHOL AND COCAINE USE IN DUALLY-DEPENDENT PATIENTS

H. M. Pettinati, D. W. Oslin, J. R. Volpicelli, K. M. Kampman, and C. P. O'Brien

University of Pennsylvania School of Medicine, Philadelphia, PA

It is common for patients seeking addiction treatment for cocaine or alcohol to be concurrently dependent on both of these substances. Treatment offered to these patients is generally these substances. Treatment offered to these patients is generally the same as would be provided for those dependent only on cocaine, but with the recent FDA approval of naltrexone for treating alcohol dependence, we should consider aggressively treating the alcohol disorder in these patients. If successful, it may be quite possible to impact on their cocaine use as well. The purpose of this study was to conduct a preliminary, open-label investigation that tested the efficacy of giving a relatively high daily dose (150 mg/day) of naltrexone for 12 weeks to 15 treatment-seeking outpatients who were (DSM-IV) dependent on both cocaine and alcohol and alcohol. Higher daily dosing which increases the length of time that mu opiate receptors are blocked was used primarily to combat medication non-compliance and potentially rapid drug clearance frequently associated with chronic substance abuse. Naltrexone was given in the context of a physician visit where medication management was supplemented by an easy-to-follow approach for enhancing medication compliance (called BRENDA). Results indicated a reduction in the frequency of alcohol drinking (76 vs 10% days/30 days; p. 001) and of cocaine use (56 vs 6 % days/30 days; p.001) compared to use prior to treatment. The findings, although preliminary encourage the initiation of a double-blind, placebo-controlled study of naltrexone for reducing both alcohol and cocaine use in dually-dependent patients.

EFFECTS OF d-FENFLURAMINE AND d,l-FENFLURAMINE ON SIMULTANEOUS MEASURES OF HUMAN AGGRESSION AND IMPULSIVITY

D. R. Cherek, S. D. Lane, D. M. Dougherty, and F. G. Moeller

Human Psychopharmacology Laboratory, Department of Psychiatry and Behavioral Sciences, University of Texas Health Sciences Center, Houston, TX

Research subjects participated after giving their informed consent. Subjects were divided into a conduct disorder (CD) group and a matched control group. Subjects were excluded if screening indicated any history of medical or psychiatric illness, or recent drug use detected by urine drug screen analysis. An initial study established that 0.2, 0.4 and 0.8 mg/kg of d,1-fenfluramine produced dose-dependent decreases in impulsivity in CD subjects, but had no effect on the impulsivity of matched controls. Subsequent studies were initiated involving alternating sessions in which aggression and impulsivity were measured in the same subject at the same time. Subjects participated in eight sessions (4 aggression and 4 impulsivity) each day, 2 or 3 days per week. Subjects received either 0.1, 0.2 and 0.4 mg/kg of d-fenfluramine or 0.2, 0.4 and 0.8 mg/kg of d,1-fenfluramine. Each subject received 3 doses, with each dose separated by at least one week. Initial results indicate that d-fenfluramine produced substantial decreases in aggressive responding, but had no effect on impulsivity. d,1-fenfluramine produced decreases in both aggressive responding and impulsivity. The data support a relationship between serotonin or serotonin and dopamine function and human aggression and impulsivity, and this relationship may be particularly evident in subjects with a history of conduct disorder.

ACKNOWLEDGMENT: Supported by NIDA grant DA 10552-01.

DISCRIMINATIVE STIMULUS PROPERTIES OF ENADOLINE, AN OPIOID KAPPA AGONIST, IN HUMANS.

E. M. Vernotica, S. L. Walsh, and G. E. Bigelow

Johns Hopkins University School of Medicine, Baltimore, MD

This study examines the discriminative stimulus properties of the selective kappa agonist, enadoline (ENAD). in non-dependent opioid abusers. Volunteers are first trained to discriminate between ENAD and placebo and then tested for generalization to hydromorphone(HYD), butorphanol (BUT), and other doses of ENAD. During each training session, placebo or ENAD (10, 20, 40, or 80 µg/70 kg, i.m.) is given; the ENAD training dose rises in ascending order for safety. Training drugs are identified by letter codes and correct identifications are reinforced with money. Preliminary data indicate that ENAD is reliably discriminated from placebo, though only the 80 ug/70 kg dose produced 100% ENAD-appropriate responding. Generalization dose-effect curves are obtained for HYD (1, 2, 4 mg/70kg), BUT (1.5, 3, 6 mg/70kg) and ENAD (10, 20, 40, 80 µg/70kg), while the placebo/ENAD (80 µg/70kg) discrimination is maintained with intermittent training sessions. Preliminary data indicate that the lowest doses of all drugs have produced placebo-appropriate responding, while the highest doses of BUT and HYD have produced > 80% ENAD-appropriate responding. Conversely, subjective report data have shown differing profiles: all HYD doses have been identified as an opiate; low doses of BUT have been also identified as an opiate while the highest doses have been identified as sedative-like or hallucinogenic; enadoline has not been identified as an opiate, but as sedative-like or hallucinogenic at high doses.

ACKNOWLEDGMENTS: Supported by RO1 DA04089, T32 DA07209 and K05 DA00050.

DESCRIPTION, VALIDITY AND RELIABILITY OF A NEW METHOD FOR DIGITAL MEASUREMENT OF PUPIL DIAMETER

M. K. Greenwald, L. DiCerbo, D. Kish, and J. Kuennen

Department of Psychiatry and Behavioral Neurosciences, Wayne State University, Detroit, MI

We developed a new digital method to measure pupil diameter with commercially available, Macintosh-compatible technology. Apple QuickTake 150™ cameras were used to take pupil photographs of 14 participants in an opioid study (buprenorphine maintenance on 2, 4, 8 mg sl, with hydromorphone 0, 4, 8, 16 mg/70 kg i.m. challenges at each buprenorphine dose). Data from two subjects (blue- and brown-eyed) were used to test reliability. All pictures were taken at a 10 cm distance with a close-up lens and flash under constant, dim ambient lighting. There were 220 images (20 test sessions x 11 images/session) recorded for each volunteer. These were transferred from camera to disk and scored on a 17-inch color monitor using a standard digital filter (PhotoFlash™). The filtering sequence produces a black pupil bounded by a red iris. Vertical and horizontal diameters were measured (in pixels; 640 x 480 resolution) and the average of these two values served as point estimates in all analyses. There was a highly significant linear relationship (r= 0.99) between calibration standards (circles ranging from 1 to 8 mm) and measured pixel size. Thus, actual pupil size may be estimated from the digital measure. Buprenorphine and hydromorphone each produced significant dose- and time-related effects (mean of the 14 participants), indicating that this method is pharmacologically sensitive. Inter-rater reliability (Pearson correlations for each test session) of two, independent trained scorers blind to study test condition were high overall (r = 0.98). Iris color exerted a small, nonsignificant effect on inter-rater reliability with scoring of pupils with blue eye color being more reliable (mean r= 0.98; range across the 20 sessions, 0.95 - 0.99) than with brown eye color (mean r= 0.87; range across the 20 sessions. 0.56 - 0.96). Test-retest reliability of each scorer was high, regardless of iris color (range of r's, = 0.85 - 0.96). This novel digital technique is an economical, convenient, paperless, valid and reliable alternative to previous analog methods. Rapid advances in camera and monitor design now afford even greater pixel resolution (1280 x 1024).

ABSTINENCE SYMPTOMS FOLLOWING SMOKED MARIJUANA IN HUMANS

M. Haney, A. S. Ward, S. D. Comer, R. W. Foltin, and M. W. Fischman

Columbia University and NYS Psychiatric Institute, New York, NY

Symptoms of withdrawal ofter oral 9-tetrahydrocannabinol (THC) administration have been reported, yet little is known about the development of dependence on smoked marijuana (MJ) in humans. In a 21-day residential study, MJ smokers (n=12) worked on 5 psychomotor tasks during the day (0915-1700), and in the evening engaged in recreational activities (1700-2330); subjective effects measures were completed 10 times/day. Food and beverages were available *ad libitum* from 0830-2330. MJ cigarettes (0.0, 1.8, 3.1% THC) were smoked at 1000, 1400, 1800, and 2200. Placebo MJ was administered on days 1-4. One of the active MJ doses was administered on days 5-8, followed by four days of placebo MJ (days 9-12). The other concentration of active MJ cigarettes were administered on days 13-16, followed by four days of placebo MJ (days 17-20); the order in which active MJ cigarettes was counter-balanced. Both active doses of MJ increased ratings of "High" and "Good Drug Effect," and increased food intake, while decreasing verbal interaction compared to placebo baseline (Days 1-4). Abstinence from MJ increased ratings such as "Anxious," "Irritable," and "Stomach Pain," and significantly decreased food intake compared to baseline. These behavioral changes indicate that dependence develops following a relatively brief exposure to MJ, suggesting that one factor contributing to the maintenance of daily MJ use may be smoking to alleviate abstinence symptoms.

ACKNOWLEDGMENTS: Supported by NIDA grant DA03476-11 and the Aaron Diamond Fellowship Foundation (MH).

HISTORY OF MARIJUANA WITHDRAWAL AMONG PERSONS SEEKING TREATMENT FOR MARIJUANA DEPENDENCE

A. J. Budney, P. L. Novy, and K. J. Radonovich

Department of Psychiatry, University of Vermont, Burlington, VT

The DSM-IV does not recognize marijuana withdrawal as a clinically relevant criterion of dependence. Nonetheless, 65% of our marijuana-dependent patients report a history of withdrawal during a DSM Checklist Interview. We developed a Marijuana Withdrawal Symptom Checklist to more carefully assess withdrawal. At intake, participants were asked to recall the last time they stopped regular marijuana use and rate the severity of each symptom on a 4-point scale. We have collected Checklists from 54 treatment-seeking, marijuana-dependent patients, who did not currently abuse any other substances except nicotine. On average, participants reported experiencing 6.4 ± 4.7 symptoms of at least moderate severity and 3.1 ± 3.6 symptoms rated as severe. The most frequently reported symptoms were cravings (93%), irritability (87%), nervousness (80%), depressed mood (76%), restlessness (76%), increased anger (74%), sleep difficulty (67%), and decreased appetite (50%). Regression analyses were then conducted to examine predictors of withdrawal severity. Stepwise regression indicated that measures of psychiatric distress at intake and frequency of marijuana use accounted for 55% of the variance in severity scores. These data suggest that the majority of marijuana-dependent patients experience withdrawal symptoms that could influence abstinence attempts. Conclusions must be guarded given the reliance on retrospective reports and a failure to control for symptoms experienced during regular marijuana-use periods.

ACKNOWLEDGMENT: Supported by NIDA grant R29-DA08655.

MARIJUANA CRAVING: DEVELOPMENT AND VALIDATION OF A NEW QUESTIONNAIRE

S. J. Heishman[1], E. G. Singleton,[2] A. Liguori,[3] C. P. Gatto,[3] N. A. Harris[1], and R. C. Taylor[1]

[1]NIDA, Intramural Research Program, Baltimore, MD; [2]Johns Hopkins University School of Medicine, Baltimore, MD; and [3]Wake Forest University School of Medicine, Winston-Salem, NC

The Marijuana Craving Questionnaire (MCQ-Now) has been developed to measure craving at the time subjects are completing the questionnaire. The MCQ-Now was constructed based on the premise that drug craving represents a complex set of behavioral and physiological responses controlled by environmental and cognitive processes such that craving is manifested in different ways at different times. Thus, craving can involve: 1) urges and desires to use drugs, 2) intent and planning to use, 3) anticipation of positive outcomes from using drugs, 4) anticipation of relief from withdrawal or negative mood states, and 5) lack of control over drug use. The MCQ-Now has been administered to 142 subjects who reported use of marijuana at least once during the past month. The MCQ-Now was analyzed using factor analysis. Similar to questionnaires measuring alcohol, heroin, and cocaine craving. factor analysis yielded four unique dimensions of craving. Subjects did not endorse a distinction between craving as a "strong urge only" versus "any urge." Craving scores decreased as the frequency and duration of reported craving episodes increased. To our knowledge, this is the first attempt to assess marijuana craving using a multidimensional instrument.

ACKNOWLEDGMENTS: Supported by NIDA grant R03-DA10997 and NIDA Intramural Research Program.

A SURVEY OF 100 MEDICAL MARIJUANA CLUB MEMBERS

D. Harris, J. E. Mendelson, and R. T. Jones

Drug Dependence Research Center, Langley Porter Psychiatric Institute, University of California, San Francisco

Context: Thousands of people use marijuana for medical purposes, yet little is known about the uses themselves. **Objective:** to describe the reasons for medical marijuana use, the users' perceived effectiveness and side effects of marijuana and other treatments, and their drug use patterns. Design: survey using questionnaires and interview. Setting: A convenience sample was recruited through an ad posted at the Cannabis Cultivator's Club, a major dispenser of medical marijuana in San Francisco. Participants reported a variety of medical disorders for which they used marijuana regularly. A typical user was a white, unemployed man, aged 40, who most commonly used marijuana daily for appetite stimulation and weight gain for AIDS-related wasting. Main Outcome Measures: reasons for use, perceived effectiveness of the marijuana and other treatments for their illness, side effects of marijuana and other treatments, drug use patterns, psychiatric diagnoses, and urine toxicology screen. **Results:** Users perceived marijuana to be more effective with less severe side effects than other treatments. Urine drug toxicology, in addition to cannabis (94%), most commonly showed recent use of cocaine (26%.), opiates (14%), and amphetamine (12%). History of substance abuse or dependence was present in 87% and of other psychiatric disorders in 83%. **Conclusions:** Medical marijuana users reported beneficial effects of marijuana in a number of medical disorders. Perception of effectiveness and tolerance to side effects may have been influenced by pre-illness use. Medical supervision of medical marijuana use would allow more effective monitoring of therapeutic and unwanted effects, some of which may go unrecognized by the patient.

ACKNOWLEDGMENT: Supported by NIDA grant DA-01696.

STRESS, COPING AND MARIJUANA USE: LONGITUDINAL RELATIONSHIPS AMONG A COMMUNITY SAMPLE

V. Johnson and R. J. Pandina

Rutgers University Center of Alcohol Studies, Piscataway, NJ

This study tested the hypothesis that longitudinal trajectories of both stress and coping styles are differentially associated with marijuana use, abuse and dependence. Data were obtained from a random, non-clinical, sample of 411 male and female subjects who were originally tested in 1979-81 at the age of 12. Subjects returned 3, 6 and 13 years later to provide longitudinal information up to the age of 25. Marijuana use outcomes were defined using problems related to use and by employing categories associated with DSM-IV criteria including: role neglect, hazardous behaviors, legal and social problems, tolerance, and withdrawal were used. Based upon these criteria at T3 (age of 18) and T4 (age of 25), subjects were categorized into one of three groups: 1) no marijuana abuse problem, 2) abuse or 3) dependence. Stress was examined in terms of life events and perceived distress as a result of lack of a) self-acceptance, b) personal competence and c) social competence. Coping methods were assessed using five categories: substance use, cognitive reappraisal, emotional support seeking, emotional outbursts, and distraction. Results of analyses found that there were no outcome group differences in the levels of stress until T3, when dependent subjects reported more stressful events and greater levels of personal incompetence. While these abusing or dependent subjects used substances more often to cope than their non-problem counterparts, it is interesting to note that they also used outbursts and distraction methods more often as well. It is the *ratio* of substance use coping with the total of all other coping that is the most predictive of subsequent marijuana problems. Also noteworthy is that the highest level of this ratio appeared at T3 when subjects provided data regarding their behaviors from age 15-18.

ACKNOWLEDGMENTS: Supported by NIDA 03395 and NIAAA 05823, 11699.

SENSITIVITY OF MARIJUANA USE IN SCHIZOPHRENICS TO CONTINGENCY MANAGEMENT

S. C. Sigmon, S. T. Higgins, S. Steingard, C. J. Wang, and J. W. Tidey

Substance Abuse Treatment Center, University of Vermont, Burlington, VT

Substance abuse is common among schizophrenics. Marijuana and other drug abuse can interfere with diagnoses, exacerbate symptomatology, and impede recovery. For these reasons, effective interventions for marijuana and other substance abuse among schizophrenics are sorely needed. However, there has been little research on how to treat substance abuse among the mentally ill. Contingency management interventions have been effective in reducing drug abuse in persons without severe mental illness. We are now interested in examining the efficacy of contingency management procedures in reducing drug use among mentally ill individuals. Our group recently completed a study examining the feasibility of using monetary incentives to reduce cigarette smoking among schizophrenic adults (Roll *et al.,* in press). The use of incentives significantly reduced cigarette smoking by these subjects. As the next step in this line of investigation, we are conducting a feasibility study to examine whether incentives can be used to initiate and maintain abstinence from illicit-drug use (i.e. marijuana smoking) in schizophrenics. Our current study is a within-subject, reversal design that will systematically assess the efficacy of contingent monetary reinforcement in reducing marijuana use among 18 schizophrenic adults.

LATE ABS

RECENT WEAPON CARRYING AND SUBSTANCE USE AMONG US VIRGIN ISLANDS YOUTH

J. J. Lloyd, J. Delva, and A. M. Arria

Johns Hopkins University, School of Hygiene and Public Health, Department of Mental Hygiene

Objective: To examine associations between recent weapon carrying and alcohol, cigarette, and illicit drug use among United States Virgin Islands (USVI) youth. while holding constant other factors suspected to be associated with weapon carrying. **Design:** Cross-sectional analyses of the 1995 Centers for Disease Control and Prevention's Youth Risk Behavior Survey using the conditional form of logistic regression. **Setting:** Public schools in the USVI. **Participants:** 1124 USVI students in grades 7-12. **Main Outcome Measure:** Carrying a weapon within 30 days prior to the survey. **Results:** Compared with youth who did not carry a weapon within 30 days prior to the survey, youth who carried a weapon were more likely to be male and more likely to be recent cigarette. alcohol and illicit drug users. After matching on school and controlling for age. sex, race. neighborhood characteristics, and affiliation with friends who use alcohol and drugs, the associations between recent weapon carrying and cigarette smoking and recent weapon carrying and illicit drug use remained both moderate and statistically significant (odds ratio [OR] = 4.31, $p < 0.001$; OR = 2.99, $p < 0.001$, respectively): the association with recent alcohol use lost both strength and statistical significance (OR = 1.14, $p = 0.616$). **Conclusion:** In this study, recent cigarette smoking and illicit drug use were associated with an increased occurrence of recent weapon carrying. These findings identify a potentially high-risk population that could be targeted for interventions to reduce weapon carrying among youth.

ACKNOWLEDGMENTS: Supported by NIDA training grant DA07292 and grant 95-0020 from the Center for Substance Abuse Treatment.

PHARMACOTHERAPY OF POST-TRAUMATIC STRESS DISORDER IN SUBSTANCE ABUSERS

T. R. Kosten[1,2] M. Sernyak,[1,2] A. Fontana,[2] and R. Rosenheck[1,2]

Department of Psychiatry, Yale University School of Medicine,[1] VA Connecticut Healthcare System,[2] West Haven, CT

In a recent (1997) national VA follow-up of 680 veterans after inpatient treatment for post-traumatic stress disorder (PTSD), 50% had substance abuse or dependence and 71% were placed on medication after discharge. Only 9% of the patients received an agent other than benzodiazepines or antidepressants. The utilization of outpatient mental health services for the year after discharge was lowest for those patients with substance abuse who were treated with both antidepressants and benzodiazepines (35 vs 49 visits) ($F=7$; $P<0.01$), but treating patients with antidepressants alone appeared to be associated with about 50% greater outpatient visits regardless of substance abuse history (33 vs. 49 visits) over the one year follow-up ($F=5.4$, $P<0.001$). Inpatient utilization and demographics did not differ among the four groups and covariance adjustments for severity of PTSD, previous psychiatric and substance abuse hospitalizations did not affect the strength of this association. No other outcome measures showed significant interactions with medication type except drug abuse severity at 8 months on the ASI, which was greatest for the combined therapy group who were not diagnosed as substance abusers (0.4 vs. 0.2) ($F=8.3$; $P<0.005$) after covarying for ASI severity at baseline. Benzodiazepine augmentation of antidepressants has not been systematically studied in PTSD, but this appears to be a common clinical practice that might save $600 to $1,200 per patient, per year, in outpatient care. Because of the high rates of substance abuse in PTSD and our 8 month follow-up data, future studies controlling the dosage and duration of benzodiazepine treatment in a placebo controlled design should also monitor for its abuse.

ACKNOWLEDGMENTS: Supported by NEPEC, the VA Cooperative Studies Program, and NIDA grants P50-DA04060 and P50-09250.

ANTIPLATELET THERAPY FOR REGIONAL CEREBRAL PERFUSION DEFICITS IN CHRONIC COCAINE ABUSERS: PRELIMINARY RESULTS OF PLATELET AND SPECT ANALYSES FROM A PLACEBO-CONTROLLED CLINICAL TRIAL WITH ASPIRIN AND AMLORIDE

C. Gottschalk, H. Rinder, S. Sanabria, and T. Kosten

Departments of Psychiatry, Neurology, Laboratory Medicine and Radiology, Yale School of Medicine; West Haven, CT

We are investigating the relationship of highly abnormal platelet activation in chronic cocaine abusers to regional cerebral blood flow (rCBF) defects identified with Tc-HMPAO-SPECT. We are currently engaged in a randomized clinical trial comparing a standard clinical dose of amiloride with daily aspirin therapy or placebo. Our group has identified platelet abnormalities, especially increased alpha-granule release, in this population that can be reversed rapidly and specifically in vitro by amiloride. Preliminary data from our group and others indicate that these rCBF defects are reversible and potentially responsive to medication; their pathophysiology is unknown. Subjects are active cocaine abusers without another Axis I diagnosis; they cannot have HIV or any medical condition or treatment that might alter rCBF. Each subject is randomized to Aspirin, Amiloride, or placebo in a double-blind protocol. SPECT scanning is performed with a Picker PRISM 3000XP on days 2, 14, and 30. Platelet studies and neuropsychological tests are administered the same days. A preliminary analysis of our current data on platelet function and rCBF indicate that the dose of amiloride used is achieving neither significant normalization of platelet function nor significant restoration of rCBF; aspirintherapy is associated with a 10-20% improvement of rCBF over placebo and with normalization of platelet aggregation and turnover. No treatment group showed normalization of elevated alpha-granule release, as measured by expression of membrane P-selectin. We therefore plan a dose-ranging study to examine its potential effects at an optimized dose.

ACKNOWLEDGMENTS: Supported by NIDA P-50 DA-04060 and DA 00167.

A CATALYTIC ANTIBODY AGAINST COCAINE ATTENUATES COCAINE'S CARDIOVASCULAR EFFECTS IN MICE

*R. J. Briscoe, C. L. Cabrera, G. Winger, J. H. Woods, and *D. W. Landry*

Department of Pharmacology, University of Michigan Medical School, Ann Arbor, MI and *Columbia University, New York, NY

The acute toxicity of cocaine frequently results in severe and often fatal cardiovascular events. Despite decades of effort, no useful antagonist of cocaine's toxic cardiovascular effects have been identified. A number of difficulties to the development of an effective cocaine antagonist led to the development of a catalytic antibody for cocaine. The murine monoclonal antibody 15A10 was generated through repetitive hybridoma preparation, and it has been shown to be a potent artificial esterase for cocaine (Yang *et al.,* 1996). Balb/c mice were surgically implanted with a jugular vein catheter (utilized for antibody or vehicle infusion) and femoral arterial catheter (utilized for mean arterial pressure and heart rate measurement). Following surgery the mice were allowed to recover for 24 hours prior to the onset of antibody infusion. Mab 15A10 (100 mg/kg) or vehicle were infused in the first group 15 minutes prior to cocaine and 24 hours prior to cocaine in a second group. Following pretreatment, cocaine was administered (100 mg/kg ip) and cardiovascular parameters were monitored. The mice were awake and freely moving during the measurement of the cardiovascular parameters. The cocaine-induced increase in mean arterial pressure was shown to be significantly attenuated following cocaine in the Mab 15A10 groups with both the 15 minute and 24 hour pretreatments when compared to vehicle pretreated mice. Additionally, the Mab 15A10 reduced mortality. For example, 2 of the 8 vehicle pretreated mice expired between 6 and 7 minutes following cocaine administration, whereas none of the Mab 15A10 pretreated mice expired in the 15 minute pretreatment group. These results demonstrate a clear and significant attenuation of the cocaine-induced increase in mean arterial pressure when the animals are pretreated with Mab 15A10.

ACKNOWLEDGMENTS: Supported by DA00254, DA07268, and ONDCP.

CHRONIC COCAINE USE IS ASSOCIATED WITH REGIONAL BRAIN BLOOD-FLOW ABNORMALITIES DURING SEQUENCE LEARNING

G. S. Berns, R. E. Tarter, and J. D. Cohen†*

Department of Psychiatry, University of Pittsburgh; *Department of Psychiatry, Emory University; and †Psychology Department, Princeton University

Chronic cocaine use has been associated with both depressed glucose metabolism and decreased dopamine release in frontal cortico-striatal circuits. Using a sequence learning task that has previously been shown to activate these circuits, we hypothesized decreased functional responsivity after chronic cocaine use. Seven subjects with cocaine dependence (< 6 months abstinence) and 6 control subjects performed a sequence learning task. The regional brain blood flow response was measured with 15O-water PET during the course of learning. To measure the response to both novelty detection and response competition, trial blocks of a 2nd sequence were introduced in a counterbalanced design during the latter half of the experiment. A total of 14 PET scans were obtained. Using a mixed-effects model, regional differences between groups were identified by the statistical parametric map of the interaction between sequence (1 or 2) and group (coc vs. nl). The L ventral striatum, including the nucleus accumbens, showed significantly less activation with the sequence change in the patients ($p<.0001$). Other regions showing significantly less activation in the patients included bilateral inferior temporal cortices, R anterior and posterior cingulate, and L dorsolateral prefrontal cortex (all $p<.0001$). All regions showing functional hypoactivity in the patients correlate with regions of high dopamine receptor density. This suggests that the chronic effects of cocaine are associated with functional changes in brain regions corresponding to the sites of cocaine action. In the context of sequence learning, these regions may subserve the cognitive functions of novelty detection, attention, and autonomic reactivity. Chronic cocaine use may impair these functions by virtue of its regional effects, either through receptor down-regulation or vascular changes.

ACKNOWLEDGEMENT: Supported by the Stanley Foundation (GSB).

EXPOSURE OPPORTUNITY: A MECHANISM TO LINK TOBACCO SMOKING WITH MARIJUANA USE

F. A. Wagner and J. C. Anthony

Department of Mental Hygiene, Johns Hopkins University, Baltimore, MD

We used data from the 1991 National Household Survey on Drug Abuse to test the hypotheses that (a) tobacco smokers are more likely to be exposed to an opportunity to use marijuana than non tobacco smokers; and that (b) given an opportunity to use marijuana tobacco smokers are more likely to use marijuana than non tobacco smokers. We created a synthetic longitudinal dataset from this cross-sectional survey to allow for the analysis of first cigarette smoking, first opportunity to try marijuana and first marijuana use as time-varying characteristics. Discrete time survival analysis was used because hazards were not proportional. It was found that tobacco smokers are an estimated 23 times more likely than nonsmokers to have an opportunity to use marijuana (Relative Hazards, RH= 23.36, 95% Confidence Interval, 95% CI, 19.80-27.56), and that smokers are an estimated 25 times more prone to actually use marijuana than non-smokers, given the first opportunity to use it (RH= 5.42; 95% CI, 15.98-40.45). Males were estimated to be twice as likely than females to have an opportunity to use marijuana (RH= 2.16; 95% CI, 1.84,2.54). However, differences between males and females were not statistically significant to actually use marijuana once an opportunity has occurred. Subgroup variations by race/ethnicity was found for both opportunity to use marijuana and actual marijuana use with cigarette smoking, but require replication before firm conclusions can be established. Findings from this study strengthen our understanding of epidemiology of opportunities to use drugs and may help explain the observed association between tobacco smoking and later use of drugs, such as marijuana.

ACKNOWLEDGMENTS: Supported by scholarship 110421 from the National Council on Science and Technology (CONACYT), Mexico (FAW) and NIDA grant DA 09897 (JCA).

ATTENUATION OF COCAINE SELF-ADMINISTRATION IN MONKEYS BY THE DOPAMINE D_1 AGONIST SKF 83959

J. Bergman and S. R. Goldberg

Department of Psychiatry, Harvard Medical School-McLean Hospital ADARC, Belmont, MA and IRP, NIDA/NIH, Baltimore, MD

Dopamine D_1 agonists have been forwarded as candidate medications to combat addiction to the indirect dopamine agonists cocaine and methamphetamine. D_1 high-efficacy agonists have been shown to at least partially substitute for cocaine or methamphetamine in drug discrimination and drug self-administration procedures in monkeys; D_1 low-efficacy agonists, like receptor blockers, appear to attenuate the effects of the psychomotor stimulants in both procedures. In the present experiments, modification of i.v. cocaine self-administration or, in a separate group, food-maintained behavior by the dopamine D_1 agonist SKF 83959 was studied in squirrel monkeys that responded under fixed-ratio 15 schedules of reinforcement. The effects of pretreatment with saline or graded doses of SKF 83959 (0.3 3.0 mg/kg) were determined by administering i.m. doses 30-min prior to the daily session. Each dose was studied at least once in all monkeys. Results show that SKF 83959 produced dose-related downward shifts in the dose-effect function for cocaine-maintained rates of responding and some decreases in food-maintained behavior. Additional experiments were conducted to determine whether i.v. SKF 83959 or, for comparison, the D_1 high-efficacy agonist R-(+)-6-BrAPB, served to maintain self-administration behavior. Results indicate that one or more i.v. doses of R-(+)-6-BrAPB, but not SKF 83959, maintained responding under the FR schedule in cocaine-experienced monkeys. These data, in conjunction with previous findings of stimulant-antagonist effects in drug discrimination experiments in monkeys, suggest that SKF 83959 may modify abuse-related effects of psychomotor stimulant drugs in a therapeutically benficial manner. It is unknown whether other behavioral effects of such D_1 agonists may limit their clinical application.

ACKNOWLEDGMENTS: Supported by DA03774 and DA 10566.

THE EFFECTS OF ANXIETY AND STRESSORS ON EVENT-RELATED POTENTIAL MEASURES IN BOYS AT RISK FOR SUBSTANCE ABUSE

J. Brigham[1], *H. B. Moss*[2], *and L. Kirisci*[3]

SRI International, Menlo Park, CA[1]; University of Pittsburgh School of Medicine, Pittsburgh PA[2]; Center for Education and Drug Abuse Research[3]; Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine

Components of cognitive event-related potentials (ERPs) have been considered in relation to various disorders and predispositions, including the liability for substance use based on parental history of substance abuse or dependence. The predisposition and response of the subject generally is not taken into consideration in these or other ERP analyses, despite the known sensitivity of ERP measures to the subject's mental and emotional state. This study examines the effects of anxiety and home environmental on ERPs measured in preadolescent boys at varying risk for a substance-use disorder, based on paternal history. ERPs were collected from midline (Fz, Cz, Pz) and parietal (P3, P4) electrode leads during an auditory oddball task. Covariates reflecting parental stress, regularity of daily sleep, and subjective anxiety accounted for a significant amount of variance in MANCOVA examining ERP differences among boys (1) at risk for abuse of or dependence on multiple substances including alcohol, (2) at risk for alcoholism, and (3) at low risk for a substance-use disorder. The findings underscore the need to explore internal and external sources of variance in studying populations at risk.

ACKNOWLEDGMENTS: Supported by NIDA grant P50-DA05605 and NIAAA grant AA 07453-12.

BIOLOGICAL EVALUATION OF COMPOUNDS FOR THEIR PHYSICAL DEPENDENCE POTENTIAL AND ABUSE LIABILITY. XXII. DRUG EVALUATION COMMITTEE OF THE COLLEGE ON PROBLEMS OF DRUG DEPENDENCE (1998)

A. E. Jacobson

Laboratory of Medicinal Chemistry, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD

PURPOSES OF THE DRUG EVALUATION COMMITTEE (DEC)

The organizational structure and functions of DEC evolved as the College on Problems of Drug Dependence (CPDD) developed over the past ca. 70 years. The CPDD traces its origin to a 1929 Committee on Drug Addiction in the National Research Council of the National Academy of Sciences (NAS) (Acker 1995: Eddy 1973; May and Jacobson 1989). The precursor of the contemporary Drug Evaluation Committee (DEC) might be considered the pharmacology research component of that early NAS committee. Dr. Nathan Eddy was initially assigned. by the 1929 NAS Committee, to direct that pharmacology component at the University of Michigan (UM). Eddy moved to the National Institutes of Health (NIH) in about 1940; over the next several decades he held many positions in the CPDD. In fact, if not in name, he acted as the Biological Coordinator for the various university and governmental groups involved in the testing programs and research on analgesics until 1967. when Dr. Everette May at the NIH assumed the role of coordinator (Jacobson 1997). I have been the Biological Coordinator from late 1976 to date; during which time the CPDD became the College on Problems of Drug Dependence. The separation of the activities of DEC from those of CPDD occurred slowly, and DEC is now an independent group of researchers under the sponsorship of the CPDD, involved with the research and testing of analgesic, stimulant and depressant classes of drugs for their physical dependence potential and abuse liability.

The history of the CPDD and DEC have been placed online in the CPDD's home page by Dr. Ronald Wood (New York University Medical Center) and the Electronic Communications Subcommittee of the CPDD (http://views.vcu.edu/cpdd/; click on the "Drug Evaluation Committee"), as are my Annual Reports from 1990. 1997, and the Analgesic, Stimulant, and Depressant Drug Indices. These Indices are a compilation of the NIH numbers, common names, and some part of the chemical names of all of the drugs which have been evaluated in monkeys at Virginia Commonwealth University (Medical College of Virginia Campus, VCU-MCV) and at UM. as well as those which have been examined by the Stimulant/Depressant groups, and relates the NIH or CPDD numbers assigned to the drugs to the year of the publication of the data obtained with those compounds. Early data (up to 1977) are in NAS published volumes of the CPDD Annual Scientific Meetings and are, unfortunately, out of print. as are many of the NIDA Monographs (from 1978) which contain the later work of the DEC. The CPDD itself published volumes containing the 1977 and 1978 DEC Annual Reports, and these are also not likely to be easily found. Sets of all of these volumes are owned by a few individuals; we are now considering how older DEC data can be made more generally available.

DEC MEMBERS

In order to evaluate the various classes of drugs, the DEC is divided into an Analgesic Testing Group and a Stimulant/Depressant Testing Group. Researchers in two universities are involved with the former and three universities with the latter. The Analgesic Testing Groups are at VCU-MCV in Richmond (Drs. Mario Aceto, Louis Harris, Everette May, and Edward Bowman), and at the University of Michigan Medical School in Ann Arbor (Drs. James Woods, John Traynor, and Gail Winger). The Stimulant/Depressant Testing Groups are at the University of Mississippi Medical School (Dr. William Woolvcrton), the University of Michigan Medical School (Drs. Gail Winger and James Woods), and at the Louisiana State University Medical Center (Dr. Charles France).

As formerly noted (Jacobson 1998), membership in DEC is available to anyone who has the expertise and resources to carry out drug testing, and who is the principal investigator on a grant or contract. This drug testing must complement or extend existing drug testing programs, and the principal investigator should consider DEC drug testing as a priority for them. Inclusion into DEC is gained by majority vote of the voting members of DEC.

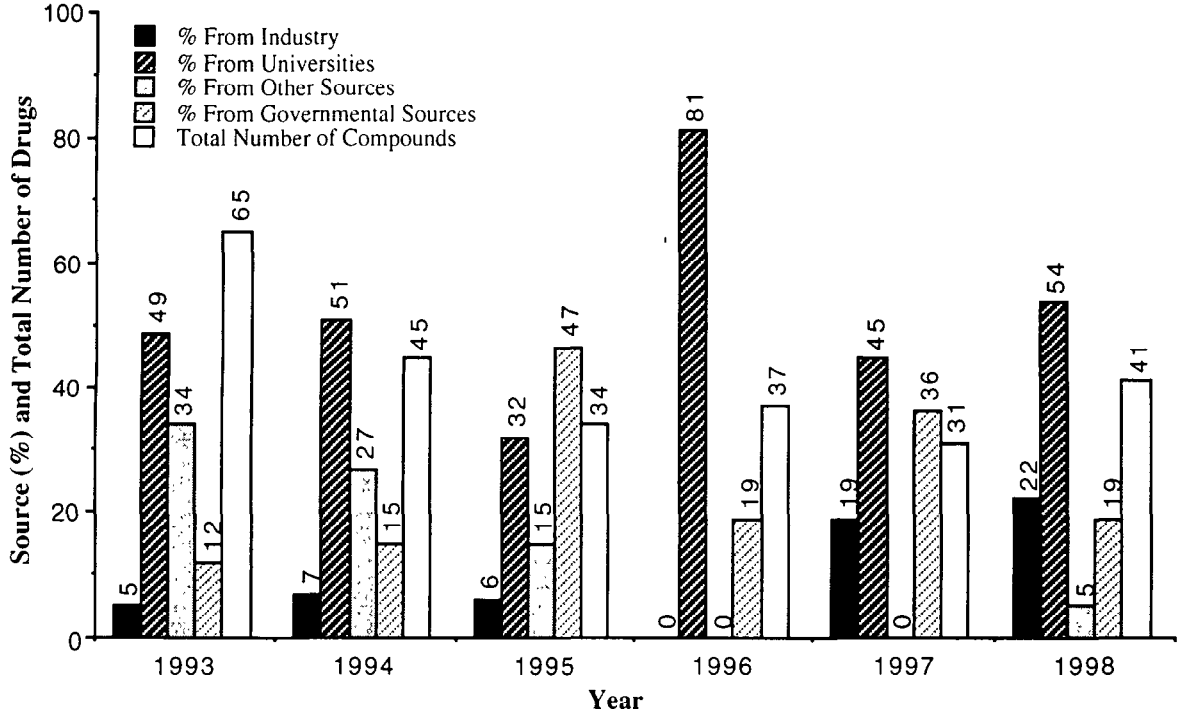
STATISTICS

The source and number of the evaluated analgesics released for publication from 1993 - 1998 can be seen in Fig. 1. In 1998 as in 1997, but unlike the previous several years, pharmaceutical industry was one of the major suppliers of analgesic drugs (22%). Most of the evaluated compounds came from universities (54%); others from governmental

sources and a non-profit institute. Data on five (CPDD 0046-0050) of the six compounds examined by the Stimulant/Depressant Testing Groups were requested by the World Health Organization (WHO, a governmental source), and the sixth compound (CPDD 0045) was obtained from pharmaceutical industry.

The total number of compounds evaluated as analgesics which were released for publication this year was considerably greater than the number released for the last several years, as shown in Fig. 1, and there are some interesting drugs among them (see Experimental Observations section).

FIG. 1. DEC ANALGESIC PROGRAM. PERCENT, TOTAL NUMBER, AND SOURCE OF EXAMINED DRUGS (1993- 1998)



EXPERIMENTAL OBSERVATIONS

Table 1 relates the chemical or common names and assigned NIH or CPDD numbers of the compounds released this year, and the table in which their molecular structure and their in vitro and/or in vitro data appear. Tables 2 - 8 present the molecular structures and a summary of the biological activities of compounds evaluated as analgesics, as obtained from work at VCU-MCV, and at UM (Aceto *et al.* 1999; Woods *et al.* 1999), and the work of the Stimulant/Depressant group (Winger *et al.* 1999) is summarized in Table 9. The compounds in Tables 2 - 8 are grouped according to their molecular structure) in order to facilitate recognition of the relationship between their molecular structure and biological activity (e.g., 4,5-epoxymorphinans, morphinans, 6,7-benzomorphans, methadols, and a miscellaneous set of drugs).

In Tables 2 and 3, the DEC work is shown on the 4,5-epoxymorphinans. (-)-Thebaine and (-)-oripavine (NIH 00088 and 09821) were examined for comparison with data which will be obtained with a series of (+)-4,5-epoxymorphinans. This will be eventually be published as a joint DEC Analgesic Group and NIDDK, NIH, paper.

The structurally interesting thiazalomorphinan, NIH 10888 in Table 2, binds with remarkably high affinity but with little selectivity to opioid receptors; in contrast, the indolomorphinan NIH 10889 (Table 3), a naltrindole-like compound with a C_{14} alkyl substituent, binds with high affinity and good selectivity to the δ-opioid receptor. The N-benzylnoroxymorphone, NIH 10921, was found to be one of the few N-benzyl analogs, of the many which were synthesized in the morphinan, 6,7-benzomorphan, and ketobemidone series, to show agonist or antagonist activity. The complete study of these compounds will be published as a joint DEC Analgesic Group and NIDDK, NIH, paper

(May *et al.* 1998). It remains uncertain why N-benzyl substituted compounds are generally inactive when molecularly similar substituents have shown good in vivo and in vitro activity.

Our binding data [Woods *et al.* 1999] on the well-known BNTX (NIH 10923, Table 2) are in good agreement with that of Nelson's group (Palmer *et al.* 1997; Portoghese *et al.* 1994). Naltriben (NIH 10924, Table 3) (Ohkawa *et al.* 1997; Takemori *et al.* 1992) was also evaluated. We found [Woods *et al.* 1999] that both BNTX and naltriben have good affinity for the δ-opioid receptor, as determined by displacement of [^{3}H]*p*-CI-DPDPE; BNTX was relatively non-selective, and naltriben was found to have higher affinity and better selectivity (μ1/δ = 34) than BNTX for the δ-opioid receptor. Portoghese *et al.* have reported that naltriben binds with considerably higher affinity to a δ_2-opioid receptor subtype than to the δ_1-opioid receptor. Naltriben has agonist activity in the PPQ assay, and both it and BNTX show antagonist activity in the tail flick vs morphine assay; BNTX displays considerably greater potency as an antagonist than naltriben (Aceto *et al.* 1999; Woods *et al.* 1999).

Three azamorphinans were evaluated (Table 4, 10910-10912). The (+)-3-azamorphinan 10912, had far higher affinity for the μ-receptor than either of the two enantiomeric 2-azamorphinans. The classical morphinans have an hydroxyl group attached to the C_3 position, thus they, like the (+)-3-azamorphinan and unlike the 2-azamorphinans. can be considered electron-rich in that molecular area. The (+)- and (-)-optical rotations for morphinans relate to their absolute configuration such that, with few exceptions, the (-)-opioid enantiomer in the morphinan family is almost always the enantiomer which interacts with opioid receptors, and is the natural product. The absolute configurations of 10910-10912 are not known, insofar as I am aware. Thus, there is no way of knowing which represents the natural or unnatural opioid series. Generally, the (+)-morphinans represent the unnatural series and are relatively inactive as analgesics, compared with their (-)-enantiomers.

The N-cyanoalkyl-substituted 6,7-benzomorphans in Table 5 have, in common with many benzomorphans, high affinity for μ and κ opioid receptors. However, NIH 10861 (Table 5) interacts with δ and κ opioid receptors, not with μ and κ receptors. These compounds will be more fully discussed in a future joint article from researchers at VCU-MCV, UM, and NIDDK. The methadols in Table 6 are, with the exception of 10905 (β-(-)-methadol), good agonists in one or another antinociceptive assay, and all completely substitute for morphine in monkeys. These were examined as potential narcotic treatment medication agents, among other reasons, but their advantage over methadone or LAAM, if any, is not known at this time.

Two of the piperidines in Table 7, 10900-10901, may be pro-drugs for 10902-10903. The latter displayed morphine-like agonist activity. SNC80 (NIH 10815 in Table 7) was further examined for its antinociceptive activity in the mouse tail-flick assay using an icv route of administration. It was found to be inactive up to a dose of 5 μg/brain. Thus, although it was shown to have high affinity and selectivity for the δ-opioid receptor (μ/ δ = 542), in our hands only the PPQ assay showed its agonist action *in vivo,* and in that assay it was a very weak antinociceptive (ca. one-tenth the activity of morphine).

In Table 9, new work is shown on six compounds evaluated by the Stimulant/Depressant Group (CPDD 0045, 0046, 0047, 0048, 0049, 0050). The procedures used, and the complete data on these compounds, will be published this year in a separate Stimulant/Depressant Group report (Winger *et al.* 1999). Five of these compounds, CPDD 0046-0050, may be subject to critical review for scheduling purposes at an upcoming WHO meeting in Geneva.

Monkeys self-administered the ephedrine enantiomers (CPDD 0047 and 0048) the racemic mixture (CPDD 0046), and (+)-pseudoephedrine (CPDD 0050) but not (-)-pseudoephedrine (CPDD 0049). The latter was tested up to a dose of less than 1.0 mg/kg/inj; larger doses could not be tested because of the insolubilty of (-)-pseudoephedrine in water. All of the drugs (CPDD 0046 - 0050) were at least partially amphetamine-like as discriminative stimuli; the racemate and (-)-ephedrine (CPDD 0046 and 0047, respectively) more so than the others. The data indicate that all of these compounds (CPDD 0046 - 0050) may have some abuse potential, with the possible exception of (-)-pseudoephedrine (CPDD 0049).

There was no drug-appropriate responding in amphetamine or pentobarbital discrimination and rate of lever pressing was not affected by the imidazole CPDD 0045 in Table 9, nor were there benzodiazepine agonist or antagonist effects. However, variable effects were seen in self-administration with methohexital-trained monkeys. It is unlikely that CPDD 0045 will have stimulant or benzodiazapine-like abuse potential, nor as much potential for abuse as methohexital.

TABLE 1. NIH NUMBERS, CHEMICAL NAMES, TABLE NUMBER, AND EVALUATING GROUP

NIH#	NAME	TABLE #-Evaluator
00088	(-)-Thebaine hydrochloride	2-MCV
09821	(-)-Oripavine hydrochloride	2-MCV
10815	SNC80	7-MCV
10820	(-)-Eseroline (L)-ascorbate	7-MCV
10861	(-)-2-(2-Cyanoethyl)-5,9α-dimethyl-2'-hydroxy-6,7-benzomophan hydrochloride	5-MCV/UM
10888	2'Amino-17-cyclopropylmethyl-6,7-dehydro-3,14-dihydroxy-4,5 α-epoxy-6,7:4'5' thiazolomorphinan dihydrochloride	2-UM
10889	3-Hydroxy-6,7-didehydro-4,5 α-epoxy-17-methy-14 β-(3-methyl)butyl-6,7,2',3'-indolomorphinan hydrochloride	3-MCV/UM
10900	11-[4-Hydroxy-4-(3-trifluoromethylphenyl)piperidin-1-yl]-2-methyl-6,11-dihydrodibenz[b,e]oxepine sulfuric acid	7-UM
10901	11-(4-Hydroxy-4-phenylpiperidin-1-yl)-2-methyl -6,11-dihydrodibenz[b,e]oxepine fumaric acid	7-UM
10902	11-[4-Hydroxy-4-(3-trifluoromethylphenyl)piperidin-1-yl]-2-hydroxymethyl-6,11 dihydrodibenz[b,e]oxepine fumaric acid	7-UM
10903	11-(4-Hydroxy-4-phenylpiperidin-1-yl)-2-hydroxymethyl-6,11-dihydrodibenz[b,e]oxepine	7-UM
10904	α-(+)-Acetylmethadol hydrochloride	6-MCV
10905	β-(-)-Methadol hydrochloride	6-MCV
10906	β-(-)-Acetvlmethadol hydrochloride	6-MCV
10907	β-(+)-Acetylmethadol hydrochloride	6-MCV
10909	(+)-N-[3-(4'-Fluorobenzoyl)propyl]-3-hydroxymorphinan hydrochloride	4-MCV/UM
10910	(+)-N-Methyl-2-azamorphinan dihydrobromide	4-MCV/UM
10911	(-)-N-Methyl-2-azamorohinan dihydrobromide	4-MCV/UM
109 12	(+)-N-Methyl-3-azamorphinan dihydrobromide	4-MCV/UM
10915	(+)-(2*S*,5*S*,9*S*)-2-(4-Cyanobutyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl	5-MCV/UM
10916	(-)-(2R,5R,9R)-2-(4-Cyanobutyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl	5-MCV/UM
10920	(±)-N-Propyl-N-norisonicotine dioxalate	8-MCV/UM
10921	7-Benzylnoroxymorphone hydrochloride	2-MCV/UM
10922	17-Benzylnoroxymorphindole hydrochloride	3-MCV/UM
10923	7-Benzylidene-7-dehydronaltrexone (BNTX) hydrochloride	2-MCV/UM
10924	Naltriben (NTB) methanesulfonate	3-MCV/UM
10925	3-Deoxy-3-methylnaltrindole hydrochloride	3-MCV/UM
10926	(+)-(2*S*,5*S*,9*S*)-2-(5-Cyanopentyl)-5,9-dimethyl-2'-hydroxy-6,7-benzonlorphan.HCl	5-MCV/UM
10927	(-)-(2*R*,5*R*,9*R*)-2-(5-Cyanopentyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl	5-MCV/UM
10928	(-)-N-[3-(4'-Fluorobenzoyl)propyl]-3-hydroxymorphinan hydrochloride	4-MCV/UM
10930	Hydroxyzine	8-MCV/UM
10934	(-)-(2*R*,5*R*,9*R*)-2-(6-Cyanohexyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl	5-MCV/UM
10935	(+)-(2*S*,5*S*,9*S*)-2-(6-Cyanohexyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl	5-MCV/UM
10937	17-Cyclohexylmethylnoroxymorphone hydrochloride	2-MCV/UM
10929	Anandamide	8-MCV/UM
10938	17-Cyclohexylmethylnoroxymorphindole hydrochloride	3-MCV/UM
10939	(+)-Dihydromorphine hydrochloride	2-MCV/UM
10941	3-Deoxy-3-methyloxymorphindole hydrochloride	3-MCV/UM
10946	Melatonin	8-MCV/UM

TABLE 1. NIH NUMBERS, CHEMICAL NAMES, TABLE NUMBER, AND EVALUATING GROUP (CONTINUED)

NIH#	NAME	TABLE #-Evaluator
10948	Mianserin hydrochloride	8-MCV/UM
CPDD 0045	2-Phenyl-4(5)-[4-((2-pyrimidinyl)-piperazin-1-yl)-methyl]-imidazole dimaleate	9-SD
CPDD 0046	(±)-Ephedrine hydrochloride	9-SD
CPDD 0047	1*R*,2*S*-(-)-Ephedrine hydrochloride	9-SD
CPDD 0048	1S,2R-(+)-Ephedrine hydrochloride	9-SD
CPDD 0049	1*R*,2*R*-(-)-Pseudoephedrine	9-SD
CPDD 0050	1*S*,2*S*-(+)-Pseudoephedrine hydrochloride	9-SD

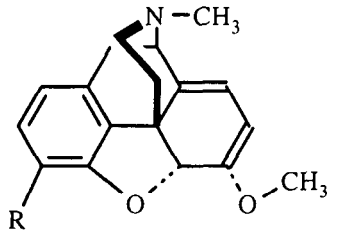
NOTES FOR TABLES 2 - 9

Rounded numbers are used; precise values and details of the procedures are given in the VCU-MCV (Aceto *et al.* 1999) and UM (Woods *et al.* 1999) reports.

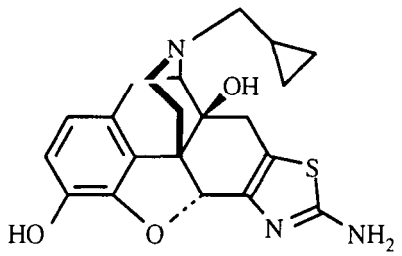
1) Antinociceptive reference data:
Morphine ED_{50} (confidence limits): Hot Plate = 0.8 (0.3-1.8); Phenylquinone = 0.23 (0.20-0.25); Tail-Flick = 5.8 (5.7-5.9)
Tail-Flick Antagonism vs. morphine (naltrexone AD_{50}= 0.007 (0.002-0.02); naloxone AD_{50}= 0.035 (0.01-0.093)).

2) *In Vitro* - Subtype selective binding affinity using monkey brain cortex membranes. Selectivity for μ,δ_1, and κ_1-opioid receptors determined with [^{3}H]-DAMGO, [^{3}H]-*p*-Cl-DPDPE and [^{3}H]-U69,593, respectively. Affinities of labeled ligands: [^{3}H]DAMGO 0.57 nM, [^{3}H]*p*-Cl-DPDPE 1.2 nM, [^{3}H]U69,593 0.95 nM.

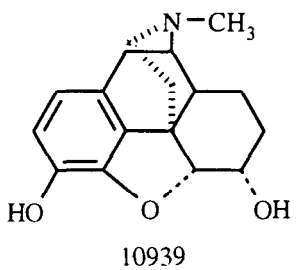
TABLE 2. 4,5-EPOXYMORPHINANS



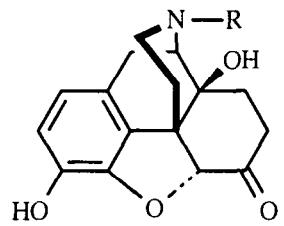
00088 ((-)-Thebaine): R = OCH_3
09821 ((-)-Oripavine): R = OH



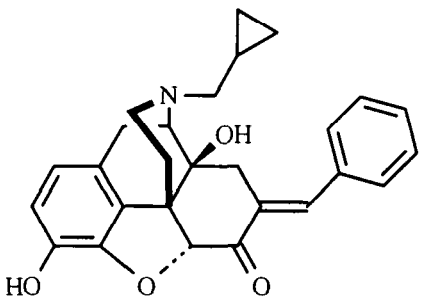
10888



10939



10921: R = Benzyl
10937: R= Cyclohexylmethyl



10923 (BNTX)

ANTINOCICEPTIVE/ANTAGONIST ASSAYS IN VITRO MONKEY

NIH #	Hot Plate	Phenylquinone	Tail Flick	Tail Flick Antagonist	Binding Affinity, nM	Substitution-for-Morphine (sc, mg/kg)
00088	-	-	Inactive[a]	-	-	-
09821	1.5[b]	1.7[b]	3.0[b]	Inactive[b]	-	No substitution (0.5-2.0)[b]
10888	-	-	-	-	μ=0.16, δ=0.67, κ=0.61[c]	-
10921	Inactive	Inactive	Inactive	0.52	μ=138, δ=529, κ=134	Exacerbates withdrawal. Dose-dependently precipitates withdrawal in PptW assay
10923	Inactive	Inactive	Inactive[d]	0.05	μ=9.1, δ=6.8, κ=30	-
10937	Inactive	Inactive	Inactive	11.3	μ=13, δ=310, κ=795	Partial suppression at relatively high dose[e]
10939	Inactive	Inactive	Inactive	45%@3	-	-

a) Convulsions, lethal @ 20, 30 mg/kg. Pretreatment with naloxone or naltrindole does not prevent lethality.

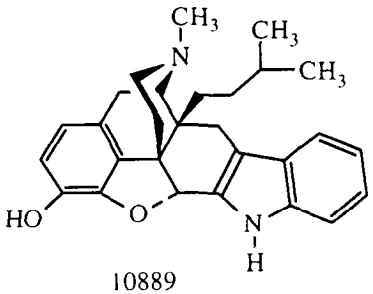
b) Previously reported, 1981. β-FNA (icv) and naltrindole pretreatment indicate μ-δ activity, and lethality not due to μ-δ interaction. Naltrindole AD_{50} = 4.6.

c) Potent non-selective antagonist in mouse vas deferens assay; highest affinity at μ.

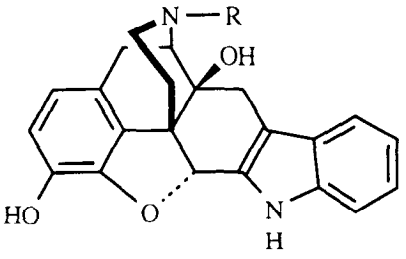
d) Naloxone AD_{50} = 1.1, DPDPE (icv) AD_{50} = 0.04, sufentanil (icv) AD_{50} = 4.0, U69593 AD_{50} = 27% @ 10 mg/kg.

e) One experiment, supply exhausted.

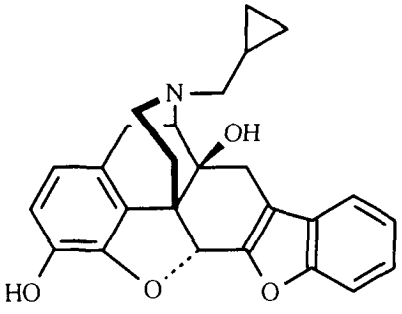
TABLE 3. 4,5-EPOXYMORPHINANS (CONTINUED)



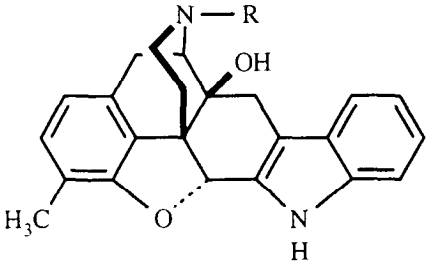
10889



10922: R = Benzyl
10938: R = Cyclohexylmethyl



10924 (Naltriben)



10925: R = Cyclopropylmethyl
10941: R = Methyl

ANTINOCICEPTIVE/ANTAGONIST ASSAYS IN VITRO MONKEY (MOUSE ED50/AD50, sc, mg/kg)

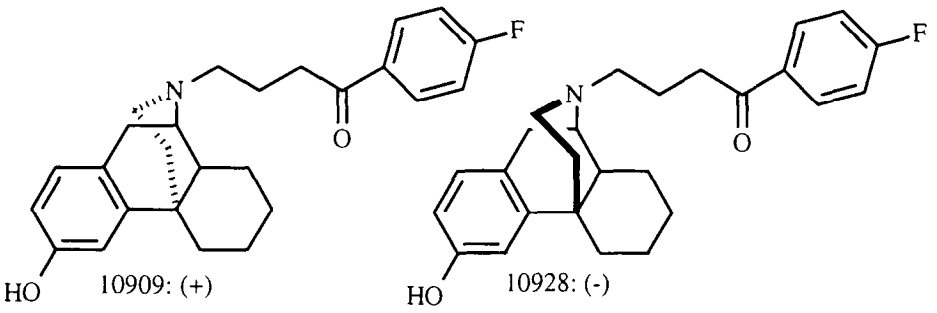
NIH #	Hot Plate	Phenylquinone	Tail Flick	Tail Flick Antagonist	Binding Affinity, nM	Substitution-for-Morphine (sc, mg/kg)
10889	Inactive	6.7	Inactive	Inactive	μ=186, δ=1.4, κ=204	-
10922	Inactive	Inactive	Inactive	Inactive	μ=5330, δ=115, κ=1537	-
10924	Inactive	4.2	Inactive a,b	0.99	μ=12.4, δ=0.36,	-
10925	Inactive	Inactive	Inactive	58%@30	μ=3536, δ=106, κ=6634	-
10938	Inactive	Inactive	Inactive	Inactive	μ=1925, δ=95, κ=1115	Partial suppression[c]
10941	-	-	-	-	μ=>10000, δ=315, κ=>10000	

a) Naltrindole pretreatment did not abolish lethal effects.

b) Convulsions, lethal @ 30 mg/kg.

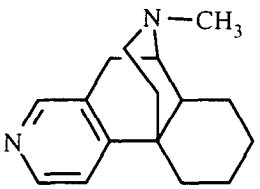
c) Dose-dependently attenuated withdrawal, but major withdrawal signs persist in 2/3 monkeys.

TABLE 4. MORPHINANS



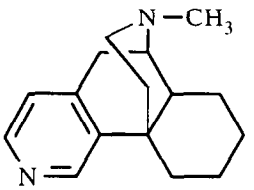
10909: (+)

10928: (-)



10910: (+)

10911: (-)



10912

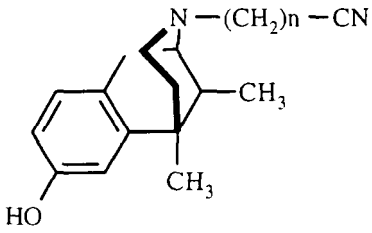
ANTINOCICEPTIVE/ANTAGONIST ASSAYS IN VITRO MONKEY (MOUSE ED50/AD50, sc, mg/kg)

NIH #	Hot Plate	Phenylquinone	Tail Flick	Tail Flick Antagonist	Binding Affinity, nM	Substitution-for-Morphine (sc, mg/kg)
10909	Inactive	0.25	Inactive[a]	Inactive	μ=59, δ=>10000, κ=1227	Non-dose related attenuation of withdrawal[b]
10910	-	-	-	-	μ=2870, δ=> 10000, κ=>10000	-
10911	-	-	-	-	μ=1310, δ=> 10000, κ=>10000	-
10912	-	-	-	-	μ=14.1, δ=971, κ=344	-
10928	Inactive	4.5	Inactive	Inactive	--	-

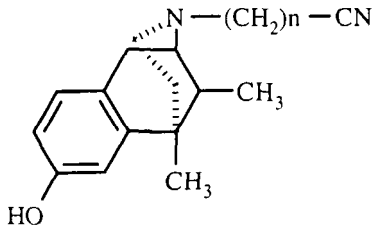
a) sc and iv.

b) Profile does not suggest opioid properties; appears to have CNS depressant effects.

TABLE 5. 6,7-BENZOMORPHANS



10861: n = 2
10916: n = 4
10927: n = 5
10934: n = 6



10915: n = 4
10926: n = 5
10935: n = 6

ANTINOCICEPTIVE/ANTAGONIST ASSAYS IN VITRO MONKEY (MOUSE ED50/AD50, sc, mg/kg)

NIH #	Hot Plate	Phenylquinone	Tail Flick	Tail Flick Antagonist	Binding Affinity, nM	Substitution-for-Morphine (sc, mg/kg)
10861	0.12	0.05	0.3[a]	Inactive	μ=24.5, δ=0.9, κ=2	Partial suppression (0.3-3)[b]
10915	Inactive	Inactive	Inactive	Inactive	μ=4760, δ=10000, κ=1260	Non-dose-related attenuation of withdrawal
10916	Inactive	303	14.6[c]	Inactive	μ=18, δ=160, κ=6.9	Complete suppression (3-12), ca. 0.5x morphine
10926	Inactive	Inactive	Inactive	Inactive	μ=1167, δ=10000, κ=512	-
10927	-	-	-	-	μ=91, δ=216, κ=11	-
10934	Inactive	9.4	Inactive	Inactive	μ=15 δ=350, κ=38	Brief substitution @ 3[d]
10935	Inactive	Inactive	Inactive	Inactive	μ=694, δ=10000, κ=1296	None-dose-related attenuation of withdrawal

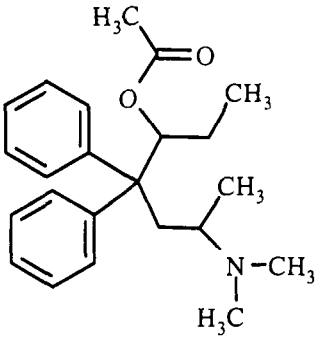
min pretreatment) = 3.7. Antagonized by nor-BNI and naloxone.

b) Positive reinforcer; abuse liability probably less than heroin.

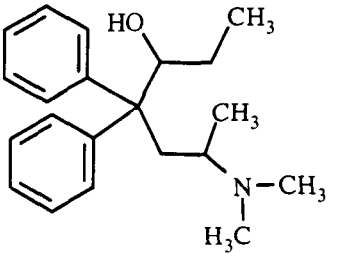
c) Naloxone AD_{50} = 0.009.

d) Robust, non-significant elevation of cumulative withdrawal score at high dose (12 mg/kg).

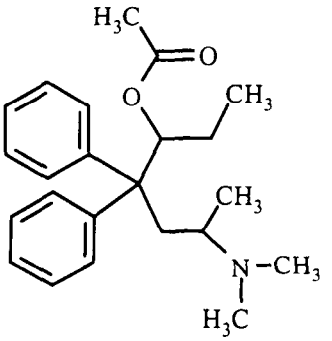
TABLE 6. METHADOLS



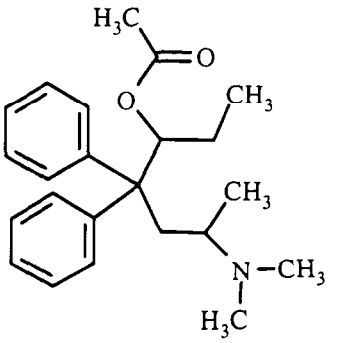
10904: (α-(+)-Acetylmethadol



10905: β-(-)-Methadol



10906: β-(-)-Acetylmethadol



10907: β-(+)-Acetylmethadol

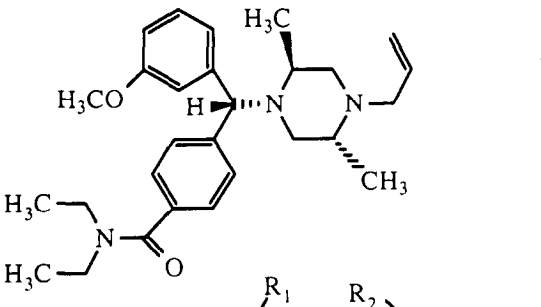
ANTINOCICEPTIVE/ANTAGONIST ASSAYS IN VITRO MONKEY (MOUSE ED50/AD50, sc, mg/kg)

NIH #	Hot Plate	Phenylquinone	Tail Flick	Tail Flick Antagonist	Binding Affinity, nM	Substitution-for-Morphine (sc, mg/kg)
10904	0.58	0.29	0.59	Inactive	-	CS, ca. 6x morphine
10905	Inactive	Inactive	Inactive	Inactive	-	CS, ca. 0.2x morphine[a]
10906	6.0	1.5	4.3	Inactive	-	CS, morphine-like
10907	0.56	0.11	0.29	Inactive	-	CS, 3-4x morphine[b]

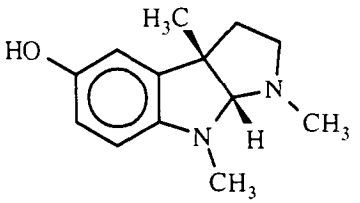
a) Short duration of action.

b) Duration of action at least as long as morphine.

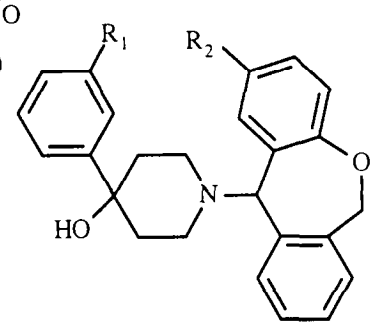
TABLE 7. MISCELLANEOUS



10815: SNC80



10820: (-)-Eseroline



10900: $R_1 = CF_3$, $R_2 = CH_3$
10901: $R_1 = H$, $R_2 = CH_3$
10902: $R_1 = CF_3$, $R_2 = CH_2OH$
10903: $R_1 = H$, $R_2 = CH_2OH$

ANTINOCICEPTIVE/ANTAGONIST ASSAYS IN VITRO MONKEY (MOUSE ED50/AD50, sc, mg

NIH #	Hot Plate	Phenylquinone	Tail Flick	Tail Flick Antagonist	Binding Affinity, n M	Substittion-for-Morphine s c , mg/kg)
10815	Inactive[a]	3.8[a]	Inactive[a,b]	Inactive[a]	μ=488, δ=0.9, κ=1170[a]	NS; no excerbation of withdrawal[a]
10820	3[c]	0.3[c]	2.4[c,d]	Inactive[c]	1600[c,e]	CS, ca. morphine-like[c]
10900	Inactive[1]	Inactive[t]	Inactive[1]	Inactive[1]	μ=29, δ=967, κ=935	Non-dose-related suppression of withdrawal. Possible pro-drug[f]
10901		7.6[t]	Inactive[t]	Inactive[1]	μ=69, δ=1292, κ=327	CS, 0.2x morphine Possible pro-drug[f]
10902	0.98[t]	1.1[t]	12.9[f,g]	Inactive[1]	μ=9.6, δ=1162, κ=1110	CS(2,8). Rapid onset, duration of action >2.5 hr
10903	2.2[t]	0.6[t]	1.1[t,h]	Inactive[t]	μ=11.7, δ=111, κ=242	CS, 3x morphine

a) Previously reported, 1995, 1996.

b) TF, iv and icv = inactive (0.1-10 mg/kg, and 5 μg/brain, respectively).

c) Previously reported in 1986, 1997.

d) Naloxone AD_{50} = 0.16 (high)[c]; atropine vs ED_{80} in TF: inactive.

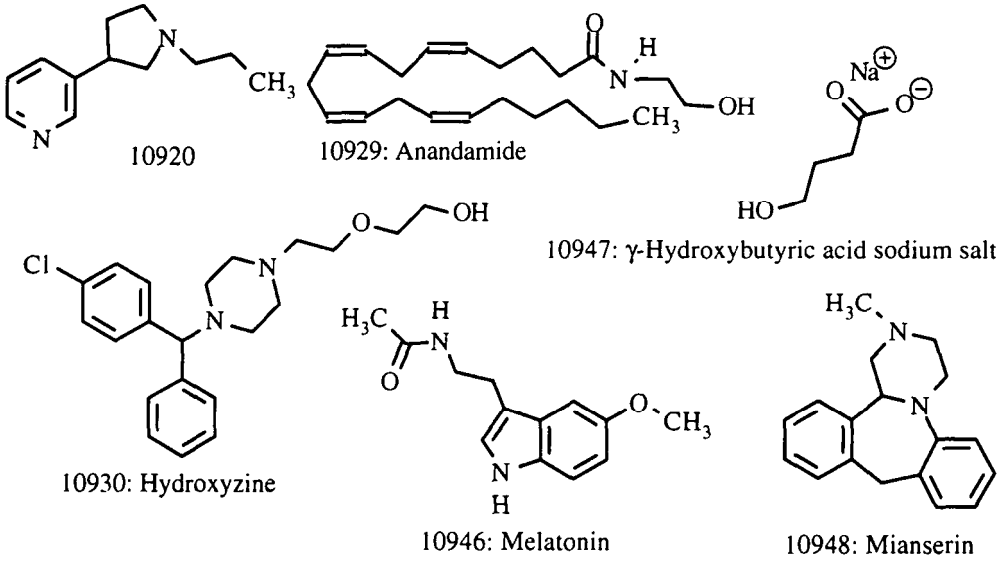
e) Radioligand: [^{3}H]-etorphine, using rat brain homogenates.

f) Previously reported, 1997.

g) Naloxone AD_{50} = 0.12 (high, suggesting heterogeneous opioid properties).[f]

h) Naloxone AD_{50} = 0.06.[f]

TABLE 8. MISCELLANEOUS (CONTINUED)



ANTINOCICEPTIVE/ANTAGONIST ASSAYS IN VITRO MONKEY (MOUSE ED50/AD50, sc, mg/kg)

NIH#	Hot Plate	Phenylquinone	Tail Flick	Tail Flick Antaonist	Binding Affinity, nM	Substitution-for-Morphine (sc, mg/kg)
10920	11.0	4.7	Inactive	Inactive	μ, δ, κ =>10000	NS(2.5,10)
10929	-	-	23.3[a]	-	-	-
10930	Inactive	8,6[b]	Inactive	Inactive	-	-
10946	Inactive	Inactive	Inactive	Inactive	-	NS(0.75,3)
10947[d]		iv:30.9	Inactive[c]	-	-	-
10948	50%@10	0.09[f]	Inactive	Inactive	-	-

a) SKF 141716A AD_{50} vs ED_{80} 10929: 12.8 (after 15 min pretreatment with SKF 141716A, sc, and 5 min pretreatment with 10929, iv: antagonism of antinociceptive effect.

b) Naloxone AD_{50}: 7% antagonism at 1, 10 mg/kg. Weak antinociceptive effect not involving opioid system.

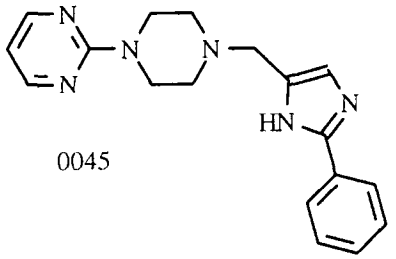
c) Mild convulsions at cumulative 9 mg/kg dose.

d) Previously published as CPDD 0044 (examined by Stimulan/Depressant group), 1996.

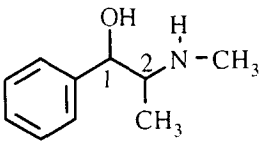
e) Inactive sc, iv (20 min pretreatment), or po (pretreat). Coadministration with ED25 of morphine sulfate (MS) gave dose-related synergism. In mice tolerant to MS, 10947 in combination with MS partially restored antinociception; naloxone nearly abolished this effect.

f) Naloxone AD50 = 1.07. NIH 10948, a serotonin antagonist, has antinociceptive activity which can be antagonized by naloxone.

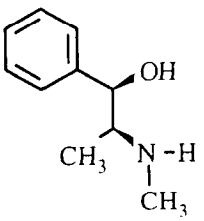
TABLE 9. EVALUATION OF STIMULANT/DEPRESSANT DRUGS



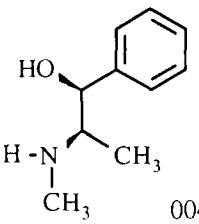
0045



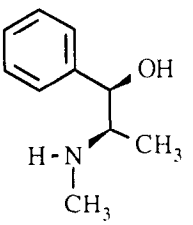
0046: (±)-Ephedrine



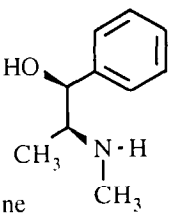
0047: 1*R*,2*S*-(-)-Ephedrine



0048: 1*S*,2*R*-(+)-Ephedrine



0049: 1*R*,2*R*-(-)-Pseudoephedrine



0050: 1*S*,2*S*-(+)-Pseudoephedrine

CPDD#	Discriminative Stimulus Effects In Monkeys. Comparison To Flumazenil & Triazolam (sc)	Monkey Self-Administration (iv)	Monkey Drug Discrimination (intragastric)
0045	No benzodiazepine agonist or antagonist action	Variable, perhaps slight, reinforcing effect in methohexital-trained monkeys	Pentobarbital-trained: No drug-appropriate responding Amphetamine-trained: No drug-appropriate responding
0046	No benzodiazepine agonist or antagonist action	Reinforcer in cocaine-trained monkeys	Amphetamine-like[a,b]
0047	No benzodiazepine agonist or antagonist action	Reinforcer in cocaine-trained monkeys	Amphetamine-like[a,b]
0048	-	Reinforcer in cocaine-trained monkeys	Amphetamine-like[b,c,d]
0049	-	No reinforcing effects in cocaine. trained monkeys	Amphetamine-like[b,c]
0050	-	Reinforcer in cocaine-trained monkeys	Some amphetamine-like properties[b,c]

a) In 2 out of 3 monkeys.
b) No drug-appropriate responding in pentobarbital-trained monkeys.
c) In 1 out of 3 monkeys.
d) At the highest dose (30 mg/kg), a maximum selection of 45% was obtained in a second monkey, and that monkey was visibly stimulated.
e) Considerable variability was observed.

REFERENCES

Aceto, M. D.; Bowman, E. R.; Harris, L. S.; and May, E. L.: Dependence Studies of New Compounds in the Rhesus Monkey, Rat and Mouse (1998). In: L. S. Harris, ed. Problems of Drug Dependence 1997, NIDA Research Monograph, Washington, D.C., 1999.

Acker, C. J. Addiction and the Laboratory. The Work of the National Research Council's Committee on Drug Addiction, 1928-1939. Isis 86:167-193, 1995.

Eddy, N. B.: The National Research Council Involvement in the Opiate Problem. 1928-1971, National Academy of Sciences, Washington, D.C., 1973.

Jacobson, A. E.: The history and current activities of the Drug Evaluation Committee (DEC) of the College on Problems of Drug Dependence (CPDD). In: L. S. Harris, ed. Problems of Drug Dependence 1996, pp. 314-322, NIDA Research Monograph 174, Washington, D.C, 1997.

Jacobson, A. E.: Biological evaluation of compounds for their physical dependence potential and abuse liability. XXI. Drug Evaluation Committee of the College on Problems of Drug Dependence, Inc. (1997). In: L. S. Harris, ed. Problems of Drug Dependence 1997, pp. 346-362, NIDA Research Monograph 178, Washington, D.C, 1998.

May, E. L. and Jacobson, A. E. The Committee on Problems of Drug Dependence: a legacy of the National Academy of Sciences. A historical account. Drug Alcohol Depend 23:183-218, 1989.

May, E. L.; Jacobson, A. E.; Mattson, M. V.; Coop, A.; Aceto, M. D.; Bowman, E. R.; Traynor, J. R.; Woods, J. H.; and Harris, L. S. Synthesis, *in vitro* and *in vivo* activity of *N*-*p*-substituted-benzyl- (-) and (+)-*N*-normetazocines, (-) and (+)-*N*-normorphinans, *N*-norketobemidones, and (-)-*N*-nor-4,5-epoxymorphinans. Med Chem Res in press, 1998.

Ohkawa, S.; DiGiacomo, B.; Larson, D. L.; Takemori, A. E.; and Portoghese, P. S. 7-spiroindanyl derivatives of naltrexone and oxymorphone as selective ligands for delta opioid receptors. J Med Chem 40:1720-1725, 1997.

Palmer, R. B.; Upthagrove, A. L.; and Nelson, W. L. (*E*)- and (*Z*)-Arylidenenaltrexones: Synthesis and opioid receptor radioligand displacement assays. J Med Chem 40:749-753, 1997.

Portoghese, P. S.; Sultana, M.; Moe, S. T.; and Takemori, A. E. Synthesis of Naltrexone-Derived delta-Opioid Antagonists - Role of Conformation of the delta Address Moiety. J Med Chem 37:579-585, 1994.

Takemori, A. E.; Sultana, M.; Nagase, H.; and Portoghese, P. S. Agonist and Antagonist Activities of Ligands Derived from Naltrexone and Oxymorphone. Life Sci 50:1491-1495, 1992.

Winger, G.; Rowlett, J. K.; Woolverton, W. L.; France, C.; and Gerak, L. R.: Progress Report From the Testing Program for Stimulant and Depressant Drugs (1998). In: L. S. Harris, ed. Problems of Drug Dependence 1998, NIDA Research Monograph, Washington, D.C., 1999.

Woods, J. H.; Medzihradsky, F.; Smith, C. B.; Winger, G. D.; and Traynor, J.: Evaluation of New Compounds for Opioid Activity (1998). In: L. S. Harris, ed. Problems of Drug Dependence 1998, NIDA Research Monograph, Washington, D.C., 1999.

ACKNOWLEDGMENT

The DEC is indebted to Dr. Ronald W. Wood and the Electronic Communications Subcommittee of the CPDD for their excellent work in placing DEC data within the CPDD home page (http://views.vcu.edu/cpdd], enabling facile public access of the often difficult-to-find DEC data and publications. Among these data, the Analgesic, Stimulant and Depressant Drug Indices were never formally published before appearing on the CPDD home page.

DEPENDENCE STUDIES OF NEW COMPOUNDS IN THE RHESUS MONKEY, RAT AND MOUSE (1998)

M. D. Aceto, E. R. Bowman, L. S. Harris and E. L. May

Department of Pharmacology and Toxicology, School of Medicine, Virginia Commonwealth University, Richmond, VA

All compounds, except, (-)-thebaine, (-)-oripavine, hydroxyzine, melatonin, γ--hydroxybutyric acid, anandamide and mianserin were unknown to us when submitted by Dr. Arthur Jacobson, Laboratory of Medicinal Chemistry, NIDDK, NIH. These studies were conducted under the auspices of the Drug Evaluation Committee in association with of the College on Problems of Drug Dependence. See summary of new data in Table 1.

Dependence-Liability Studies in Rhesus Monkeys

Substirufion-for-Morphine (SDS) Test. Male and female rhesus monkeys (M. mulatta) weighing 2.5-7.5 kg were used, and they received 3 mg/kg, s.c., of morphine SO_4 every 6 h. All the animals had received morphine for at least 3 months and were maximally dependent on morphine (Seevers and Deneau 1963). A minimal 2-week recuperation period was allowed between tests. At least 3 monkeys/dose were used. The assay (Aceto and co-workers, 1977 and 1978) was initiated by a subcutaneous injection of the test drug or control substances (morphine and vehicle) into animals in a group that had not received morphine for 14-15 h and showed definite signs of withdrawal. Each animal was randomly chosen to receive one of the following treatments: a) a dose of the compound under investigation; b) morphine control, 3.0 mg/kg; and c) vehicle control, 1 ml/kg. The animals were scored for suppression of withdrawal signs during a 2.5-h observation period. The observer was "blind" regarding the choice of treatments. At the end of the study, the data were grouped according to dose and drug. The mean cumulative score ± SEM was calculated and the data illustrated in figure form. If indicated, the data were analyzed using the Kruskal-Wallis Anova and posthoc Mann-Whitney U-Tests.

Precipitated- Withdrawal (PPT- W) Test. This evaluation was done under the same conditions as described above, except that the animals were administered a test compound 2-3 h after the last dose of morphine. These animals were not in withdrawal. Naloxone HCI (0.05 mg/kg, s.c.) served as the positive control.

Primary-Physical-Dependence (PPD) Study. Drug-naive monkeys were medicated with drug, using escalating dose regimens, periodically challenged with naloxone or placed in abrupt withdrawal. They were observed for overt behavioral signs during drug administration and when they were challenged with antagonist or abruptly withdrawn from the drug.

Rat-Infusion Studies

The continuous-infusion method was reported by Teiger (1974) and certain modifications are indicated as follows. Rats were anesthetized after which each was fitted with a specially prepared cannula which was passed subcutaneously from the nape of the neck to the lateral side of the lower abdomen and then inserted into the peritoneal cavity. The cannula was anchored at both ends with silk sutures and attached to a flow-through swivel mechanism which allowed the animal to move about in the cage and eat and drink normally. The swivel was connected to a syringe which was attached to a syringe pump. The animals received 7-10 ml of solution every 24 h. Occasionally, when deemed necessary, as with cocaine, infusions were given *via* the right jugular vein.

Substitution-for-Morphine (SM) Test. The rats received morphine SO_4 (50 mg/kg/24 h on the first day, 100 mg/kg/24 h on the second day, and 200 mg/kg/24 h from days 3 and 4). Then, a test drug was substituted for 2 days. The morphine controls received an infusion of sterile water for injection. The animals were observed for changes in body weight and for behavioral-withdrawal signs for 0.5 h at 6, 24, 48, 72 and/or 96 h after stopping the infusion of morphine.

Table 1. SUMMARY OF NEW DATA

NIH No.	Chemical Name or Generic Class	MOUSE					RAT		MONKEY		
		TF	TFvsM	PPQ	HP	pA2	SM	PPD	SDS	PPT-W	PPD
00088	(-)-Thebaine	T [a]									
09821	(-)-Oripavine	T [b]									
10820	(-)-Eseroline (L)- Ascorbate	T [c]									
10861	6,7-Benzomorphan	T [d]	T	T	T				T		
10889	Indolomorphinan	T	T	T	T						
10904	α--(+)-Acetylmethadol	T [e]	T	T	T						
10905	β--(-)-Methadol	T	T	T	T				T		
10906	β--(-)-Acetylmethadol	T	T	T	T				T		
10907	β--(+)-Acetylmethadol	T [i]	T	T	T				T		
10909	(+)-3-Hydroxymorphinan	T	T	T	T				T		
10915	(+)-6,7-Benzomorphan	T	T	T	T				T		
10916	(-)-6,7-Benzomorphan	T [g]	T	T	T						
10920	(±)-Isonicotine	T	T	T	T				T		
10921	17-Benzylnoroxymorphone	T	T	T	T				T	T	
10922	17-Benzylnoroxymorphindole	T	T	T	T						
10923	7-Benzylidenenaltrexone	T	T	T	T						
10924	Naltriben	T [i]	T	T	T						
10925	3-Deoxy-3-methylnaltrindole	T	T	T	T						
10926	(+)-6,7-Benzomorphan	T	T	T	T						
10929	Anandamide	T [j]									
10930	Hydroxyzine	T	T	T	T						
10934	(-)-6,7-Benzomorphan	T	T	T	T				T		
10935	(+)-6,7-Benzomorphan	T	T	T	T				T		
10938	17-Cyclohexylmethylnornaltrindole	T	T	T	T				T		

Table 1. SUMMARY OF NEW DATA (continued)

10939	(+)-Dihydromorphine	T	T	T	T						
10946	Melatonin	T	T	T	T				T		
10947	γ- -Hydroxybutyric Acid	T[k]		T							
10948	Mianserin	T	T	T	T						

T = Test Performed

Special naltrindole and naloxone pretreatments. [h]Special /3-FNA, nor-BNI and naltrindole pretreatmants. [c]Special atropine vs ED80 of NIH 10820. [d]Special naloxone AD50 vs ED80 of NIH 10861 in TF. [e]Special naloxone AD50 vs ED80 of NIH 10904 in TF. [1]Special naloxone AD50 vs ED80 of NIH 10907 in TF. [g]Special naloxone AD50 vs ED80 of NIH 10916 in TF. [h]Preliminary SDS test. [i]Special naltrindole pretreatment. [1]Special SR 141716A AD50 vs ED80 of NIH 10929 in TF, also, SR 141716A and anandamide pretreatment. [k]Special i.v. and p.o. pretreatment.

Primary-Physical-Dependence (PPD) Study. The rats received test compound, as specified above, for 4-6 days and then, were placed in abrupt withdrawal and observed for overt behavioral signs.

Mouse-Antinociception Tests

Male mice, weighing 20-30 g, were used. All drugs were dissolved in distilled water or in the vehicle indicated and injected subcutaneously (s.c.). At least three doses were tested, and 6-10 animals per dose were used. When applicable, ED50's were calculated by using computerized probit analysis. The results obtained with reference compounds are summarized in Table 2. Occasionally, when requested, drugs were given orally (p.o.) or intravenously (i.v.) and the pretreatment times are indicated in the text.

Tail-Flick (TF) and (TF vs *M) Assays.* The procedure and modifications were described (D'Amour and Smith, 1941 and Dewey et al., 1970 and 1971) in the literature. Briefly, the mouse's tail was placed in a groove which contained a Slit under which was located a photoelectric cell. When the heat source of noxious stimulus was turned on, the heat focused on the tail, and the animal responded by flicking its tail out of the groove. Thus, light passed through the slit and activated the photocell which, in turn, stopped the recording timer. The heat source was adjusted to produce tail flick of 2-4 s under control conditions. Mice were injected with drug or vehicle and tested 20 m later. In the assay for antagonism of the antinociceptive effect, the potential antagonists were administered 10 m before the agonist, and evaluation occurred 20 m later.

Phenylquinone Abdominal-Stretching (PPQ) Assay. The procedure was reported previously (Pearl and Harris, 1966). The mice were injected with test drugs and 10 m later received 2.0 mg/kg intraperitoneally (i.p.) of a freshly prepared paraphenylquinone (PPQ) solution. The mice were then placed in cages in groups of two each. Ten m after the PPQ injection, the total number of stretches per group were counted over a l-m period. A stretch was characterized by an elongation of the mouse’s body, development of tension in the abdominal muscles, and extension of the forelimbs. The antinociceptive response was expressed as the percent inhibition of the PPQ-induced stretching response.

Hot-Plate (HP) Assay. The method was also reported previously (Eddy and Leimbach, 1953 and Atwell and Jacobson, 1978). The hot plate was held at 55°C. Mice were placed on the hot plate and activity was scored if the animal jumped or licked its paws after a delay of 5 s or more, but no more than 30 s beyond the control time.

Table 2

Comparative Data (ED50, mg/kg s.c.) [95% C.L.] of Selected Standards in 4 Mouse Agonist-Antagonist Tests

Drug	Tail-Flick	Tail-Flick Antagonist	Phenylaquinone	Hot-Plate
Pentazocine	15% at 10.0	18 (12-26) (1.0-2.5)	1.7	13% at 30.0
Cyclazocine	17% at 1.0[a]	0.03 (0.02-0.78)	0.01 (0.005-0.03)	25% at 9.0
Nalorphine•HCl	None at 10.0	2.6 (0.7-1.0	0.6 (0.03-1.44)	13% at 30.0
Naloxone•HCl	None at 10.0	0.04 (0.0-0.09)	No Activity	- - - -
Naltrexone•HCI	None at 10.0	0.007 (.002-0.02)	No Activity	- - - -
Morphine-$S0_4$[b]	1.92 (0.89-4.14)	Inactive	0.4[b] (0.2-0.8)	0.85 (0.39- 1.86)
Codeine•$P0_4$	- - - -	Inactive	8.25 (5.12-13.29)	6.4 (2.4-16.8)
Meperidine•HCl	8.37 (4.59-15.27)	Inactive	- - - -	4.6 (1.18-11.7)

[a]Mice were ataxic at 3.0 and 10.0 mg/kg but there was no further increase in reaction time

[b]ICR - Harlan-Sprague-Dawley Inc.

Calculation of Apparent pA2 . Using the tail-flick assay, the apparent pA2 and 95% confidence limits were calculated using Schild and constrained plots as described in Tallarida and Murray (Manual of Pharmacologic Calculations with Computer Programs, 2nd ed., Springer Verlag, NY., 1987).

Briefly, mice were pretreated with vehicle or various doses of antagonist followed 10 m later by an injection of agonist. The mice were tested 30 m after receiving the antagonist. Dose-response lines for antinociception were plotted using at least 3 doses of each opioid agonist in the presence of vehicle or one of the selected doses of antagonist. ED50s were estimated according to the method of Litchfield and Wilcoxon (J. Pharmacol. Exp. Ther., 96, 399, 1949). Each dose ratio (x) was calculated by dividing the ED50 of the opioid in the presence of a given dose of antagonist by that of the agonist alone. Log (x-l) was plotted against the negative logarithm of the molar dose of the antagonist. At least 3 logs (x-l) were plotted. The pA2 values for the antagonist were calculated from the point of intersection of the regression line with the abscissa. See Table 3 for summary of results.

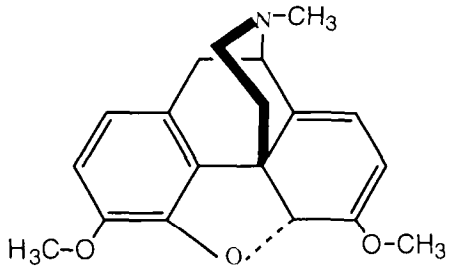
Table 3. Apparent pA2 values[a] using the mouse tail-flick assay

Treatment Antagonist/Agonist	Schild Plot pA2 (95% C.L.) Slope	Constrained Plot pA2 (95% C.L.)
1) Naloxone/Morphine	7.2 (7.0-7.4)-1.2	7.3 (7.1-7.6)
2) Nalmefene/Morphine	8.0 (7.6 - 8.3)-l. 1	8.0 (7.7 - 7.6)
3) Naltrexone/Morphine	7.7 (4.9 - 10.5)-0.8	7.6 (7.1 - 8.3)
4) (-)-Quadazocine/Morphine	6.8 (6.7 - 7.0)-0.9	6.8 (6.1 -0 7.6)
5) Naloxone/Sufentanil	7.0 (6.9 - 7.1)- 1.0	7.0 (6.9 - 7.0)
6) Naloxone/Sufentanil	7.0 (6.5 - 7.5)-1.0	7.0 (6.8 - 7.1)
7) Naloxone/Mirfentanil	7.6 (7.3 - 8.0)-0.7	7.2 (6.9 - 7.5)
8) Naloxone/(-)-Nicotine	5.3 (5.3-5.3)-0.5	7.0 (6.9 - 7.0)
9) Naloxone/U-50,488	6.6 (6.3 - 6.9)-1.1	7.2 (6.9 - 7.5)
kappa agonist		6.6 (6.3 - 7.0)
10) NaloxoneMIH 10672	6.1 (5.6 - 6.6)-1.2	6.2 (5.9 - 7.3)
selective kappa agonist		
11) (-)-Quadazocine/NIH 10672	6.2 (6. 1 - 6.2)-1.7	6.7 (6.6 - 6.8)
12) nor BNI/NIH 10672	6.5 (5.9 - 7.0)-1.3	6.6 (5.9 - 7.3)
13) Mecamylamine/(-)-Nicotine	6.6 (6.2 - 6.9)-0.9	6.5 (6.4 - 6.6)

[a]Negative logarithm of the molar concentrations of antagonist required to produce a two-fold shift of the agonist dose-response curve to the right. Competitive antagonism can be assumed when slope = -1. pA2 provides a measure of the relative potency and affinity of the antagonist. When the slope differs significantly from unity, this may indicate non-equilibrium conditions, interactions with multireceptors, receptor sensitization, precoupling mechanisms, or multiple drug properties. With a constrained plot, the slope of the regression line is restricted to slope=-1.

Special Intracerebroventricular Tail-Flick and PPQ Assays. In order to develop an in-vivo agonist and antagonist model to correlate with the in-vitro binding data of the various opioid receptor types (mu, kappa and delta), we chose the mouse Tail-Flick and PPQ tests and a variety of routes of administration. The intracerebroventricular (i.c.v.) route was chosen to accommodate the fact that no delta agonist is available which is active by peripheral routes of administration

NIH 00088 (-)-Thebaine·HCl



MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

1) TF - Inactive at 1, 3, 10, 20 and 30[a]
2) TF vs M -
3) PPQ -
4) HP-

[a]Convulsions at 20 and at 30, all died.

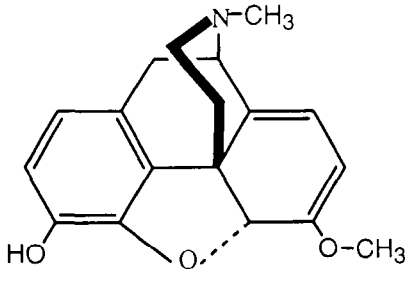
Special: Opioid Subtype Tests.

All mice receiving (-)-thebaine had convulsions and died:
5/6 died after 0.1 mg/kg naloxone pretreatment;
2/6 died after 1.0 mg/kg naloxone pretreatment;
3/6 died after 3.0 mg/kg naloxone pretreatment;
5/6 died after naltrindole pretreatment (1 and 10 mg/kg).

MONKEY DATA
(SDS)

Comment: It seems that the convulsions and lethality associated with (-)-thebaine are not entirely due to opioid activity, especially delta opioid activity. (-)-Thebaine may also act by inhibiting glycine and GABA-receptor binding (Goldfinger *et al.,* Gen. Pharmacol. 23, 1981).

NIH 09821 (-)-Oripavine·HCl



MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

1) TF - a) 3.0 (1.4 - 6.6). Toxic at 10.[a]
b) 13% at 1, 20% at 3 and 62% at 6.
All convulsed and died at 10.
2) TF vs M - a) Inactive at 1 and 10. Toxic at 10.[a]
3) PPQ - 1.7 (0.8 - 3.3)[a]
4) HP - 1.5 (1.1 - 2.0)[a]

[a]Reported previously in NIDA Monog. 41, 1981.

NIH 09821 (-)-Oripavine (Continued)

Special: Opioid Subtype Tests.

1) β-FNA (i.c.v., 4 h pretreatment) vs NIH 09821 (10 mg/kg, lethal dose, s.c.) - All 6 died at 30 µg/brain and 4/6 died at 10 µg/brain of β-FNA.
2) β-FNA (i.c.v., 4 h pretreatment) vs NIH 09821 (6 mg/kg, analgesic dose, s.c.) - 100% antagonism at 30 µg/brain and 68% antagonism at 10 µg/brain of β-FNA.
3) nor-BNI (s.c., 2 h pretreatment) vs NIH 09821 (6 mg/kg, analgesic dose, s.c.), gave 62% increase in MPE. Inactive at 1 and 10 mg/kg of nor-BNI.
4) Naltrindole (s.c., 30 m pretreatment) vs NIH 09821 (6 mg/kg, analgesic dose, s.c., gave 62% increase in MPE). AD50 of naltrindole was 4.6 (2.5 - 8.3).
5) Naltrindole (s.c., 30 m pretreatment) vs NIH 09821 (10 mg/kg, lethal dose, s.c.) - All 6 convulsed and died with 10 and 30 mg/kg of naltrindole.

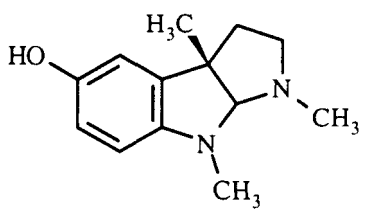
MONKEY DATA Reported in NIDA Res. Monog. 41, 1981.
(SDS)

Did not substitute for morphine at 0.5, 1.0 and 2.0 mg/kg s.c. Severe tremors in preliminary study at 5.6 mg/kg. Treated with pentobarbital 30 mg i.p. and morphine at 3 mg/kg.

Comment: Oripavine is an intermediate in the synthesis of morphine from thebaine in the poppy plant and mammalian brain (Kodaira et al., Proc. Natl. Acad. Sci. 85, 1988; Kodaira and Spector, Proc. Natl. Acad. Sci. 83, 1986; and Donnerer et al., Proc. Natl. Acad. Sci. 83, 1986.

Our studies provide evidence that this important intermediate has mu and delta opioid properties. Importantly, the convulsant and lethal effects are probably not attributable to mu or delta opioid activity.

NIH 10820 (-)-Eseroline (L)-ascorbate



MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

1) TF - 2.4 (1.2 - 4.5)
2) TF vs M - Inactive at 1, 10 and 30.
3) PPQ - 0.3 (0.1 - 0.7)
4) HP - 3.0 (1.5 - 6.0)

5) Special: Naloxone vs ED_{80} of NIH 10820 in TF: AD_{50} = 0.16 (0.05 - 0.55).
6) Special: Naloxone - NIH 10820 pA_2 in TF = 6.9 (4.2 - 9.6); Slope - 0.33.
7) Special: Nor-binaltorphamine (a kappa antagonist) vs ED_{80} of NIH 10820 in TF; (0% antagonism 1, 10, 30 and 60 mg/kg).
8) Special: Atropine (muscarinic antagonist) vs ED_{80} of NIH 10820 in TF; (20% at 3, 41% at 10 and 48% at 30).

Note: All of the above except the atropine study were reported previously (NIDA Res. Monog. 178, 370, 1998).

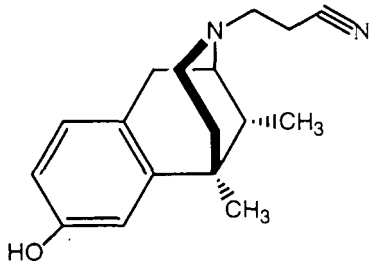
NIH 10820 (Continued)

MONKEY DATA
(SDS)

Dose-dependently substituted completely for morphine at 2.5 and 10.0 mg/kg (Reported previously in NIDA Res Monog. 178, 370, 1998).

Comment: Although naloxone antagonized the antinociceptive effects of eseroline, the slope of the regression line in the pA_2 test was less than unity. This suggested a non-competitive steady-state condition. In addition, this compound was devoid of kappa-agonist properties. Finally, atropine was not an effective antagonist suggesting that the muscarinic system was minimally involved in its antinociceptive action.

NIH 10861 (-)-(2*R*,5*R*,9*R*)-2-(2-Cyanoethyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan•HCl



MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

1) TF - 0.3 (0.1 - 0.8)
2) TF vs. M - Inactive at 1.0, 10.0 and 30.0
3) PPQ - 0.05 (0.03 - 0.08)
4) HP - 0.12 (0.05 - 0.28)

Special: Naloxone vs NIH 10861 in TF. AD_{50} = 0.66 (0.33 - 1.3)

Special: Intracerebroventricular(i.c.v.) and opioid Subtype Studies

1) NIH 10861 - ED50 (i.c.v.) = 2.14 (0.75 - 6.09) µg/brain
2) NIH 10861 vs selective opioid antagonists
    a) Nor-BNI (s.c.) - 0% at 1, 0% at 10 and 24% at 30
    b) Naltrindole (s.c.) - 3% at 1, 19% 10 and 62% 30
    c) β--FNA (i.c.v.) - AD50 = 2.5 (0.8 - 7.5) µg/brain

Special: Apparent pA_2 Study
Naloxone pA_2 - in TF = 6.52 (5.4 - 7.6)
(See Fig. Naloxone-NIH 10861))

Special: Intrathecal Opioid Subtype and Cannabinoid antagonist Studies

1) NIH 10861 administered intrathecally (i.t.) in TF Test
    a) 5 m pretreatment - ED50 = 0.09 (0.03 - 0.3)
    b) 20 m pretreatment - ED50 = 3.7 (1.5 - 9.4)
    c) Naltrindole, Nor-BNI and naloxone (i.t.) and naloxone (s.c.) antagonized NIH 10861 (i.t.)
    d) SR 141716A (Cannabinoid Antagonist) (i.p.) 0% at 30

NIH 10861 (Continued)

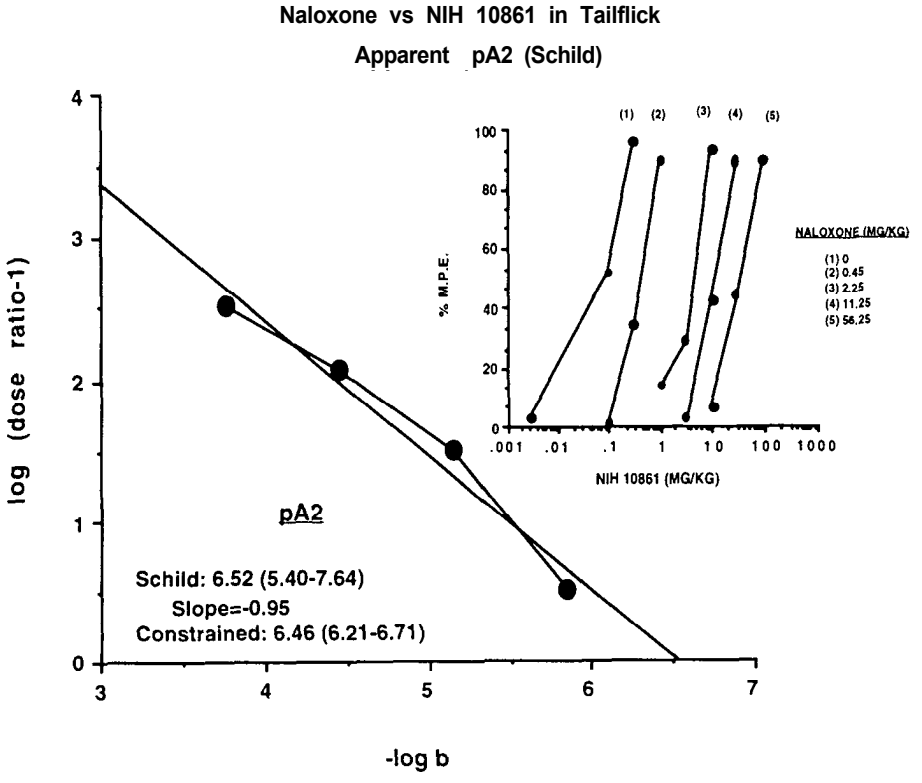


Fig. Naloxone-NIH 10861. Naloxone vs NIH 10861 apparent pA_2.

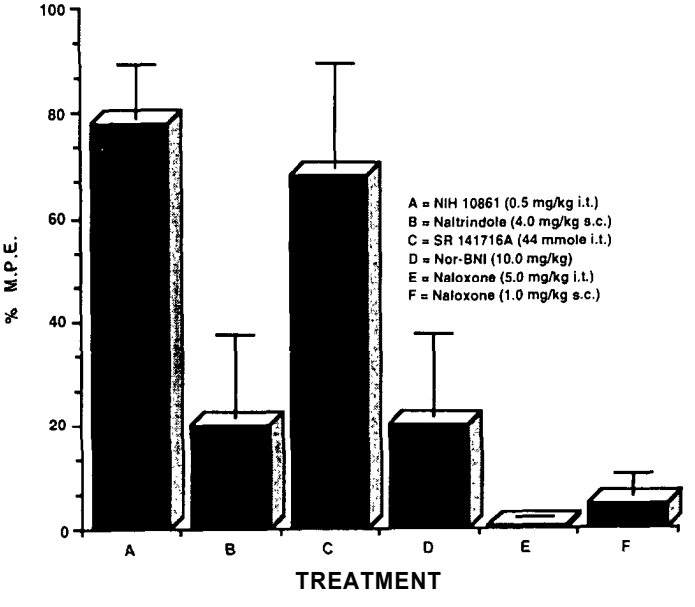


Fig 1. Effect of opioid and tetrahydrocannabinol antagonists vs NIH 10861 (i.t.).

NIH 10861 (Continued)

MONKEY DATA

(SDS)

Although NIH 10861 attenuated withdrawal, it never substituted completely for morphine (see depicted data). At the highest dose tested, pronounced jaw sag, slowing, eyelid ptosis, salivation and decreased respiratory rate were observed.

Comment: The rather high naloxone AD50 and the results of the opioid-subtype studies in the mouse suggests heterogenous opioid properties. This suggestion is supported by the many side effects noted at the highest dose in monkeys.

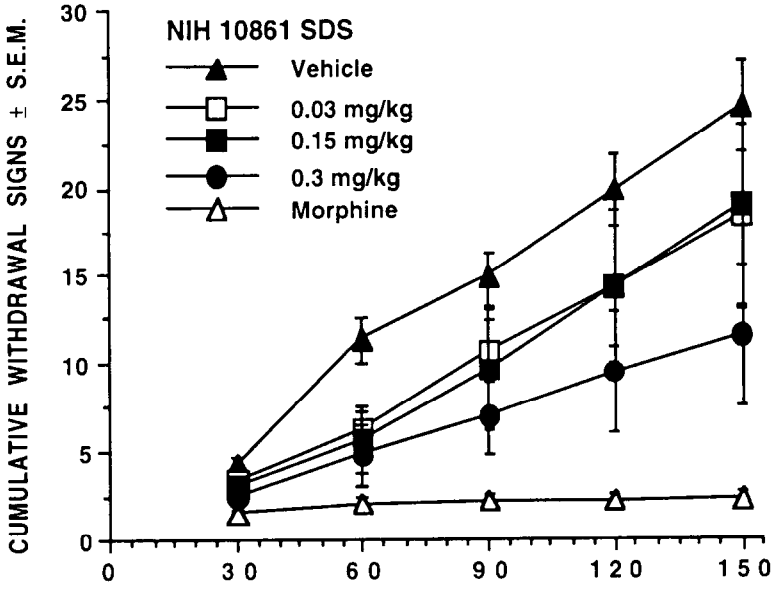
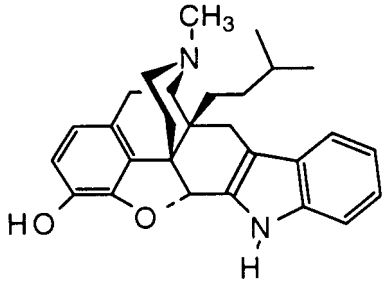


Fig. NIH 10861 Results of study in which NIH 10861 was substituted for morphine in morphine-dependent monkeys in withdrawal.

NIH 10889 3-Hydroxy-6,7-didehydro-4,5 α-epoxy-l7-methyl-14 β-(3-methyl)butyl- 6,7,2',3'-indolomorphinan·HCl; 14β-(3-Methyl)butylmorphindole)



MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

1) TF - 8% at 1.0, 5% at 10.0 and 38% at 30.0[a]
2) TF vs. M - Inactive at 1.0, 10.0 and 30.0[a]
3) PPQ - 6.73 (3.14 - 14.45)[a]
4) HP - Inactive at 1.0, 10.0 and 30.0[a]

[a]Vehicle - 5% DMSO in water + heat

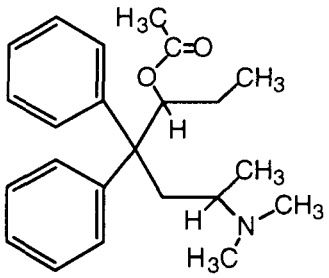
NIH 10889 (Continued)

MONKEY DATA
(SDS)

Not tested.

Comment: NIH 10889 does not display a remarkable antinociceptive profile in mice. It has some weak activity in the PPQ assay.

NIH 10904 α-(+)-(3*R*)-Acetoxy-(6*R*)-dimethylamino-4,4-diphenylheptane·HCl; α-(+)-Acetylmethadol·HCl



MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

1) TF - 0.59 (0.32 - 1.08)
2) TF vs. M - Inactive at 1.0, 10.0 and 30.0
3) PPQ - 0.29 (0. 14 - 0.62)
4) HP - 0.58 (0.25 - 1.35)

Special Test: Naloxone AD_{50} vs ED_{80} of NIH 10904 in TF = 0.013 (0.005 - 0.030)

MONKEY DATA
(SDS)

NIH 10904 replaced morphine at 0.5 and 2.0 mg/kg (see fig. NIH 10904). Onset was rapid and offset was 2.5 h. Potency estimate is approximately 6 times that of morphine.

Comment: The profile of activity in mice and monkeys is indicative of a mu-opioid agonist

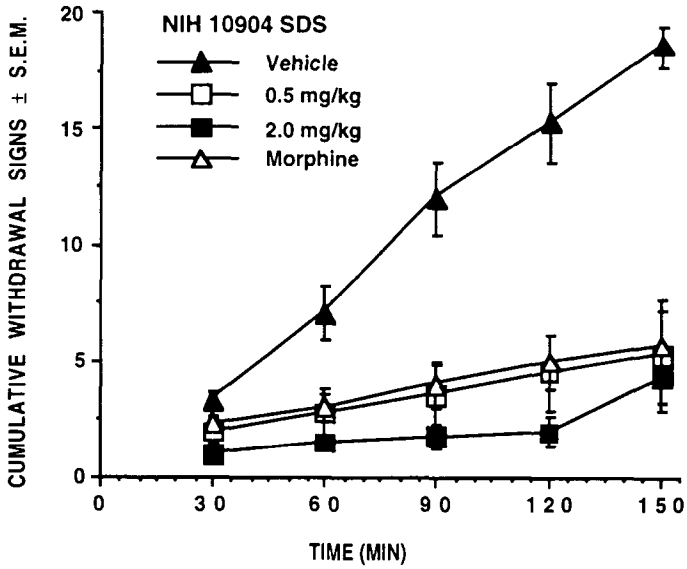
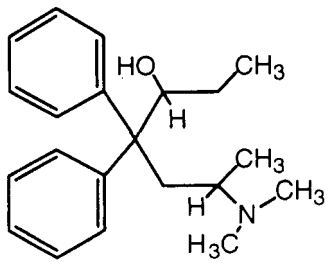


Fig. NIH 10904 Results of study in which NIH 10904 was substituted for morphine in morphine-dependent monkeys in withdrawal.

NIH 10905 β-(-)-6*R*-Dimethylamino-4,4-diphenyl-3 *S*-heptanol·HCl; β-(-)-Methadol



MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

1) TF - 1% at 1.0, 4% at 10.0 and 13% at 30.0
2) TF vs. M - 9% at 1.0, 11% at 10.0 and 11% at 30.0
3) PPQ - 14% at 1.0, 20% at 10.0 and 46% at 30.0
4) HP - 13% at 1.0, 0% at 10.0 and 63% at 30.0

MONKEY DATA
(SDS)

As illustrated in the fig., NIH 10905 briefly replaced morphine at the high dose. The drug acted promptly, however duration of action was waning at 90 min. Potency is estimated at about 1/5 that of morphine.

Comment: The compound does not display remarkable antinociceptive activity in the mouse. However, it briefly suppressed withdrawal signs in the monkey. Perhaps NIH 10905 is rapidly metabolized.

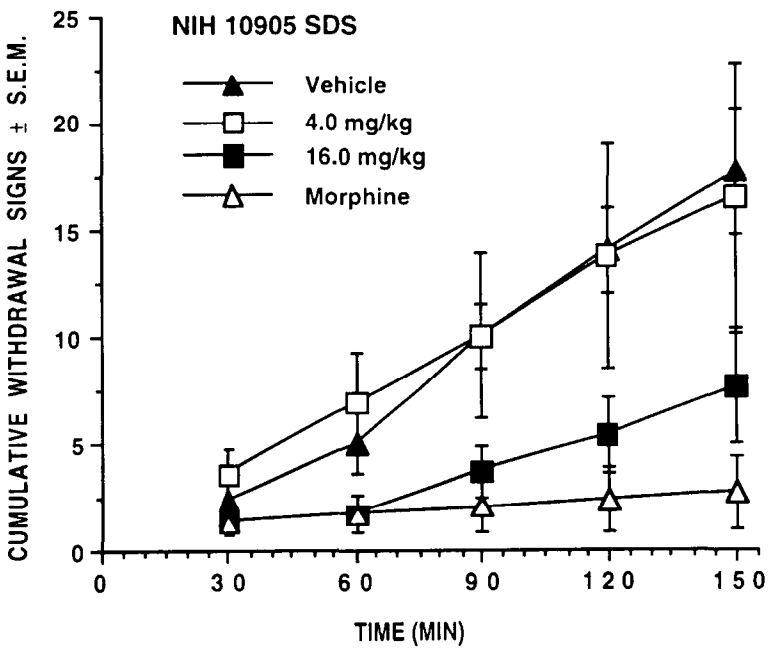
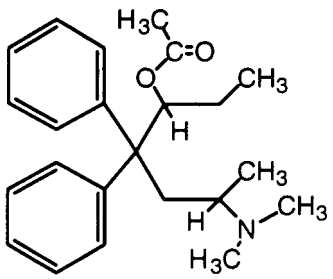


Fig. NIH 10905 Results of study in which NIH 10905 was substituted for morphine in morphine-dependent monkeys in withdrawal.

NIH 10906 β-(-)-(3*S*)-Acetoxy-(6,*R*)-dimethylamino-4,4-diphenylheptane·HCl; β-(-)-Acetylmethadol·HCl



MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

1) TF - 4.32 (2.06 - 9.05)
2) TF vs. M - 10% at 1.0, 5% at 10.0 and 0% at 30.0
3) PPQ - 1.50 (0.67 - 3.33)
4) HP - 6.04 (3.11 - 11.75)

MONKEY DATA
(SDS)

NIH 10906 substituted completely for morphine at 2 and 8 mg/kg. At the high dose, the signs designated slowing, scratching and body sag were observed suggesting that this dose was supra- maximal. The drug acted quickly and was effective for at least 2.5 h. Potency is approximately equivalent to that of morphine.

Comment: The results in mice and monkeys have a profile of activity not unlike that observed with mu opioid agonists.

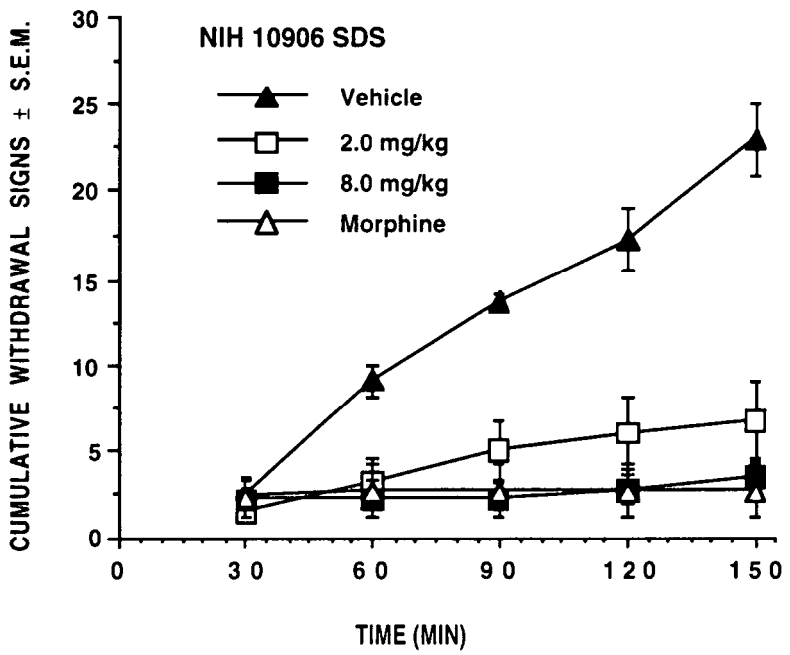
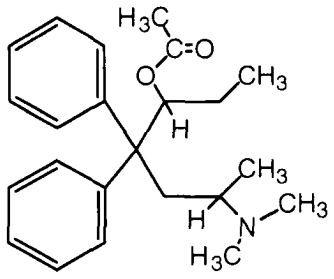


Fig. NIH 10906 Results of study in which NIH 10906 was substituted for morphine in morphine-dependent monkeys in withdrawal.

NIH 10907 β-(+)-(3*R*)-Acetoxy-(6*S*)-dimethylamino-4,4-diphenylheptane•HCl;
β-(+)-Acetylmethadol·HCl



MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

I) TF - 0.29 (0.11 - 0.75)
2) TF vs M - Inactive at 1, 10 and 30
3) PPQ - 0.11 (0.03 - 0.49)
4) HP - 0.56 (0.33 - 0.94)

Special Test: Naloxone AD_{50} vs ED_{80} of NIH 10907 in TF = 0.008 (0.004 - 0.02)

MONKEY DATA
(SDS)

As shown in the illustrated data (see figure), NIH 10907 dose-dependently substituted for morphine in monkeys in withdrawal. Onset of action was prompt and duration was at least as long as that of morphine, namely 2 1/2 h. Potency is 3 - 4 times that of morphine.

Comment: It is apparent that NIH 10907 interacts with mu-opioid receptors.

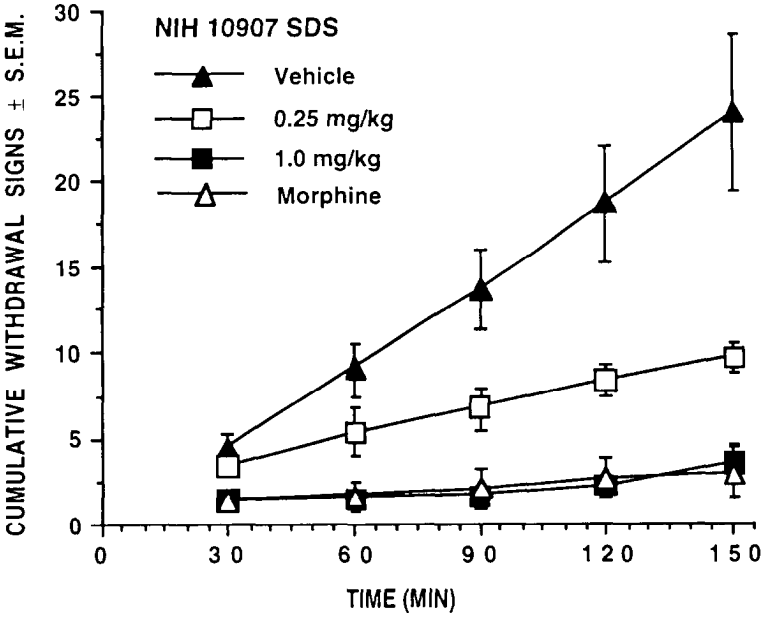
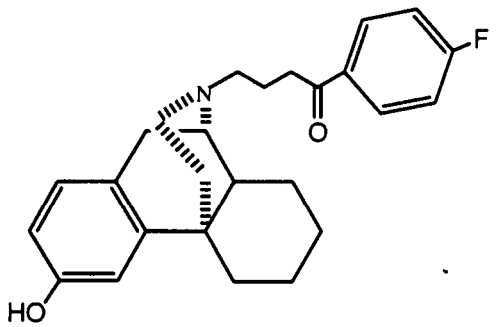


Fig. NIH 10907 Results of study in which NIH 10907 was substituted for morphine in morphine-dependent monkeys in withdrawal.

NIH 10909 (+)-N-[3-(4-Fluorobenzoyl)propyl]-3-hydroxymophinan•HCl



MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

1) TF (s.c.) - 1% at 1, 26% at 10 and 3% at 3[()a,b]
   TF (i.v.) - 0% at 1, 3% at 10 and 39% at 30[a,c,d]
2) TF vs M - Inactive at all doses[a]
3) PPQ - 0.25 (0.1 - 0.6)"
4) HP - 0% at 1, 38% at 10 and 30[a,e]

[a]10% Hydroxypropyl-β-cyclodextrin
[b]At 10 and 30 immobility and eyelid ptosis
[c]Eyelid ptosis at all doses
[d]Immobility at 10 and 30
[e]Eyelid ptosis at 30. Immobility and clonic movement of hind limbs

MONKEY DATA
(SDS)

Withdrawal signs were attenuated at both doses. However, the results were not dose related (see figure NIH 10909). In addition, at both doses the signs eyelid ptosis and jaw sag were also noted. Drug supply was exhausted and only 2 monkeys were used for the highest dose tested. Vehicle was 10% hydroxypropyl-β-cyclodextrin in water.

Comment: NIH 10909 does not exhibit a profile of activity suggestive of opioid properties. Instead, the drug appears to have CNS depressant effects.

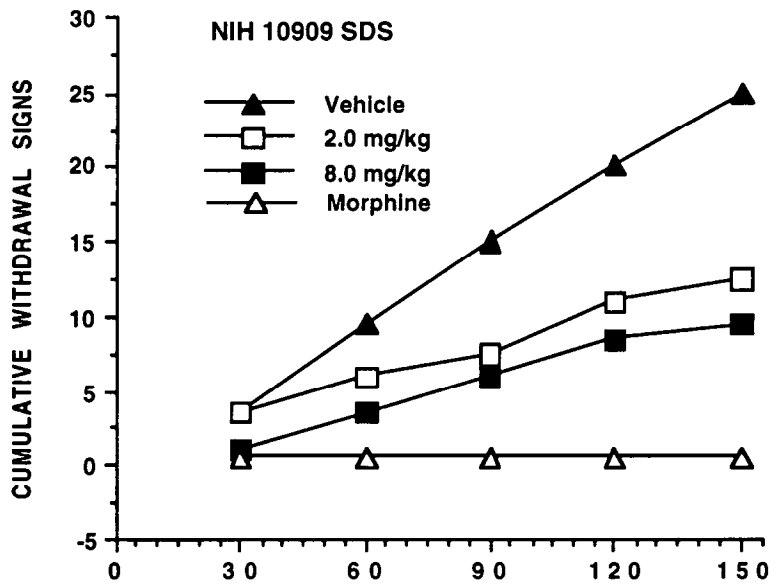
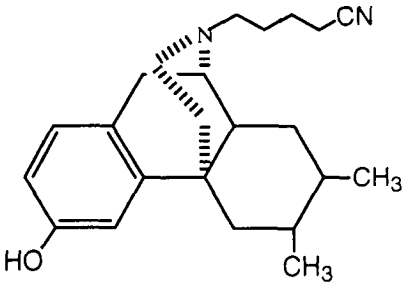


Fig. NIH 10909 Results of study in which NIH 10909 was substituted for morphine in morphine-dependent monkeys in withdrawal.

NIH 10915 (+)-(2S,5*S*,9*S*)-2-(Cyanobutyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan·HCl



MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

1) TF - Inactive at 1, 10 and 30
2) TF vs M-0% at 1,6%at 10 and 0% at 30
3) PPQ - 9% at 1, 3% at 10 and 23% at 30
4) HP - 0% at 1 and 10, 13% at 30

MONKEY DATA
(SDS)

NIH 10915 produced a non-dose related reduction of withdrawal signs. Interestingly, the withdrawal signs vocalization when palpated and abdominal muscle rigidity were attenuated.

Comment: This compound does not possess mu-like opioid-receptor activity. It may have CNS muscle relaxant and/or analgesic properties.

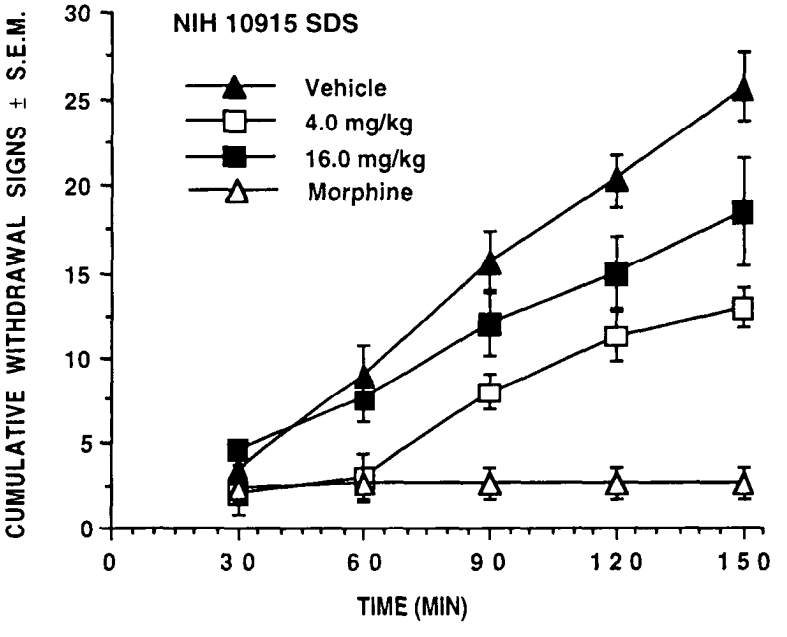
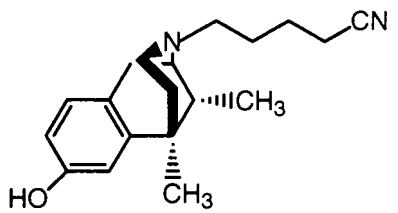


Fig. NIH 10915 Results of study in which NIH 10915 was substituted for morphine in morphine-dependent monkeys in withdrawal.

NIH 10916 (-)-(2*R*,5*R*,9*R*))-(Cyanobutyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCL



MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

1) TF - 14.6 (4.6 - 58.9)
2) TF vs M - 28% at 1, 17% at 10 and 18% at 30
3) PPQ - 3.3 (1.2 - 8.9)
4) HP - (a) 13% at 1, 13% at 10 and 38% at 30
(b) 13% at 1, 25% at 10 and 38% at 30

Special Test: Naloxone AD_{50} vs ED_{80} of NIH 10916 in TF = 0.009 (0.0029 - 0.028)

MONKEY DATA
(SDS)

As shown in figure NIH 10916 SDS, this compound dose-dependently substituted for morphine at doses of 3 to 12 mg/kg. At the high dose, jaw sag and body sag were noted. Onset was prompt and offset was evident at 2 1/2 h. Potency estimate is approximately 1/2 that of morphine. Vehicle was 10% hydroxypropyl-β-cyclodextrin in water.

Comment: The low naloxone AD50 suggests that NIH 10916 has mu-opioid receptor activity. The lack of antinociceptive effects in the hot-plate test indicates that this drug may not act at the supraspinal level.

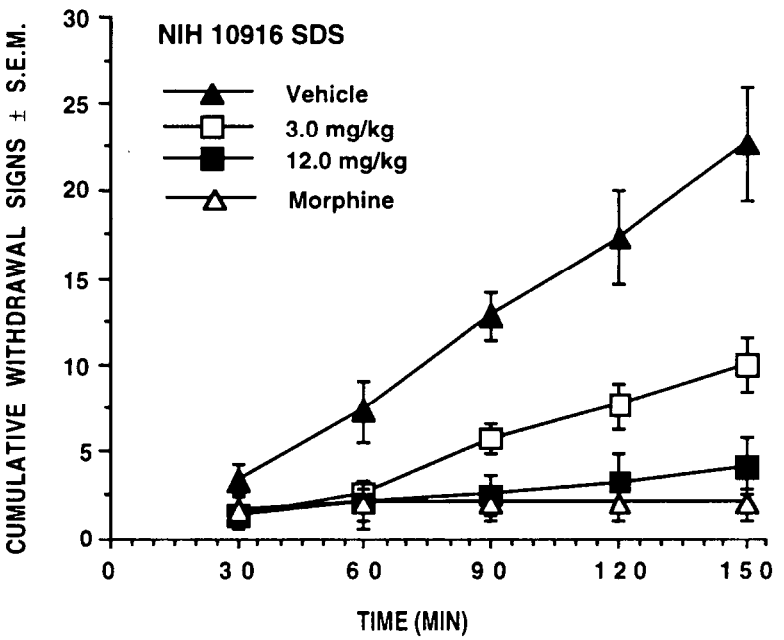
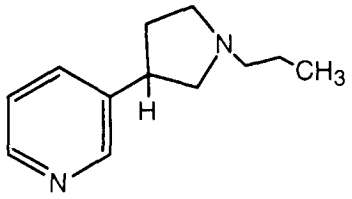


Fig. NIH 10916 Results of study in which NIH 10916 was substituted for morphine in morphine-dependent monkeys in withdrawal.

NIH 10920 (±)-N-Propyl-N-norisonicotine dioxolate



MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

1) TF - 0% at 1,8% at 10 and 55% at 30[a]
2) TF vs M - 0% at 1, 6% at 10 and 0% at 30
3) PPQ - 4.67 (2.0 - 10.93)
4) HP - 11.0 (6.23 - 19.78)

[a]At 30, two of six convulsed.

MONKEY DATA
(SDS)

As shown in the accompanying figure, the drug neither substituted for morphine nor exacerbated withdrawal at doses of 2.5 and 10 mg/kg.

Comment: This drug does not display remarkable activity in morphine-dependent monkeys. Some antinociceptive activity was observed in mice.

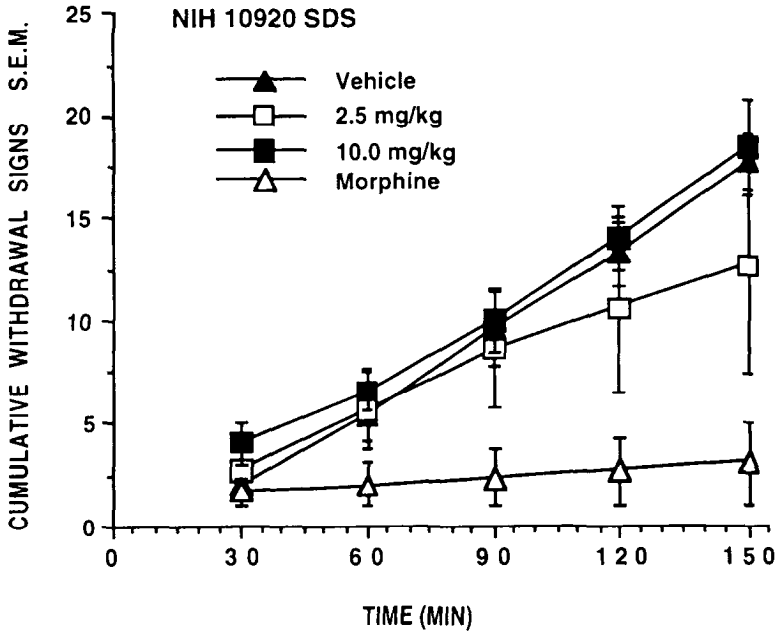
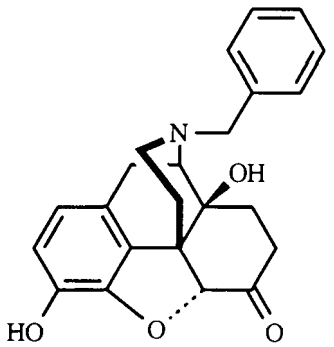


Fig. NIH 10920 Results of study in which NIH 10920 was substituted for morphine in morphine-dependent monkeys in withdrawal.

NIH 10921 17-Benzylnoroxymorphone· HCl



MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

I) TF - Inactive at 1, 10 and 30
2) TF vs M - 0.52 (0.15 - 1.80)
3) PPQ - 0% at 1, 3% at 10 and 30
4) HP - 0% at 1, 13% at 10 and 0% at 30

MONKEY DATA

(Preliminarv SDS) At a cumulative dose of 0.5 mg/kg, NIH 10921 appeared to exacerbate withdrawal.

MONKEY DATA
(PPT-W)

Because NIH 10921 antagonized morphine-induced antinociception as well as exacerbating withdrawal in the preliminary SDS test in withdrawn morphine-dependent monkeys, a precipitated withdrawal test was conducted. As shown in the accompanying figure, this compound dose-dependently precipitated withdrawal. The drug acted promptly at the high dose and duration of action was shorter than that of naloxone, the reference standard.

Comment: This drug has weak mu-opioid receptor antagonist activity.

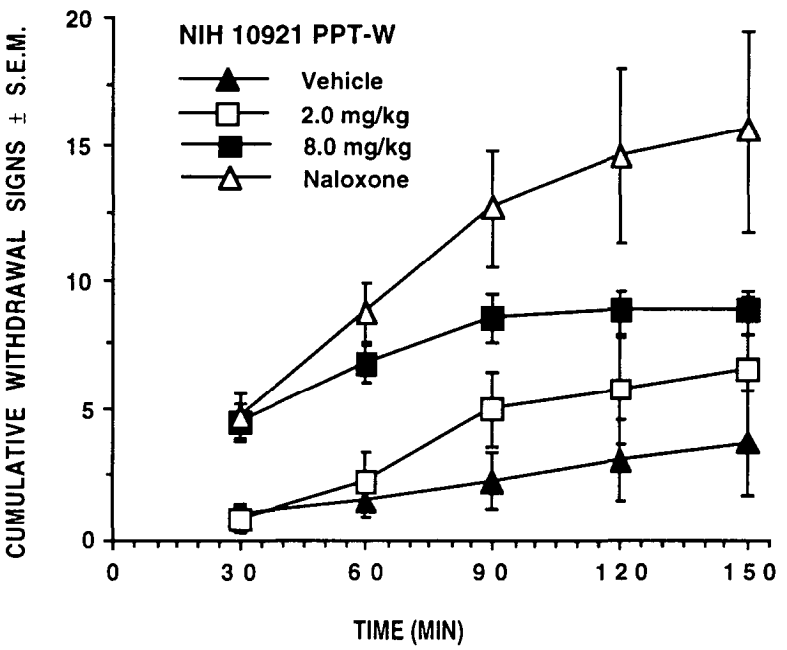
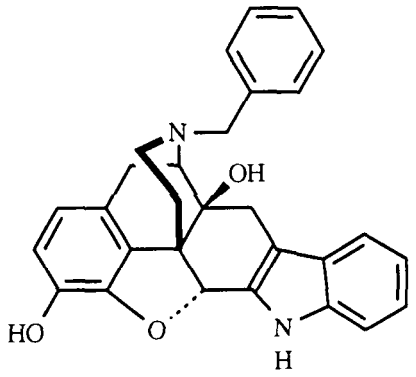


Fig. NIH 10921 Results of study in which NIH 10921 was administered to morphine-dependent monkeys (PPT-W).

NIH 10922 17-Benzylnoroxymorphindole·HCl



MOUSE DATA - ED50 OR AD50
(95% C.L.) (mg/kg or % change)

1) TF - Inactive at 1, 10 and 30[a]
2) TF vs M - Inactive at 1 and 10, 28% at 30[a]
3) PPQ- 11% at 1 and 10, 20% a 30[a]
4) HP - Inactive at 1 and 10, 13% at 30[a]

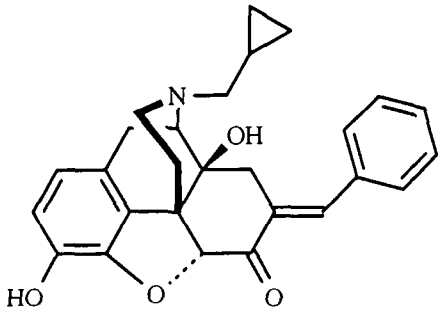
[a]10% DMSO aqueous solution.

MONKEY DATA
(SDS)

Not Tested

Comment: NIH 10922 does not demonstrate remarkable antinociceptive activity.

NIH 10923 7-Benzylidene-7-dehydronaltrexone (BNTX)·HCl



MOUSE DATA - ED50 OR AD50
(95% C.L.) (mg/kg or % change)

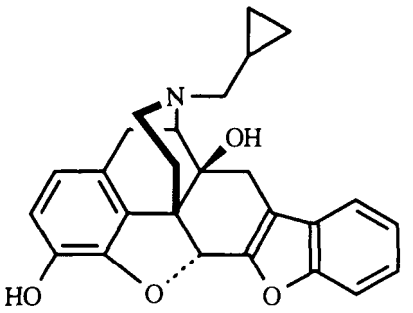
1) TF - Inactive at 1, 10 and 30
2) TF vs M - 0.05 (0.02 - 0.13)
3) PPQ - 1% at 1, 23% at 10, 37% at 30
4) HP - Inactive at 1, 10 and 30

MONKEY DATA
(SDS)

Not tested.

Comment: This compound appears to be a potent mu-opioid receptor antagonist. Potency was approximately equal to that of naloxone.

NIH 10924 Naltriben (NTB) methanesulfonate



MOUSE DATA - ED50 OR AD50
(95% C.L.) (mg/kg or % change)

1) TF - Inactive at 1, 10 and 30[a,b,c]
2) TF vs M - 0.99 (0.42 - 2.35)[a]
3) PPQ - 4.2 (3.1 - 5.7)[a]
4) HP - Inactive at 1 and 3, 25% at 30[a]

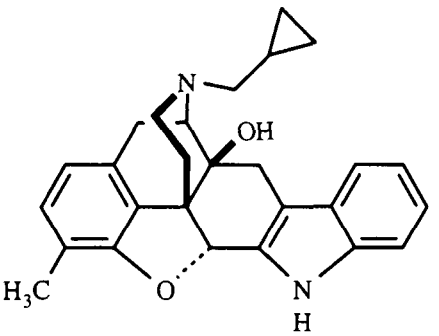
[a]10% DMSO aqueous solution.
[b]1 of 6 had convulsions and died at 10 and 6 of 6 had convulsions and died at 30.
[c]Naltrindole pretreatment did not abolish lethal effects at 30.

MONKEY DATA
(SDS)

Not Tested

Comment: NIH 10924 is a weak mu-opioid antagonist with convulsant properties. Apparently, delta opioid receptors are not involved in its action.

NIH 10925 3-Deoxy-3-methylnaltindole·HCl



MOUSE DATA - ED50 OR AD50
(95% C.L.) (mg/kg or % change)

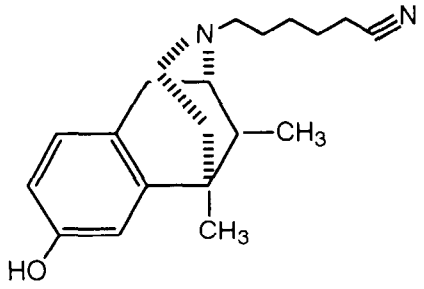
1) TF - Inactive at 1, 10 and 30
2) TF vs M- 10% at 1, 8% at 10 and 58% at 30
3) PPQ - Inactive at 1, 10 and 30
4) HP - 13% at 1 and 10, 25% at 30

MONKEY DATA
(SDS)

Not Tested.

Comment: Some weak mu-opioid antagonist properties are evident in the tail-flick test.

NIH 10926 (+)-(2*S*,5*S*,9*S*)-2-(5-Cyanopentyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan·HCl



MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

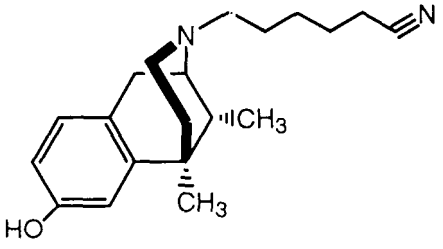
1) TF-Inactiveat 1, 10 and 30
2) TF vs M - Inactive at 1, 10 and 30
3) PPQ - Inactive at 1 and 10, 46% at 30
4) HP - Inactive at 1, 10 and 30

MONKEY DATA
(SDS)

Not tested.

Comment: This compound seems devoid of opioid properties in the mouse by the subcutaneous route of administration.

NIH 10927 (-)-2*R*,5*R*,9*R*)-2-(5-Cyanopentyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomophan·HCl



MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

1) TF - 1% at 1, 6% at 10 and 65% at 30[a]
2) TF vs. M - 9.60 (4.82 - 19.12)
3) PPQ - Inactive at 1, 10 and 30
4) HP - Inactive at 1 and 10, 25% at 30

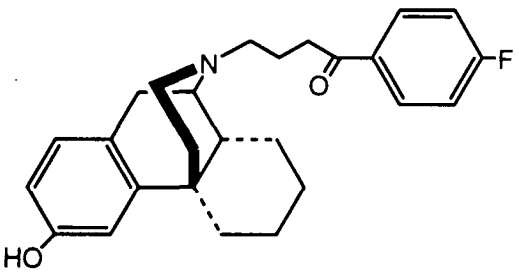
[a]Some mice had Straub tails at 30.

MONKEY DATA
(SDS)

Not tested.

Comment: The mouse data indicates weak agonist/antagonist properties.

NIH 10928 (-)-N-[3-(4-Fluorobenzoyl)proply]-3-hydroxymorphinan·HCl



MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

1) TF - 0% at 1, 4% at 10 and 43% at 30[a]
2) TF vs. M - Inactive at 1 and 10, 13% at 30[a]
3) PPQ - 4.48 (1.74 - 11.53)[a]
4) HP - 0% at 1, 13% at 10 and 63% at 30[a]

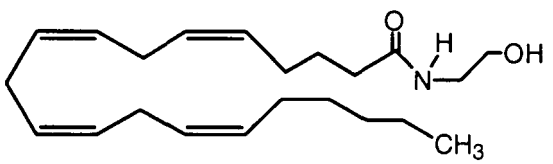
[a]Vehicle was 10% hydroxypropyl-β-cyclodextrin in water.

MONKEY DATA
(SDS)

Not tested.

Comment: This compound has weak antinociceptive properties in the mouse. The profile of activity is consistent with that of an opiate.

NIH 10929 Anandamide



MOUSE DATA - ED50 OR AD50
(95% C.L.) (mg/kg or % change)

1) TF - 23.27 (11.71 - 46.25)[a]
2) TF vs M -
3) PPQ -
4) HP -

[a](i.v. 5 min pretreatment time)

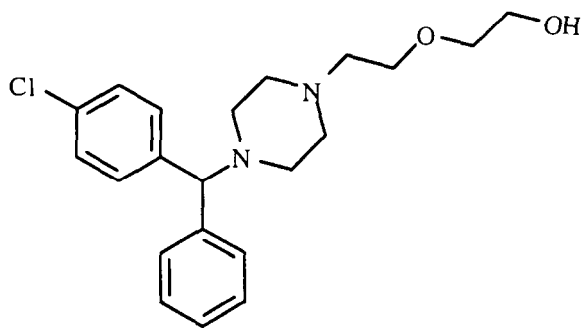
Special: SR 141716A (cannabinoid antagonist) AD_{50} vs ED_{80} of anandamide in TF = 12.8 (4.7 - 35.7)
SR 141716A 15 m pretreatment time (s.c.) and anandamide (i.v.), 5 M pretreatment.

MONKEY DATA
(SDS)

Not tested.

Comment: SR 141716A antagonized anandamide's antinociceptive effects in the TF test. The results suggest cannabinoid activity for NIH 10929.

NIH 10930 Hydroxyzine dihydrochloride



MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

1) TF - 17% at 1, 1% at 10 and 14% at 30
2) TF vs M - 0% at 1, 10 and 30
3) PQ - 8.6 (3.5 - 21.2)
4) HP- 13% at 1, 0% at 10 and 63% at 30[a]

[a]Eyelid ptosis and decreased locomotor activity.

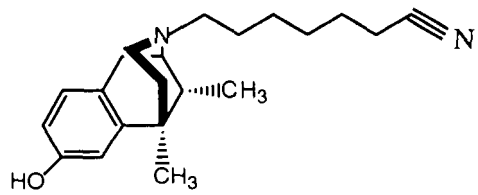
Special: Naloxone at 1 and 10 mg/kg vs ED80 of NIH 10930 in PPQ test = 7% antagonism

MONKEY DATA
(SDS)

Not Tested.

Comment: The data indicates that hydroxyzine has weak antinociceptive activity. The opioid system was not involved.

NIH 10934 (-)-(2*R*,5*R*,9*R*)-2-(6-Cyanohexy1)-5,9-dimethy1-2'-hydroxy-6,7-benzomophan·HCl



MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

1) TF - 4% at 1 and 10, 13% at 30
2) TF vs M - 0% at 1, 10 and 30
3) PPQ - 9.35 (3.26 - 26.86)
4) HP- 13% at l, 0% at 10 and

MONKEY DATA
(SDS)

NIH 10934 displayed unusual activity. At the low dose (3 mg/kg), it appeared to briefly substitute for morphine and at the high dose (12 mg/kg), it produced a robust but non significant elevation of the cumulative withdrawal score. Also at the high dose, one monkey developed eyelid ptosis.

Comment: The profile of activity of NIH 10934, in the monkey, is reminiscent of that noted with partial agonists.

NIH 10934 (Continued)

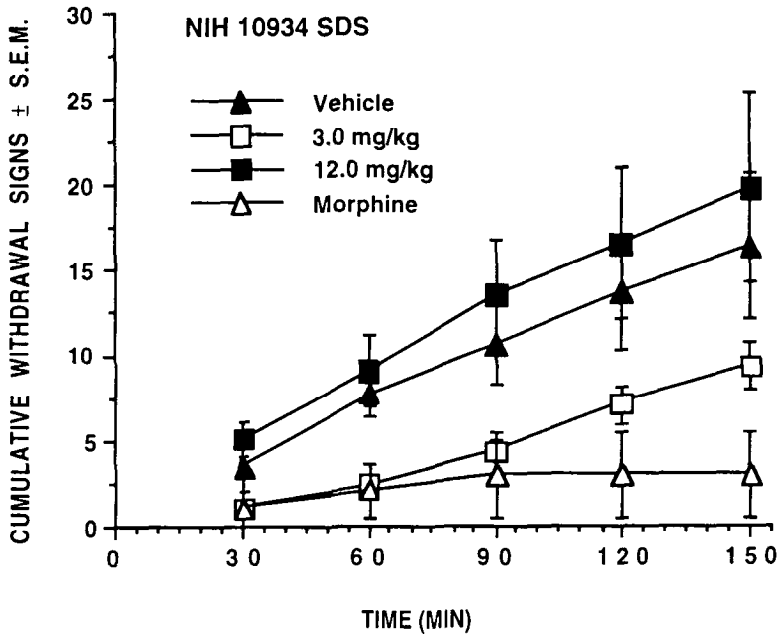
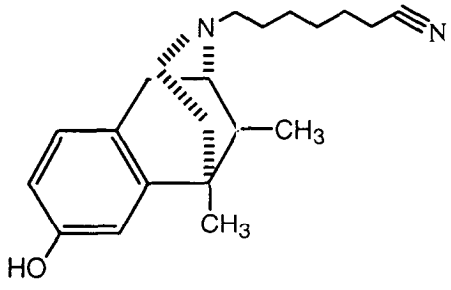


Fig. NIH 10934 Results of study in which NIH 10934 was substituted for morphine in morphine-dependent monkeys in withdrawal.

NIH 10935 (+)-(2S,5S,9S)-2-(6-Cyanohexyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan·HCl



MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

I) TF - 4% at 1, 12% at 10 and 8% at 30
2) TF vs M - Inactive at 1, 10 and 30
3) PPQ - 3% at 1, 9% at 10 and 11% at 30
4) HP - Inactive at 1, 10 and 30

MONKEY DATA
(SDS)

At doses of 3 and 15 mg/kg, this compound produced a non dose-related attenuation of withdrawal signs (see figure). One monkey receiving the high dose had diarrhea, was ataxic and appeared confused. Drug supply was exhausted.

Comment: It seems that NIH 10935 has little opioid activity. Its apparent attenuation of withdrawal signs is probably related to other CNS properties.

NIH 10935 (Continued)

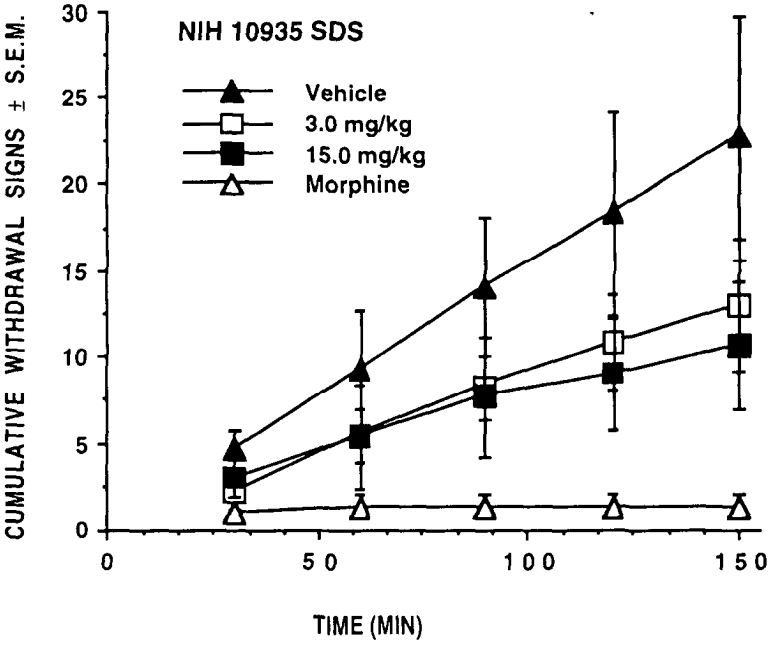
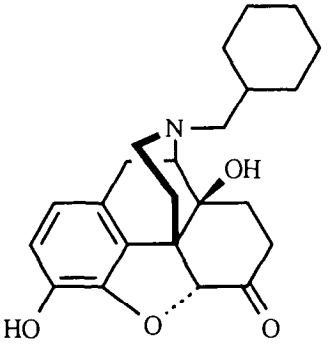


Fig. NIH 10935 Results of study in which NIH 10935 was substituted for morphine in morphine-dependent monkeys in withdrawal.

NIH 10937 17-Cyclohexylmethylnoroxymorphone·HCl



MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

1) TF - 7% at 1, 0% at 10 and
2) TF vs. M - 11.33 (4.71 - 27.23)
3) PPQ - 0% at 1 and 10, 3% at 30
4) HP - 0% at 1, 13% at 10 and 0% at 30

MONKEY DATA
(SDS)

Because drug supply was exhausted, a complete evaluation was precluded. The data illustrated in the figure is from only one experiment. The results shown in the figure suggest that NIH 10937 dose-dependently and briefly attenuated withdrawal.

NIH 10937 (Continued)

Comment: Some weak mu-opioid antagonist activity was observed in the mouse. Interestingly, attenuation of withdrawal in the monkey was observed. However, it occurred at a relatively high dose and was of short duration. These results do not portend remarkable opioid activity.

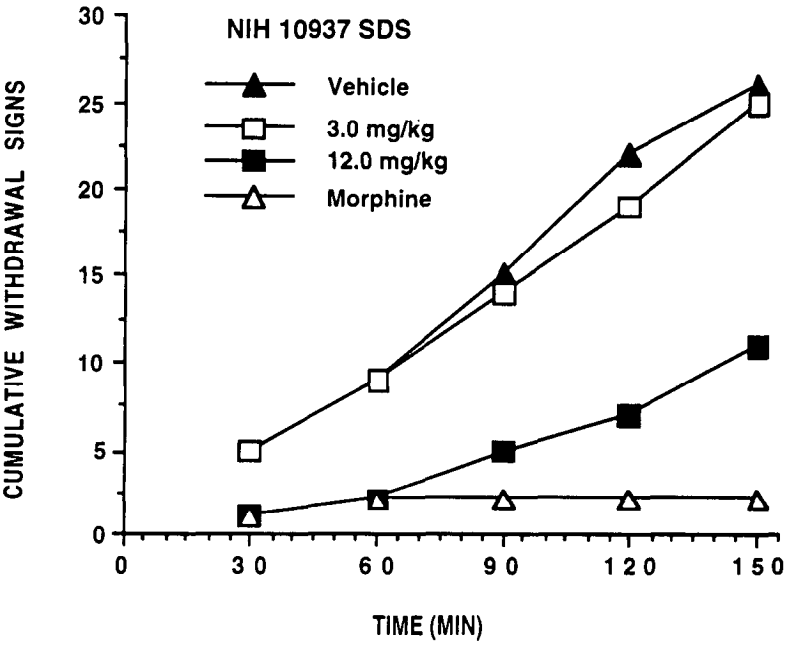
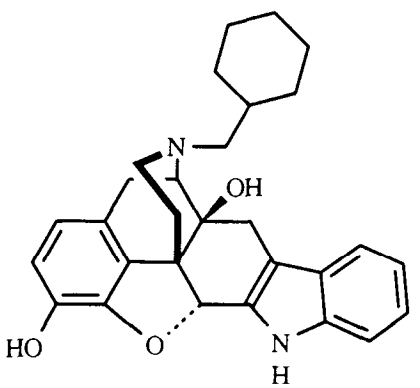


Fig. NIH 10937 Results of study in which NIH 10937 was substituted for morphine in morphine-dependent monkeys in withdrawal.

NIH 10938 N-Cyclohexylmethyl-N-nornaltrindole·HCl



MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

1) TF - Inactive at 1, 10 and 30
2) TF vs. M - 6% at 1, 13% at 10 and 5% at 30
3) PPQ - 3% at 1, 0% 10 and 30
4) HP - Inactive at 1 and 10, 13% at 30

MONKEY DATA
(SDS)

As shown in the figure, NIH 10938 dose-dependently attenuated withdrawal in morphine-dependent monkeys. However, even at the high dose, the withdrawal signs rigid abdominal muscles and vocalization when abdominal muscles were palpated were still present in 2 of the 3 monkeys. Perhaps higher doses would have completely substituted for morphine but lack of material prevented further studies.

NIH 10938 (Continued)

Comment: Lack of activity in the mouse and some attenuation of withdrawal signs in the monkey suggests that attenuation of withdrawal may be due to non mu-opioid related activity.

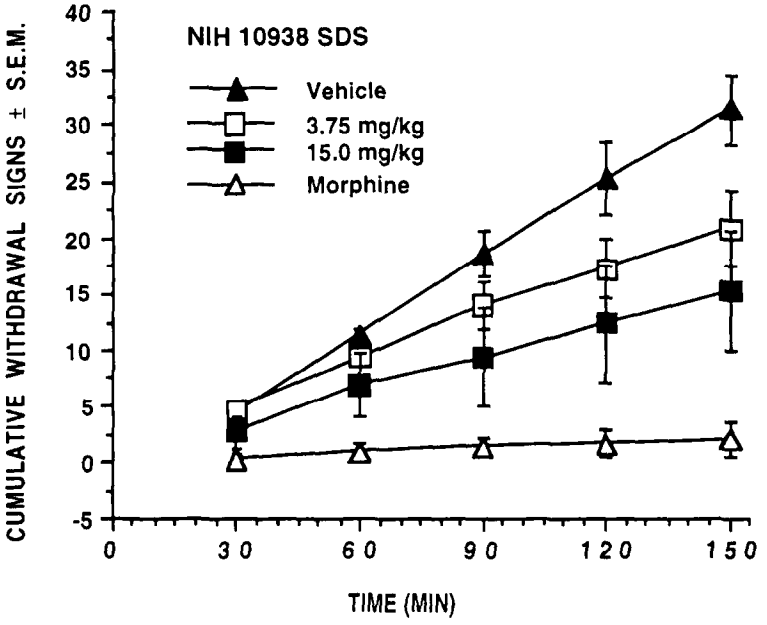
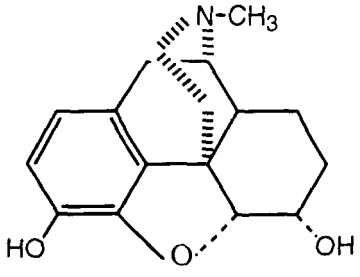


Fig. NIH 10938 Results of study in which NIH 10938 was substituted for morphine in morphine-dependent monkeys in withdrawal.

NIH 10939 (+)-Dihydromorphine·HCl



MOUSE DATA - ED50 OR AD50
(95% C. L.) (mg/kg or % change)

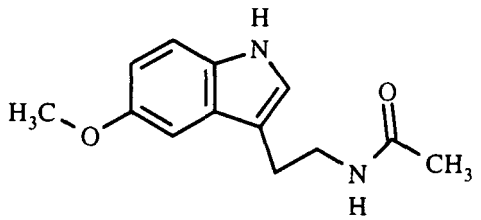
1) TF - Inactive at 1 and 10
2) TF vs M -
   1) AD50 = 0.47 (0.28 - 0.8)
   2) 22% antagonism at 10
   3) 0 % antagonism at 1
   4) 12% antagonism at 10
   5) 0% antagonism at 1
   6) 32% at 0.05, 60% at 0.1, 45% at 0.3 and 0% at 1
3) PPQ - Inactive at 1 and 10
4) HP - Inactive at 1, 10 and 30

MONKEY DATA
(SDS)

Not tested.

Comment: The results with NIH 10934 were very erratic. Apparently, this compound is devoid of agonist or antagonist properties.

NIH 10946 Melatonin



MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

1) TF - Inactive at 1, 10 and 30[a]
2) TF vs M - Inactive at 1, 10 and 30[a]
3) PPQ - Inactive at 1, 10 and 30[a]
4) HP - Inactive at 1, 10 and 30[a]

[a]Vehicle was 10% hydroxypropyl-β-cyclodextrin in water.

MONKEY DATA

(SDS)

As shown in the accompanying figure, at 0.75 and 3.0 mg/kg, melatonin did not suppress withdrawal signs in abruptly withdrawn morphine-dependent monkeys. Interestingly, at the high dose, it may have relaxed rigid abdominal muscles and reduced vocalization when the abdomen was palpated. Vehicle was 10% hydroxypropyl-β-cyclodextrin in sterile water.

Comment: Melatonin is used regularly by many for its hypnotic , antioxidant and anti-aging properties. Based on the results above, it does not seem likely that melatonin has significant antinociceptive or mu-opioid properties.

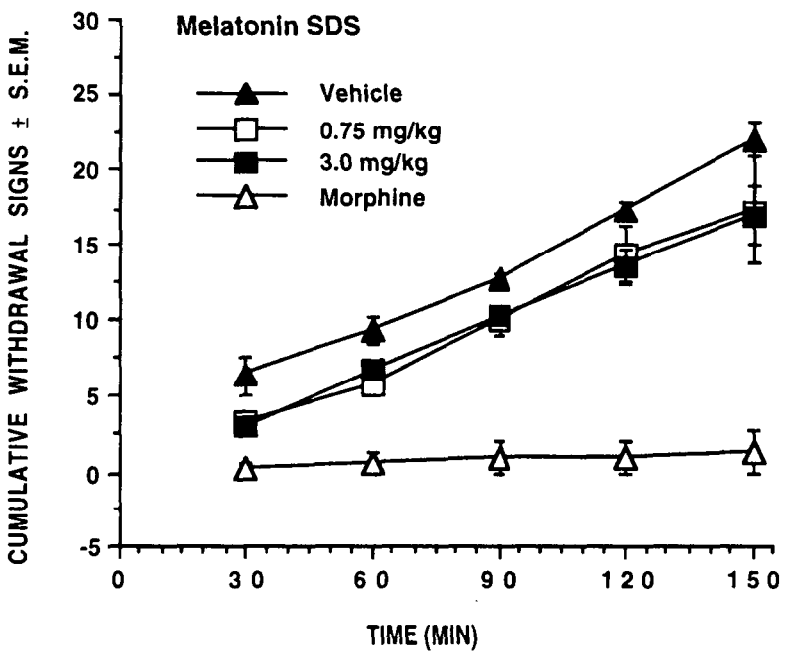
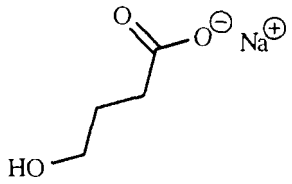


Fig. NIH 10946 Results of study in which NIH 10946 (Melatonin) was substituted for morphine in morphine-dependent monkeys in withdrawal.

NIH 10947 γ-Hydroxybutyric Acid, sodium salt (GHB)



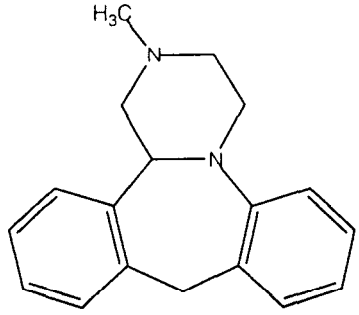
MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)
1) TF - 1) i.v. - Inactive at 60 and 52% at 120[a]
2) s.c. - Inactive at 1, 10, 30 and 60
3a) p.o. - Inactive at 60 and 120[b]
3b) p.o. - Inactive at 60 and 51 % at 120[a]
2) TF vs. M - Not tested
3) PPQ - (i.v.) 30.88 (15.34 - 62.17)
4) HP - Not Tested
[a]20 min pretreatment
[b]1 hr pretreatment

MONKEY DATA
(SDS)

Not tested.

Comment: γ--Hydroxybutyrate (GHB), a precursor and metabolite of γ· -aminobutyric acid, which has been used in Europe as a general anesthetic and hypnotic, as an aid in childbirth, in the treatment of alcoholism and in anxiety attendant with detoxification from cocaine and amphetamines, depression and other conditions, has also gained popularity as a fashionable recreational drug. Because little is known about its interaction with opioids, this study was initiated. GHB, per se, (at 30, 60, 80, and 100 mg/kg s.c.) had little effect on the normal reaction time in the tail-flick test. When these doses of GHB were co-administered with the ED25 of morphine sulfate (MS), dose-related synergism was observed. In mice made completely tolerant to MS antinociceptively (25 mg/kg s.c., 4 times a day for 4 days), GHB (60 mg/kg s.c.) in combination with M partially restored antinociception. Naloxone (1 mg/kg s.c.) nearly abolished this effect. These results suggest possible therapeutic applications and potential safety issues for GHB in abusers.

NIH 10948 Mianserin·HCl



MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

1) TF - Inactive at 1, 10 and 30
2) TF vs. M - Inactive at 1, 10 and 30
3) PPQ - 0.09 (0.04 - 0.23)
4) HP - 25% at 1, 50% at 10 and 63% at 30

Special: Naloxone AD50 vs ED80 of NIH 10948 in PPQ = 1.07 (0.45 - 2.54)

MONKEY DATA
(SDS)

Not tested.

Comment: Mianserin, a serotonin antagonist, has potent antinociceptive activity in the PPQ test which is antagonized by a large dose of naloxone. It also has some modest activity in the hot plate assay. The results suggest indirect opioid system involvement.

REFERENCES

Aceto, M.D., Flora, R.E. and Harris, L.S. The effects of naloxone and nalorphine during the development of morphine dependence in rhesus monkeys. Pharmacol, 15:1-9 1977.

Aceto, M.D., Flora, R.E. and Harris, L.S. Caffeine elicited withdrawal signs in morphine-dependent rhesus monkeys. Eur J Pharmacol, 50:203-207, 1978.

Aceto, M.D., McKean, D.B. and Pearl, J. Effects of opiates and opiate antagonists on the Straub tail reaction in mice. Br J Pharmacol, 36:225-239, 1969.

Atwell, L. and Jacobson, A.E. The search for less harmful analgesics. Lab Animal, 7:42-47, 1978.

D'Amour, F.E. and Smith, D.L. A method for determinating loss of pain sensation. J Pharmacol Exp Ther, 72:74-79, 1941.

Deneau, G.A. An analysis of factors influencing the development of physical dependence to narcotic analgesics in the rhesus monkey with methods for predicting physical dependence liability in man. Doctoral Dissertation, University of Michigan, 1956.

Dewey, W.L., Harris, L.S., Howes, J.F. and Nuite, J.A. The effects of various neurohumoral modulators on the activity of morphine and the narcotic antagonists in the tail-flick and phenylquinone tests. J Pharmacol Exp Ther, 175:435-552, 1970.

Dewey, W.L. and Harris, L.S. Antinociceptive activity of the narcotic antagonists analogues and antagonistic activity of narcotic analgesics in rodents. J Pharmacol Exp Ther, 179:652-659, 1971.

Eddy, N. B. and Leimbach, D. Synthetic analgesics. II. Dithienylbutenyl- and dithienylbutylamines. J Pharmacol Exp Ther, 107:385-393, 1953.

Jacobson, A.E. and May, E.L. Structures related to morphine. XXXI. 2'-Substituted benzomorphans. J Med Chem, 8:563-566, 1965.

Pearl, J. and Harris, L.S. Inhibition of writhing by narcotic antagonists. J Pharmacol Exp Ther, 154, 319, 1966.

Schild, M.O. pA2, A new scale for the measurement of drug antagonism. Br J Pharmacol, 2:189-206, 1947.

Seevers, M.H. Opiate addiction in the monkey. I. Methods of study. J Pharmacol Exp Ther, 56:147-156, 1936.

Seevers, M.H. and Deneau, G.A. Physiological aspects of tolerance and physical dependence. In: Root, W.S. and Hofman, F.G., eds. Physiological Pharmacology, Vol. I. New York: Academic Press, 1963. pp. 565-570.

Tallarida, R.J. and Murray, R.B. Manual of pharmacological calculations with computer programs. Second Edition: New York: Springer-Verlag, 1987. pp. 53-56.

Teiger, D.G. Induction of physical dependence on morphine, codeine, and meperidine in the rat by continuous infusion. J Pharmacol Exp Ther, 190:408-415, 1974.

ACKNOWLEDGMENTS: Supported NIDA contract DA 5-8059.

EVALUATION OF NEW COMPOUNDS FOR OPIOID ACTIVITY (1998)

J. H. Woods, G. Winger, J. R. Traynor, F. Medzihradsky, and C. B. Smith

Departments of Pharmacology and Biological Chemistry, University of Michigan, Ann Arbor, MI

This report contains information on opioid abuse liability evaluations on compounds that have been submitted to the Drug Evaluation Committee of the College and released for publication by the submitters. The information obtained can involve both *in vitro* evaluation in opioid binding assays and smooth muscle preparations. In addition, the compounds may be evaluated for discriminative and reinforcing effects. Analgesic and respiratory function assays are also possible. These behavioral assessments are conducted in rhesus monkeys. Each of these assays is described below. Usually when limited information is provided *(e.g., in vitro* assessment only), it is because the sample provided by the submitter was insufficient to carry out further evaluation.

The evaluation of new compounds by the programs at the University of Michigan and the Medical College of Virginia is coordinated by Dr. Arthur E. Jacobson, Laboratory of Medicinal Chemistry, NIDDK, National Institutes of Health, Bethesda, MD. The compounds, which come originally from pharmaceutical companies, universities, government laboratories, and international organizations are submitted to Dr. Jacobson.

At the UM and MCV laboratories, drug samples arrive from Dr. Jacobson with only the following information: (1) an identifying NIH number, (2) molecular weight, (3) solubility information and (4) a recommended starting dose. After the evaluation is complete and the report submitted to Dr. Jacobson, the submitter is requested to release the chemical structure to include with the evaluation data in the ANNUAL REPORT. The submitter has up to three years before release of the structure is required. When the structure is released all of the data on the compound are reported herein

DRUG DISCRIMINATION IN RHESUS MONKEYS

We currently use three groups of monkeys to test the discriminative stimulus effects of submitted drugs: one of these groups discriminates the administration of the κ agonist ethylketazocine (EKC); a second group discriminates the μ agonist alfentanil or fentanyl; a third group is treated daily with morphine and discriminates the opioid antagonist naltrexone.

The procedures used with the EKC-trained monkeys have been described by Bertalmio *et al.* (1982). The monkeys are removed from their home cages each day and seated in primate restraining chairs. These chairs are placed in chambers equipped with two response levers, several stimulus lights and a cup to receive Noyes, banana-flavored pellets. These monkeys are required to make 100 consecutive responses on the correct one of the two levers and receive ten 300-mg food pellets. The right lever is correct if they were given a subcutaneous injection of 0.0032 mg/kg EKC immediately prior to the start of the cycle. The left lever is designated correct if they were given a sham injection before the start of the cycle. Each cycle lasts 15-min and consists of an initial 10-min black out period followed by a period of as long as 5 min, during which a blue light is illuminated in the chamber and the monkey can respond for food. If the food pellets are delivered before the 5 min period is completed, the lights are extinguished for the remainder of this time. Typically, a daily session consists of several 15 min cycles. During a training session, if EKC is given, it is given on the penultimate cycle of that session. Responding on the drug-appropriate lever is reinforced during that cycle and on the subsequent, final cycle of the day. These last two cycles may be preceded by from zero to four sham cycles on a training day. A training session of six sham cycles is also scheduled from time to time.

With this type of multiple, discrete-cycle training, the animals can be tested with a cumulative dosing procedure. On a test session, the first cycle is preceded by an injection of saline, and prior to subsequent cycles, increasing, cumulative doses of the test drug are administered. One hundred consecutive responses on either lever are reinforced throughout the test session, The test drug is administered in increasing doses until the monkey either responds on the drug-appropriate lever, the response rate falls to less than half of the saline-control rate, or six cycles are given. In the latter situation, it is assumed that the selected dose range is too low, and the test is continued at higher doses on the next test session. Each test session is preceded and followed by a training session. The criterion for satisfactory performance must be met on each training session that is followed by a test session. This criterion is that at least 90% of the responses during each cycle of a training session must be on the injection-appropriate lever, either sham or EKC.

The procedure for the alfentanil-trained monkeys is similar, but not identical. These animals are also trained and tested in a discrete, multiple-cycle procedure. The main difference between the alfentanil procedure and the EKC procedure is that the alfentanil monkeys are required to make 20 rather than 100 responses, and they receive a single pellet for correct responses. They can receive as many as 10 pellets during the 5-min, food-availability period of each cycle, but each pellet is delivered after 20 responses. Because in this procedure, monkeys can switch from one lever to another following the delivery of food, an additional criterion is added for satisfactory performance. In addition to making 90% or more of their responses on the correct lever, the monkeys must make fewer than 20 responses on the incorrect lever prior to delivery of the first food pellet of each cycle. Tests of the discriminative stimulus effects of submitted drugs in the alfentanil-trained monkeys are also done using a cumulative dosing procedure with dosing criteria identical to those used in the EKC-trained monkeys.

The procedure for studying discriminative stimulus effects in morphine-treated monkeys has been described previously (France and Woods, 1989). Daily sessions are comprised of a 10-min time out during which lever presses have no programmed consequence and a 5-min response period during which green stimulus lights are illuminated and signal the activation of a schedule of stimulus-shock termination. Sessions consist of between two and six discrete, 15-min cycles with each cycle. Under these experimental conditions electric shock is scheduled to be delivered to the subject's feet every 15 seconds; monkeys can terminate the lights and postpone scheduled shocks for 30 seconds by pressing five times consecutively *(i.e.,* fixed-ratio 5) the lever appropriate for the solution administered during the first minute of the time out (left lever, saline; right lever, naltrexone). Monkeys receive an injection of saline (0.1 ml/kg) or drug (0.01 mg/kg naltrexone) during the first minute of each time out. On drug training days a single injection of naltrexone is administered during one time out and for that cycle and all subsequent cycles on that day only responding on the right lever postpones shocks. A variable number of saline cycles (0-5) precede the naltrexone cycle and on some days saline is administered during the time out of all cycles. Under these conditions monkeys switch their response choice from the saline lever to the naltrexone lever with complete generalization occurring in all three subjects at a dose of 0.01 mg/kg. Responding on the naltrexone lever is accompanied by other behavioral effects indicative of opioid withdrawal (e.g., irritability, miosis, salivation). Moreover, when saline is substituted for the daily injection of 3.2 mg/kg of morphine monkeys respond predominantly on the naltrexone lever and show directly observable signs of withdrawal; the discriminative stimulus and other effects produced by morphine abstinence are reversed by some opioid agonists (e.g., alfentanil; France and Woods, 1989; France *et al.,* 1990).

For test sessions increasing doses of drug are administered during the first minute of consecutive time outs and five consecutive responses on either lever postpone shocks. In monkeys that receive 3.2 mg/kg of morphine 3 hours earlier, increasing doses of a test compound are administered up to doses that produce an average of at least 80% responding on the naltrexone lever or to doses that disrupt responding and result in the delivery of electric shock. Drugs that do not substitute for naltrexone *(i.e.,* precipitate withdrawal) are also studied for their ability to reverse responding on the naltrexone lever in morphine-abstinent *(i.e.,* withdrawn) subjects. Test compounds are studied using a cumulative-dosing procedure in morphine-abstinent monkeys up to doses that reverse completely responding on the naltrexone lever (<20%) or to doses that disrupt responding. Some compounds that substitute for naltrexone also are studied for their capacity to prevent the effects of cumulative doses of opioid agonists. Monkeys that receive saline three hours earlier, rather than the daily injection of morphine, receive saline (control) or a single injection of test compound during the first cycle and increasing doses of agonist (alfentanil or morphine) during subsequent cycles. Agonists are administered up to doses that produce a switch from the naltrexone lever to the saline lever or to doses that disrupt responding and result in the delivery of electric shock.

THERMAL ANALGESIA IN RHESUS MONKEYS

The tail withdrawal procedure used to study analgesic effects of test compounds in rhesus monkeys has been described previously (Dykstra and Woods, 1986). Monkeys are restrained loosely at the neck and arms while seated in Plexiglas primate chairs. For tests of tail withdrawal latency, the lower 10-12 cm of the shaved tail is immersed in a thermos containing water at 40°, 50°, or 55°C and the latency until the tail is withdrawn from the thermos is recorded for each monkey at each temperature. When the tail is not withdrawn within 20 seconds (cut-off latency) the experimenter removes the thermos and a latency of 20 seconds is recorded. Experimental sessions begin with several exposures to 40°C water. Four or five monkeys are tested consecutively and the time between tail immersions for individual monkeys is 5 minutes. Generally, 40°C water does not produce tail withdrawal in rhesus monkeys (Dykstra and Woods, 1986); however, if a monkey fails to keep its tail in 40°C water for 20 seconds on at least 3 of 4 immersions, that animal is not tested further for that particular session. In a subsequent pre-test component, tails are immersed in 40°, 50°, and 55° C water. The order in which the three temperatures are presented is varied among subjects. If the Iatencies for tail withdrawal in the pre-test component are at or near 20 seconds for 40°C water and less than 5 seconds for 55°C water, monkeys receive the test compound. The test is identical to the

pre-test, except that monkeys receive s.c. injections of drug 10 minutes prior to tail immersion. The time between immersions for individual subjects is 5 minutes or less and the order in which temperatures are presented varies among subjects and across cycles. The interinjection interval typically is 30 minutes and between four and six doses are studied in a single experiment using the cumulative dosing procedure. For some studies a single dose of an opioid antagonist is administered prior to the test compound and for other studies a single dose of test compound is administered prior to increasing doses of a μ (e.g., alfentanil) or κ (e.g., U-50,488) opioid agonist.

RESPIRATORY STUDIES IN RHESUS MONKEYS

The effects of test compounds on ventilatory function are studied in rhesus monkeys breathing air or 5% CO_2 in air (France and Woods, 1990; Howell *et al.,* 1988). Monkeys are restrained at the neck and waist while seated in a Plexiglas primate chair. Normal air or 5% CO_2 in air is delivered at a rate of 10 1/min into a sealed helmet placed over the subject's head. Changes in pressure within the helmet are measured and recorded by a transducer and a microprocessor, and are transformed according to known standards to frequency of respiration (f) in breaths/minute and to tidal volume (V_T) in ml/inspiration. Data are recorded continuously during 23-minute exposures to air alternating with 7-minute exposures to CO_2. The last 3 minutes of exposure to CO_2 are used for data analyses and are compared to the last 3 minutes of exposure to air only. Increasing doses of drug are administered during the first minute of consecutive time outs so that the interinjection interval is 30 minutes. For some studies a single injection of an opioid antagonist is administered prior to increasing doses of a test compound and for other studies a single injection of test compound is administered prior to cumulative doses of a standard compound (e.g., alfentanil).

SELF-ADMINISTRATION BY MONKEYS

Tests of self-administration determine the ability of the drug to maintain responding in monkeys trained to self-inject codeine. Each of at least three monkeys is studied with saline as a negative control and a number of doses of the test compound until a maximum rate of responding was obtained or until, in the absence of evidence of a reinforcing effect, observable changes in behavior are produced by the compound.

The schedule of intravenous drug delivery is a fixed-ratio 30; when a light above a lever is illuminated, the 30th response produce an intravenous drug injection accompanied by another light that is illuminated during drug delivery. After each injection, a 45 sec timeout period occurs. A component of the session ends after 20 injections have been received or 25 min have passed, whichever occurs first. Different doses of the drug are available during each of four components of a session. Other procedural details are given in Winger *et al.* (1989).

DISPLACEMENT OF RADIOLABELED LIGAND BINDING

Details of the binding assay based on the displacement of ^{3}H-ligands in monkey cortex membranes have been described previously (Emmerson *et al.,* 1984). Briefly, aliquots of a membrane preparation from monkey cortex are incubated with ^{3}H-DAMGO (μ),m ^{3}H-DPDPE (δ))or ^{3}H-U69593 (κ`) in the presence of different concentrations of the drug under investigation at 25 C for 1 hr. Specific, *i.e.,* opioid-receptor-related binding is determined as the difference in binding obtained in the absence and presence of 10μM naloxone. The potency of the drugs in displacing the specific binding of ^{3}H-ligand is determined from data using Graphpad Prism (GraphPAD, San Diego, CA) and converted to Ki values by the method of Cheng and Prussoff, 1973).

The selection of **monkey brain** as the tissue for the selective binding assays strengthens the correlation between this in vitro assessment and the behavioral evaluation of the tested compounds. In the **ANNUAL REPORT,** the results of the selective binding assays are listed under "Binding in monkey brain cortex" and is given as means ± SEM from three separate experiments, ceach performed in duplicate. Ki Values for standrad compounds are: μ (DAMGO, 0.79nM; morphine 1.06 nM), δ (BW373U86, 0.32 nM) and κ (U69593, 0.87 nM).

ISOLATED, ELECTRICALLY-STIMULATED MOUSE VAS DEFERENS PREPARATION

The development of new, highly selective antagonists such as the reversible κ receptor antagonist norbinaltorphimine (Smith *et al.,* 1989) and the competitive δ receptor antagonist ICI-174864 have made possible the evaluation of selectivity of opioid agonists and antagonists by use of the mouse vas deferens preparation. Male, albino ICR mice, weighing between 25 and 30 g, are used. The mice are decapitated, the vasa deferentia removed, and 1.5 cm segments are suspended in organ baths which contain 30 ml of a modified Kreb's physiological buffer. The buffer contains the following (mM): NaCl, 118; KCl, 4.75; $CaCl_2$, 2.54; $MgSO_4$, 1.19; KH_2PO_4, 1.19; glucose, 11; $NaHCO_3$, 25; pargyline HCl, 0.3; and disodium edetate, 0.03. The buffer is saturated with 95% O_2 -

5% CO_2 and kept at 37°C. The segments are attached to strain gauge transducers and suspended between two platinum electrodes. After a 30-min equilibration period, the segments are stimulated once every 10 sec with pairs of pulses of 2 msec duration, 1 msec apart and at supramaximal voltage. See table I for potencies of representative agonists.

The following antagonists are studied: naltrexone HCl, ICI- 174864 [N,N-diallyl-Tyr-Aib-Aib-Phe-Leu-OH] and norbinaltorphimine. The antagonists are added to the organ baths 15 minutes before the determination of cumulative concentration-effect relationships for the various agonists. See table III for the potencies of different competitive antagonists studied in relation to prototypic agonists. EC_{50}'s are calculated by probit analysis, and pA_2 values are determined to assess relative potencies of antagonists.

All drugs which are submitted for evaluation are studied in the following manner: 1) the submitted drug is tested on the vas deferens preparation in the absence and in the presence of a concentration of naltrexone sufficient to block μ, κ and δ receptors. 2) If the submitted drug inhibits the twitch and its actions are blocked by naltrexone, it is evaluated further in the absence and presence of ICI-174864 and norbinaltorphimine used in concentrations at which these antagonists are selective for δ and κ receptors, respectively. 3) If the submitted drug is a partial agonist or devoid of agonistic activity at opioid receptors, it is evaluated further as an antagonist against the following agonists: sufentanil (μ selective), DSLET (δ selective) and U50,488 (κ selective). If the submitted drug has antagonistic activity against any or all of the receptor-selective agonists or upon any of the other preparations used in the Drug Evaluation Unit, the type of antagonism (competitive, noncompetitive, irreversible) is determined. For further details of the procedure and for a description of experiments in which β-funaltrexamine was used see Smith (1986). Drugs studied in the preparation prior to 1987 were evaluated with the protocol reported in the 1985 Annual Report.

TABLE I

Potencies of antagonists assessed in the mouse vas deferens

	pA_2 values* determined with three agonists		
Antagonist	Sufentanil (μ)	U50,488 (κ)	DSLET
Naltrexone	8.76	7.74	7.41
Naloxone	7.99	6.90	7.35
Cyprodime	7.41	6.15	5.98
Nalbuphine	7.23	6.31	5.76
Naltrindole	7.71	7.38	9.44
ICI-174,864	<5.00	<5.00	7.90

*The pA_2 value is the negative logarithm of the molar concentration of antagonist necessary to shift the agonist concentration-effect curve to the right by a factor of 2-fold.

SUMMARY OF TESTS PERFORMED

The compounds which were evaluated at the University of Michigan during the past year, and the individual tests which were performed are shown in table II. Also shown are dates of Reports to the Biological Coordinator, Dr. A.E. Jacobson, in which results are reported.

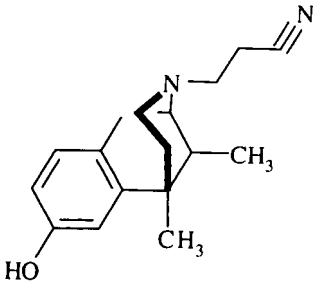
TABLE II
SUMMARY OF TESTS PERFORMED

NIH #	SA	MVD	BIND	DD	ANLG	RSP	REPORT*
10861		X	X				23 Aug 1995
10888		X	X				02 July 1996
10889			X				10 March 1998
10900			X				18 June 1997
10901			X				07 July 1997
10902			X				07 July 1997
10903			X				18 June 1997
10909			X				2 January 1998
10915			X				16 May 1997
10916			X				16 May 1997
10920			X				2 January 1998
10921			X				24 November 1997
10922			X				24 November 1997
10923			X				24 November 1997
10924			X				24 November 1997
10925			X				24 November 1997
10926			X				12 December 1997
10927			X				12 December 1997
10934			X				12 December 1997
10935			X				12 December 1997
10937			X				2 January 1998
10938			X				2 January 1998
10941			X				19 January 1998

* Date report was submitted to CPDD Biological Coordinator.

NIH 10861

(-)-2R,5R,9R-2-(2-Cyanoethyl)5,9 α -dimethyl-2'-hydroxy-6,7-benzomorphan.HCl



MONKEY CORTEX BINDING (nM)

μ-receptor:	3.50
δ--receptor:	9.18
κ–receptor:	0.26

MOUSE *VAS DEFERENS* PREPARATION

Condition	EC_{50} (nM)	Maximum Response (%)	Shift (x-fold)	n
Control	39.7 ± 4.9	100		9
Naltrexone (100 nM)	974.2 ± 243.8	100	24.5	3
ICI-174864 (100 nM)	35.2 ± 4.3	100	0.9	3
Nor-BNI (10 nM)	78.8 ± 14.1	100	2.0	3

SOL: 3 mM in H_2O

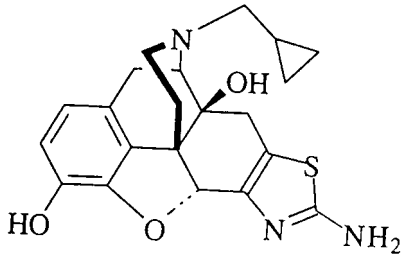
SUMMARY

NIH 10861, in concentrations of 3 nM to 300 nM, decreased the magnitude of the twitch of the electrically stimulated mouse *vas deferens* preparation. Naltrexone (a μ opioid receptor antagonist) and nor-BNI (a opioid receptor antagonist) shifted the NIH 10861 concentration-effect curve to the right. ICI-174864 (a δ opioid receptor antagonist) did not shift the NIH 10861 concentration-effect curve significantly. None of the antagonists decreased maximum responses to NIH 10861. Thus, in the mouse *vas deferens* preparation, NIH 10861 may have exerted agonist actions through the κ -or μ-opioid receptor. In the monkey cortex assay, NIH 10861 had highest affinity for the κ followed by μ sites, although it also had quite high affinity for δ receptors, as well. The compound could have mixed agonist properties *in vivo.*

* * *

NIH 10888

2'-Amino-17-cyclopropylmethyl-6,7-didehydro-3,14-dihydroxy-4,5 α-epoxy-6,7:4',5'-thiozolomorphinan.2HCl



MONKEY CORTEX BINDING (nM)

μ-receptor:	0.163
δ-receptor:	0.667
κ -receptor:	0.609

NIH 10888 (continued)

MOUSE *VAS DEFERENS* PREPARATION

Agonist	pA_2	Slope ± S.E.	pA_2 (constrained) ± S.E.	n
Sufentanil (μ)	9.03	1.02	9.07 ± 0.25	6
DSLET (δ)	8.37	1.28	8.71 ± 0.60	4
U50,488 (δ)	8.30	1.08	8.37 ± 0.37	3

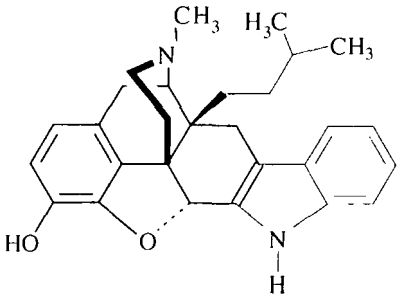
Solubility: 3 mM in H_2O

SUMMARY

NIH 10888, in concentrations of 100 nM to 30 μM, did not suppress the twitch of the isolated, electrically stimulated mouse vas deferens preparation. NIH 10888 was a very potent antagonist at mu, delta and kappa opioid receptors, with greatest affinity for mu receptors. NIH 10888 was devoid of agonist activity on this preparation. In the binding assay, NIH 10888 had significant, high affinity for each of the binding sites.

* * *

NIH 10889



3-Hydroxy-6,7-didehydro-4,5 α-epoxy-l7-methyl-l4 β-(3-methyl)butyl-6,7,2',3'-indolomorphinan.HCl (14β-(3-methyl)butylmorphindole)

MONKEY CORTEX BINDING (nM)

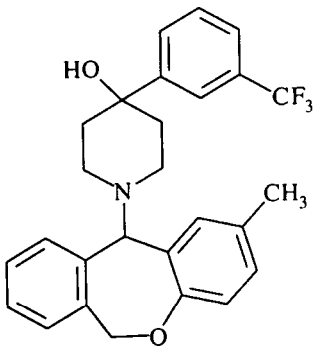
μ-receptor:	186
δ-receptor:	1.4
κ -receptor:	204

SUMMARY

NIH 10889 was a selective ligand at the delta receptor recognition site. We are currently examining its efficacy in the delta receptor clone.

NIH 10900

11-[4-Hydroxy-4-(3-trifluoromethylphenyl)piperidine-1-yl]-2-methyl-6,11-dihydrodibenz[b,e]oxepine sulfuric acid



MONKEY CORTEX BINDING (nM)

μ-receptor:	28.9 ± 6.4
δ-receptor:	967 ± 405 (range, n=2)
κ-receptor:	935 ± 24

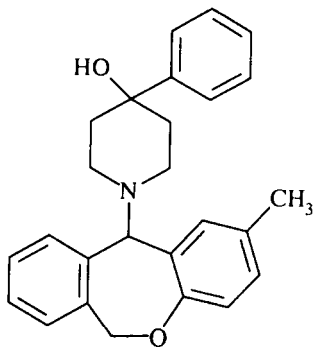
SUMMARY

NIH 10900 had good affinity for the μ opioid receptor. It had 30-fold higher affinity for μ, compared with κ and δ receptors. It has 1/50th of the affinity of the standard peptide DAMGO and an estimated 1/10th of the affinity of morphine for the μ receptor.

* * *

NIH 10901

11-[4-Hydroxy-4-phenylpiperidin-1-yl)-2-methyl-6,11-dihydrodibenzo[b,e]oxepine fumaric acid



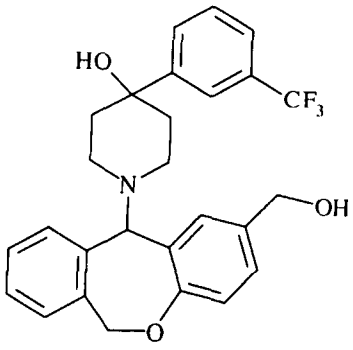
MONKEY CORTEX BINDING (nM)

μ-receptor:	69.3 ± 5.3
δ-receptor:	1292 ± 42
κ-receptor:	327 ± 11.6

SUMMARY

NIH 10901 had affinity for the μ opioid receptor, being 5-fold selective for μ/κ and 19-fold for μ/δ. The affinity of morphine at the μ receptor in an assay run concurrently was 0.86 ± 0.04 nM.

NIH 10902



11-[4-Hydroxy-4-(3-trifluoromethylphenyl)piperidin-l-yl]-2-hydroxymethyl-6,11-dihydrodibenz[b,e]oxepine fumaric acid

MONKEY CORTEX BINDING (nM)

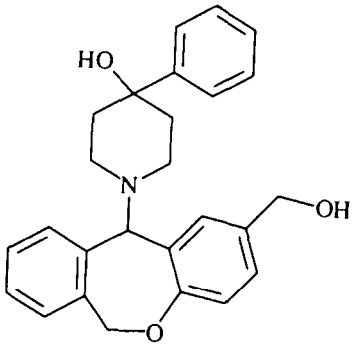
μ-receptor:	9.6 ± 1.5
δ-receptor:	1162 ± 115
κ-receptor:	1110 ± 165

SUMMARY

NIH 10902 had good affinity and selectivity for the μ opioid receptor, being >100-fold selective for μ receptors compared with both κ and δ receptors. The affinity of morphine at the μ receptor in an assay run concurrently was 0.86 ± 0.04 nM.

* * *

NIH 10903



11-(4-Hydroxy-4-phenylpiperidin-1-yl)-2-hydroxymethyl-6,11-dihydrodibenz[b,e]oxepine

MONKEY CORTEX BINDING (nM)

μ-receptor:	11.7 ± 3.1 nM
δ-receptor:	111.0 ± 28 nM (range, n=2)
κ-receptor:	242.3 ± 26.4 nM

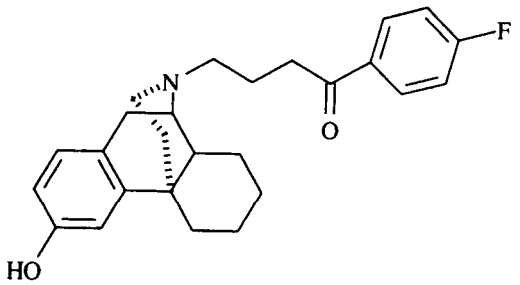
SUMMARY

NIH 10903 had good affinity for the μ > δ > κ opioid receptors and was approximately 10- and 20-fold selective for μ- over δ - and κ-receptors, respectively. It had 1/20th of the affinity of the standard peptide, DAMGO, and an estimated 1/4th of the affinity of morphine for the μ-receptor.

* * *

NIH 10909

(+)-N-[3-(4'-Fluorobenzoyl)propyl]-3-hydroxymorphinan.HCl



MONKEY CORTEX BINDING (nM)

μ-receptor:	59.1 ± 7.1
δ-receptor:	26.7 ± 9.9% inhibition at 10 μM
κ-receptor:	1227 ± 175

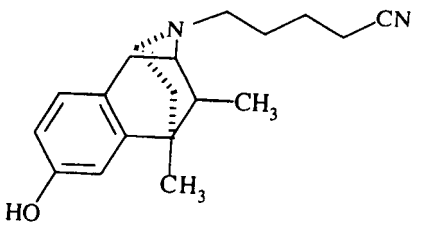
SUMMARY

NIH 10909 had some affinity for μ-opioid receptors (approximately 30-time less than morphine under the same conditions), and selectivity for μ- over κ- (21-fold) and very high selectivity for μ- over δ- (>170-fold) opioid receptors.

* * *

NIH 10915

(+)-(2*S*, 5*S*, 9*S*)-2-(4-Cyanobutyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl



MONKEY CORTEX BINDING (μM)

μ-receptor:	4.76 ± 0.60
δ-receptor:	> 10 μM (15.3% inhibition at 10 μM)
κ-receptor:	1.26 ± 0.04

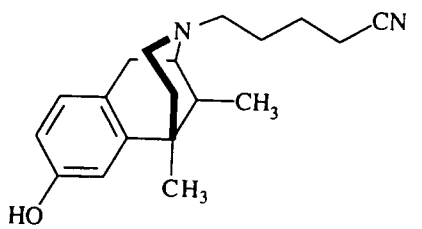
SUMMARY

NIH 10915 has low affinity for opioid receptors, in the μM range. It has especially low affinity for the δ-receptor binding site.

* * *

NIH 10916

(-)-(2*R*, 5*R*, 9*R*)-2-(4-Cyanobutyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl



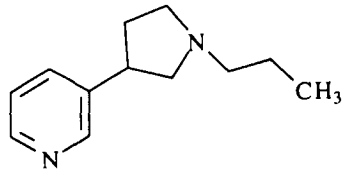
MONKEY CORTEX BINDING (nM)

μ-receptor:	18.15 ± 0.36
δ-receptor:	160.1 ± 41.6
κ-receptor:	6.87 ± 0.71

SUMMARY

NIH 10916 has high affinity for opioid receptors in the order κ>μ>δ. However, it has little selectivity, with a μ/κ ratio of 2.6 times and a δ/κ ratio of 23-times.

NIH 10920 **(±)-N-Propyl-N-norisonicotine dioxalate**



MONKEY CORTEX BINDING (nM)

μ-receptor:	32 ± 1% inhibition at 10 μM
δ-receptor:	18 ± 5% inhibition at 10 μM
κ-receptor:	52 ± 6% inhibition at 10 μM

SUMMARY

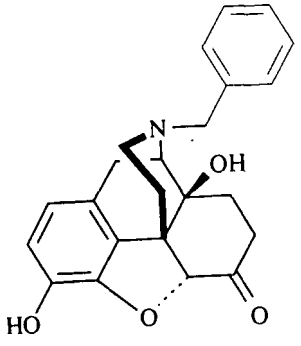
NIH 10920 had very low binding affinity at μ-,δ- and κ-opioid receptors.

* * *

NIH 10921 **17-Benzylnoroxymorphone.HCl**

MONKEY CORTEX BINDING (nM)

μ-receptor:	138 ± 22
δ-receptor:	529 ± 124
κ-receptor:	134 ± 41



SUMMARY

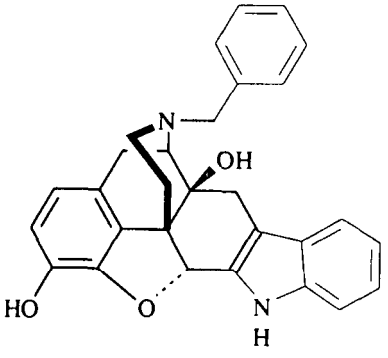
NIH 10921 had some affinity for μ-opioid receptors (approximately 170 times less than morphine), but shows no selectivity since its κ-affinity is similar and its δ-affinity is only 3.8-fold less.

* * *

NIH 10922 **17-Benzylnoroxymorphindole.HCl**

MONKEY CORTEX BINDING (nM)

μ-receptor:	5330 ± 1649
δ-receptor:	115 ± 32
κ-receptor:	1537 ± 195



NIH 10922 (continued)

SUMMARY

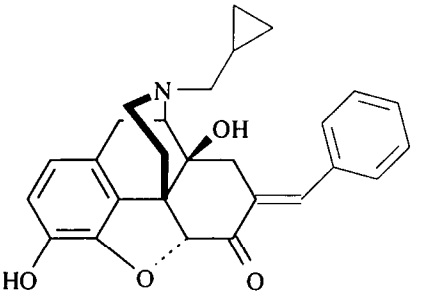
NIH 10922 had selectivity for δ-receptors over μ- and κ-opioid receptors of 46- and 13-times, respectively. However, its affinity for δ sites is 50-times less than the δ-selective peptide, DPDPE.

* * *

NIH 10923 **7-Benzylidene-7-dehydronaltrexone (BNTX).HCl**

MONKEY CORTEX BINDING (nM)

μ-receptor:	9.1 ± 3.0
δ-receptor:	6.8 ± 2.6
κ-receptor:	30.0 ± 5.3

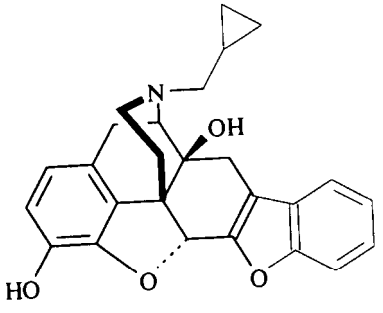


SUMMARY

NIH 10923 had high affinity for μ-, δ-, and κ-opioid receptors. There is no difference between its μ- and δ-receptor affinities, but a κ-receptors the compound is 3- to 4-fold less potent

* * *

NIH 10924 **Naltriben (NTB) methanesulfonate**



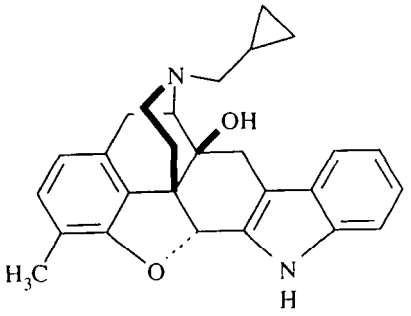
MONKEY CORTEX BINDING (nM)

μ-receptor:	12.4 ± 2.9
δ-receptor:	0.36 ± 0.14
κ-receptor:	17.5 ± 2.9

SUMMARY

NIH 10924 had very high affinity and good selectivity for the δ-opioid binding site. It has approximately 5-times higher affinity for δ receptors than the selective peptide, DPDPE, and a 34-fold preference for δ over μ sites and a 49-fold preference for δ- over κ-sites. Note that the binding at &receptors is quite variable (the experiment was done 4 times and gave Ki values of 0.6 nM, 0.6 nM, 0.05 nM, and 0.18 nM) and may suggest instability of the compound.

NIH 10925 **3-Deoxy-3-methylnaltrindole.HCl**



MONKEY CORTEX BINDING (nM)

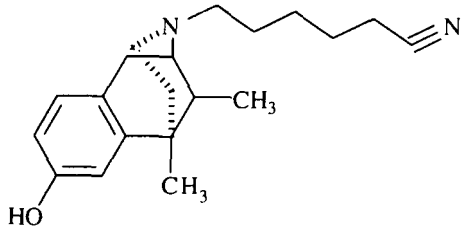
μ-receptor:	3536 ± 1134
δ-receptor:	106 ± 29
κ-receptor:	6634 ± 2218

SUMMARY

NIH 10925 had selectivity for δ-receptors over μ- and κ-opioid receptors of 33- and 63-times, respectively. However, its affinity for δ sites is 50-times less than the δ-selective peptide, DPDPE.

* * *

NIH 10926 **(+)-(2*S*, 5*S*, 9*S*)-2-(5-Cyanopentyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl**



MONKEY CORTEX BINDING (nM)

μ-receptor:	1167 ± 258
δ-receptor:	>10 (31 ± 7.9% inhibition at 10 μM)
κ-receptor:	512 ± 38

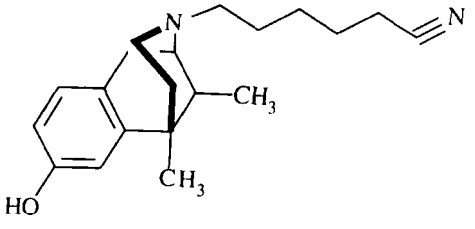
SUMMARY

NIH 10926 has weak affinity for opioid receptors in the order of κ> μ>> δ.

NIH 10927 **(-)-(2*R*, S*R*, 9*R*)-2-(5-Cyanopentyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl**

MONKEY CORTEX BINDING (nM)

μ-receptor:	15.3 ± 2.7
δ-receptor:	216 ± 44.0
κ-receptor:	11.1 ± 1.0



SUMMARY

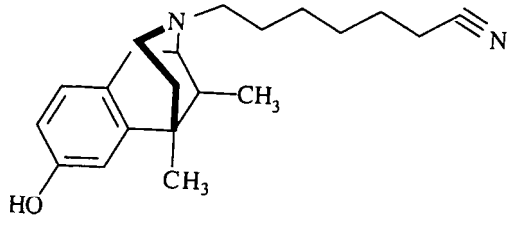
NIH 10927 had high and approximately equal affinity for μ- and κ-opioid receptors. The affinity at μ receptors was approximately 17 times lower than morphine and at κ-receptors, 11 times less than U69593. The compound had considerably lower affinity for δ-receptors.

* * *

(-)-(2*R*, 5*R*, 9*R*)-2-(6-Cyanohexyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl **NIH 10934**

MONKEY CORTEX BINDING (nM)

μ-receptor:	91.0 ± 12.6
δ-receptor:	350 ± 72
κ-receptor:	38.2 ± 7.3



SUMMARY

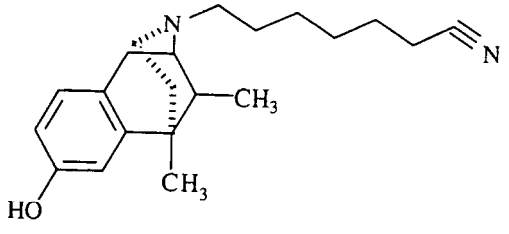
NIH 10934 had good affinity for κ-opioid receptors, with a small selectivity over μ-receptors (2.4-fold) and a 10-fold selectivity over δ--receptors. The K-receptor affinity of the compound is 40 times less than the standard agonist U69593.

* * *

NIH 10935 **(+)-(2*S*, 5*S*, 9*S*)-2-(6-Cyanohexyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl**

MONKEY CORTEX BINDING (nM)

μ-receptor:	694 ± 106
δ-receptor:	>10 μM (22.6 ± 4.7% inhibition at 10 μM)
κ-receptor:	1296 ± 112



SUMMARY

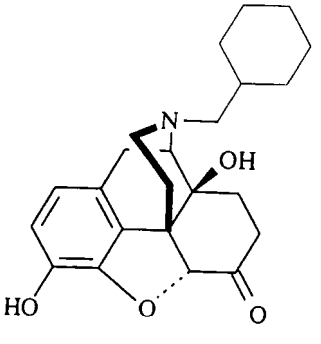
NIH 10935 has low affinity for μ- and κ--opioid receptor (approximately 1000-fold less than the standard agonists morphine and U69593), and extremely low affinity for δ-receptors.

* * *

NIH 10937 **17-Cyclohexylmethylnoroxymorphone.HCl**

MONKEY CORTEX BINDING (nM)

μ-receptor:	12.8 ± 1.9
δ--receptor:	310 ± 83.8
κ--receptor:	795 ± 179



NIH 10937 (continued)

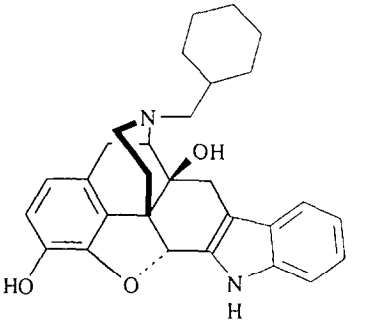
SUMMARY

NIH 10937 has good affinity for μ-opioid receptors (approximately 7-times less than morphine under the same conditions), and selectivity for μ over δ- (24-times) and κ-(62-times) opioid receptors.

NIH 10938 **17-Cyclohexylmethyl-N-nornaltrindole.HCl**

MONKEY CORTEX BINDING (nM)

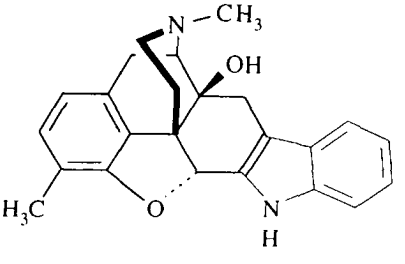
μ-receptor:	1925 ± 563
δ-receptor:	94.5 ± 13.6
κ-receptor:	1115 ± 430



SUMMARY

NIH 10938 has some affinity for δ-opioid receptors (approximately 47-times less than DPDPE under the same conditions), and selectivity for δ- over μ- (20-times) and κ -(12-times) opioid receptors.

NIH 10941 **3-Deoxy-3-methyloxymorphindole.HCl**



MONKEY CORTEX BINDING (nM)

u-receptor:	21 ± 3% inhibition at 10 uM
δ-receptor:	315 ± 49
κ-receptor:	11 ± 6% inhibition at 10 μM

SUMMARY

NIH 10941 had affinity for δ-opioid receptors, but this was approximately 150-fold less than the affinity of DPDPE. It was also at least 30-fold selective for the δ over μ- and K-receptors.

REFERENCES

Bertalmio, A.J.; Herling, S.; Hampton, R.Y.; Winger, G.; and Woods, J.H. A procedure for rapid evaluation of the discriminative stimulus effects of drugs. J Pharmacol Meth 7:289-299, 1982.

Cheng, Y.C. and Prusoff, W.H. Relationship between the inhibition constant (Ki) and the concentration of inhibitor which causes 50 percent inhibition (150) of an enzymatic reaction. Biochem. Pharmacol. 22:3099-3108, 1973.

Clark, M.J.; Carter, B.D.; and Medzihradsky, F. Selectivity of ligand binding to opioid receptors in brain membranes from the rat, monkey and guinea pig. Eur J Pharmacol 148:343-351, 1988.

Clark, M.J. and Medzihradsky, F. Coupling of multiple opioid receptors to GTPase following selective receptor alkylation in brain membranes. Neuropharmacol 26: 1763-1770, 1987.

Dykstra, L.A. and Woods, J.H. A tail withdrawal procedure for assessing analgesic activity in rhesus monkeys. J Pharmacol Meth 15263-269, 1986.

Emmerson, P.J.; Liu, M.-R.; Woods, J.H.; and Medzihradsky, F. Binding affinity and selectivity of opioids at mu, delta and kappa receptors in monkey brain membranes. J Pharmacol Exp Ther 271: 1630-1637, 1994.

France, C.P. and Woods, J.H. Discriminative stimulus effects of naltrexone in morphine-treated rhesus monkeys. J Pharmacol Exp Ther 250:937-943, 1989.

France, C.P.; de Costa, B.R.; Jacobson, A.E.; Rice, K.C.; and Woods, J.H. Apparent affinity of opioid antagonists in morphine-treated rhesus monkeys discriminating between saline and naltrexone. J Pharmacol Exp Ther 252:600-604, 1990.

France, C.P. and Woods, J.H. Respiratory effects of receptor-selective opioids in rhesus monkeys. In: Quirion, R., Jhamandas, K. and Gianoulakis, C. (Eds.), Progress in Clinical and Biological Research: The International Narcotics Research Conference (INRC) ‘89, Vol. 328. Alan R. Liss, Inc.: New York, pp. 295-298, 1990.

Howell, L.L.; Bergman, J.; and Morse, W.H. Effects of levorphanol and several -selective opioids on respiration and behavior in rhesus monkeys. J Pharmacol Exp Ther 245:364-372, 1988.

Medzihradsky, F. Novel biochemical determinants in the preclinical evaluation of opiates. NIDA Res Monogr 76:349-355, 1987.

Medzihradsky, F.; Emmerson, P.J; and Mousigian, C.A. Lipophilicity of opioids determined by a novel micromethod. J Pharmacol Meth 27:67-69, 1992.

Perrine, T.D.; Atwell, L.; Tice, I.B.; Jacobson, A.E.; and May, E.L. Analgesic activity as determined by the Nilsen method. J Pharm Sci 61:86-88, 1972.

Solomon, R.E.; Herling, S.; Domino, E.F.; and Woods, J.H. Discriminative stimulus effects of N-substituted analogs of phencyclidine in rhesus monkeys. Neuropharmacol 21:1329- 1336, 1982.

Smith, C.B. New approaches to the evaluation of opioid agonists and antagonists upon the mouse vas deferens preparation. NIDA Res Monogr 76:288-294, 1986.

Smith, C.B.; Medzihradsky, F.; Hollingsworth, P.J.; DeCosta, B.; Rice, K.C.; and Woods, J.H. Norbinaltorphimine is a reversible, noncompetitive opioid antagonist in the mouse vas deferens with high affinity for receptors in monkey brain membranes. In: Quirion, R.; Jhamandas, K.; and Gianoulakis, C. eds., The International Narcotics Research Conference (INRC) '89. A.R. Liss, Inc., pp. 65-68, 1989.

Winger, G.; Palmer, R.K.; and Woods, J.H.: Drug-reinforced responding: rapid determination of dose-response functions. Drug and Alc Depend 24: 135-142, 1989.

Woods, J.H.; Smith, C.B; Medzihradsky, F.; and Swain, H.H. Preclinical testing of new analgesic drugs. In: Beers, F.R., Jr. and Basset, E.G. eds. Mechanisms of Pain and Analgesic Compounds. New York: Raven Press, pp. 429-445, 1979.

PROGRESS REPORT FROM THE TESTING PROGRAM FOR STIMULANT AND DEPRESSANT DRUGS (1998)

G. Winger, J. K. Rowlett, W. L. Woolverton, C. P. France and L. R. Gerak

University of Michigan, Ann Arbor, MI; University of Mississippi Medical Center, Jackson, MS; and Louisiana State University Medical Center, New Orleans, LA

INTRODUCTION

The research group involved in the evaluation of stimulant and depressant compounds has been in existence for approximately 14 years. The group currently includes laboratories at Louisiana State University Medical Center (France, Gerak), University of Mississippi Medical Center (Woolverton, Rowlett), and the University of Michigan (Winger) and is part of the Drug Evaluation Committee (Dr. T. Cicero, Chair) of the College on Problems of Drug Dependence (CPDD) which is supported by both CPDD and the National Institute on Drug Abuse (NIDA). One of the purposes of the group is to evaluate new compounds, generally classified as either stimulants or depressants, for their abuse liability and physical dependence potential. Compounds are received, coded and distributed by Dr. A. Jacobson at the National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK), National Institutes of Health (NIH), for blind testing in the various laboratories. They are evaluated for discriminative stimulus effects in pentobarbital-trained monkeys (UMMC), amphetamine-trained monkeys (UMMC), midazolam- or triazolam-trained monkeys (LSUMC), flumazenil-trained monkeys that receive diazcpam daily (LSUMC) and also for reinforcing effects in monkeys with self-administration of methohexital as a reference for compounds stated to be depressants, and cocaine as a reference for compounds stated to be stimulants (UM). This report includes the results of evaluation of the following compounds: CPDD-0045, CPDD-0046, CPDD-0047, CPDD-0048, CPDD-0049 and CPDD-0050.

Not all compounds were evaluated in all assays, as shown in the following table. A "+" indicates the drug was tested in the indicated assay.

	Reinforcing Effects		Discriminative Stimulus Effects			
Test Drug	Coc.	Metho	Midazo./Triaz.	Pentobarbital	Amphetameine	Flumazenil
CPDD-0045						
CPDD-0046						
CPDD-0047						
CPDD-0048						
CPDD-0049						
CPDD-0050						

METHODS

Discriminative Stimulus Effects in Rhesus Monkeys (midazolam and flumazenil discriminations, LSUMC)

Subjects

The subjects were four adult and two juvenile rhesus monkeys *(Macaca mulatta)* weighing between 4.0 and 10.5 kg. Two juvenile monkeys and one adult participated in the flumazenil discrimination study and three adults participated in the midazolam discrimination study. Monkeys were housed individually in stainless steel cages in which water was continuously available (except for monkey LU who was water restricted to facilitate drinking punch that contained drug). Monkeys received primate chow (Harlan Teklad, Madison, WI) daily as well as fresh fruit and peanuts several days per week. All studies were conducted in accordance with the guidelines of the Institutional Animal Care and Use Committee, Louisiana State University Medical Center, New Orleans, and the Guide for the Care and Use of Laboratory Animals as adopted and promulgated by the National Institutes of Health.

Apparatus

Monkeys were seated in chairs that provided restraint at the neck. Chairs were equipped with shoes containing brass electrodes, to which brief (250 msec) electric shock could be delivered from an a.c. shock generator located adjacent to the chambers. During experimental sessions, chairs were located in sound-attenuating, ventilated chambers that were equipped with several response levers, a food cup and an array of stimulus lights.

Procedure

Triazolam or Midazolam Discrimination. CPDD-0045 was studied in monkeys discriminating 0.032 (subject MA) or 0.1 mg/kg (subject FR) of triazolam from vehicle while responding under an FR5 schedule of stimulus-shock termination. Daily sessions comprised a single cycle that included a 15min time out period, during which the chamber was dark and lever presses had no programmed consequence, followed by a response period, during which the chamber was illuminated red. In the presence of the red light, the monkeys could postpone the shock schedule for 30 sec by responding five times on the appropriate lever, as determined by the s.c. injection administered 45 min prior to the beginning of the session, 60 min prior to the beginning of the response period (e.g., left lever after vehicle, right lever after triazolam). Failure to satisfy the response requirement within 10 sec resulted in the delivery of a brief shock. The response period ended after 5 min or the delivery of 4 shocks, whichever occurred first. Responses on the injection-inappropriate lever reset the response requirement on the correct lever.

Test sessions were identical to training sessions except that various doses of triazolam or the test compound were administered 45 min prior to the session and five consecutive responses on either lever postponed shock.

CPDD-0046 and CPDD-0047 were studied in monkeys discriminating 0.56 mg/kg of midazolam from vehicle. The conditions were identical to those used for monkeys discriminating between triazolam and vehicle with three exceptions. First, daily sessions comprised 2 to 6 discrete cycles that included a 10-min time out period followed by a 5-min response period. Second, the training drug was administered at the beginning of a cycle, 10 min prior to the beginning of the response period. Finally, during test sessions, increasing doses of midazolam or the test compound were administered during the first min of each cycle with the cumulative dose increasing by 0.5 log units every 15 min.

Flumazenil Discrimination. Monkeys consumed 5.6 mg/kg of diazepam in 45-50 ml of fruit punch 3 hrs prior to daily sessions in which they discriminated between s.c. injections of 0.32 mg/kg of flumazenil and vehicle while responding under a FR 5 schedule of stimulus-shock termination. Daily training sessions consisted of several discrete, 1.5min cycles. Each cycle comprised a 10-min pretreatment period, during which the chamber was dark and lever presses had no programmed consequence, followed by a response period, during which the chamber was illuminated red and monkeys could postpone the shock scheduled for 30 seconds by responding five times on the appropriate lever as determined by the s.c. injection administered during the first min of the 10-min timeout (e.g., left lever after vehicle, right lever after flumazenil). Failure to satisfy the response requirement within 10 seconds resulted in the delivery of a brief shock. The response period ended after 5 min or the delivery of 4 shocks, whichever occurred first. Responses on the injection-inappropriate lever reset the response requirement on the correct lever.

Test sessions were identical to training sessions except that various doses of flumazenil or the test compound were administered during the first min of each timeout and five consecutive responses on either lever postponed scheduled shock.

Drugs

Diazepam (Zenith Laboratories, Northvale, NJ) was suspended in 45-50 ml (depending on body weight) of fruit punch containing suspending Agent K to yield a dose of 5.6 mg/kg/daily drinking episode. Flumazenil (F. Hoffman LaRoche, LTD, Basel, Switzerland) was dissolved in a vehicle of 10% ethanol, 40% propylene glycol and 50% saline; triazolam (Upjohn, Kalamazoo, MI)was dissolved in a vehicle of 10% ethanol, 20% emulphor and 70% water. Midazolam (Upjohn, Kalamazoo, MI) was dissolved in saline.

Discriminative Stimulus Effects of CPDD compounds in Rhesus Monkeys (pentobarbital and amphetamine discriminations, UMMC)

Subjects

The subjects were seven adult rhesus monkeys (Macaca mulatta) weighing between 9 and 11 kg. Monkeys were housed individually in stainless steel cages in which water was available continuously. They were fed 120-150 g of Teklad monkey chow after each session and were given a chewable vitamin tablet 3 days/week.

The monkeys had been trained previously to discriminate d-amphetamine (Ou3, 8515 and 8405) or pentobarbital (AQ63, Ef3, 8814 and 8902) from saline in a two-lever, discrete-trial shock-avoidance procedure. All monkeys had received other test drugs prior to testing with the compounds described here.

Apparatus

During experimental sessions animals were seated in primate restraint chairs and placed inside sound-attenuating cubicles. All chairs were fitted with shots containing brass plates in the soles that permitted delivery of electric shock produced by a shock generator (SC 903 BRS/LVE, Laurel, MD). Chambers were equipped with two response levers (PRL-001, BRS/LVE, Laurel, MD) mounted on one wall. There were four white lights above each lever. Chambers were illuminated with ceiling-mounted 40w incandescent house lights. Experimental events were programmed and recorded with an Apple Macintosh II computer in a room adjacent to the one in which animals were tested.

Procedure

The training and test procedures have been reported in detail elsewhere (Woolvcrton *et al.,* 1994). A monkey was placed in the restraint chair and either saline (1-2 ml) or the training drug was administered intragastrically (i.g.) via a nasogastric tube, followed by a 1.5 ml saline flush. Fifty-five minutes after infusion, the monkey was placed into the experimental chamber.

The session began with a 5-min timeout which was followed by 30 trials. On each trial the house light and lever lights were illuminated and responding on the correct lever postponed scheduled shock and extinguished the lights. Incorrect responses reset the response requirement on the correct lever. The correct lever was determined by the pre-session infusion (drug or saline). If the response requirement (FR 5) was not satisfied on the correct lever within 10 seconds of the onset of the lights, shock (250 msec duration, 5 mA intensity) was delivered. If the response requirement was not satisfied within 4 additional seconds of this shock, a second shock was delivered and the trial automatically ended. The session was terminated if 2 shocks were delivered during 2 consecutive trials. Trials were separated by 30-sec timeouts.

Training sessions were conducted five days a week according to the following schedule: SDDSS, DSSDD, where S denotes sessions preceded by saline and D denotes sessions preceded by drug. Discrimination training continued until at least 90% of the responses in the first trial were on the correct lever and subjects avoided shock on at least 90% of the trials (27/30) for seven out of eight consecutive sessions. When subjects failed to satisfy criteria. the training sequence was conducted until the criteria were once again satisfied.

Test sessions were identical to training sessions except that test drugs were administered and completing the response requirement on either lever avoided shock. All doses were tested at least twice.

Drugs

A stock solution of d-amphetamine sulfate (National Institute on Drug Abuse, Rockville, MD) was dissolved in saline in a concentration of 5.0 mg/ml. The training dose of amphetamine was either 0.56 or 1.0 mg/kg i.g. Pentobarbital was mixed daily by diluting Nembutal (Abbott Laboratories, N. Chicago, IL). The training dose was 10 mg/kg for all pentobarbital-trained monkeys. All drugs except CPDD-0049 were dissolved in 0.9% saline immediate before administration; doses of 1.0, 3.0, 10.0 and 17 mg/kg were evaluated at an infusion volume of 0.25 ml/kg. CPDD-0049 was first dissolved in 0.2 -0.25 ml of 85% lactic acid which was then diluted with saline.

Reinforcing Effects in Rhesus Monkeys (UM)

Subjects

Subjects were rhesus monkeys (Macaca mulatta) experienced with self-administration of sodium methohexital or cocaine hydrochloride and saline. Animals were surgically prepared with indwelling silicone rubber catheters using

10 mg/kg i.m. ketamine and 2.0 mg/kg i.m. xylazine as anesthetics. Catheters were implanted in jugular (internal or external), femoral or brachial veins as necessary. Catheters passed subcutaneously (s.c.) to the mid-scapular region, exited the body and continued, through a hollow restraining arm, to the outside rear of the cage.

Apparatus

The restraint and catheter protection devices are described in detail by Deneau *et al.* (1969). Each monkey wore a tubular stainless steel harness that protected the exit site of the catheter and allowed relatively unrestricted movements within the cage. A Teflon cloth jacket (Alice King Chatham Medical Arts, Los Angeles, CA) provided further protection for animals who tended to locate and pull their catheters. The harness was connected to a flexible spring arm that carried the catheter to the back of the cage where it joined tubing passing through a roller infusion pump (Watson and Marlow Co., Model MHRK 55, Falmouth, UK).

Monkeys were individually housed in stainless steel cages, measuring 83.3 X 76.2 X 91.4 cm deep. A 15.4 cm square stimulus panel was located on the side of each cage, approximately 10 cm from the front and 19 cm from the bottom of the cage. Across the top of the stimulus panel, 1.5 cm apart, were three circles, 2.5 cm in diameter, covered with translucent plastic and capable of being illuminated from behind by 5 W colored bulbs. The two side lights could be illuminated red and the center light green. Below each of the two red stimulus lights was a response lever (Model 121-07; BRS-LVE, Beltsville, MD) capable of being operated by a force of 0.010 to 0.015 N. Experimental control was provided by an IBM PS/2 computer programmed with Med-PC (Med-Associates, Fairfield, VT) software and located in an adjoining room.

Procedure

Reinforcing effects of CPDD-0045 were evaluated in a substitution self-administration procedure with 0.1 mg/kg methohexital serving as the reference compound. Test sessions and baseline sessions had the same general structure. At the start of each session, a red light was illuminated over one of two levers. When a monkey completed the fixed-ratio requirement of 10 presses on that lever (fixed-ratio [FR] IO), a 5-second, 1.0 ml injection of saline solution, methohexital sodium (0.1 mg/kg), or a test compound was delivered. The red light was extinguished and a center green light illuminated for the duration of the infusion. Each injection was followed by a 10-sec timeout during which all stimulus lights were extinguished and responding had no programmed consequence. No limit was placed on the number of infusions that could be obtained during a session.

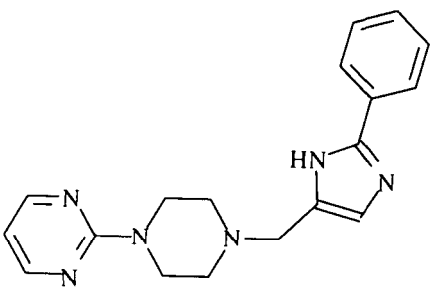
Reinforcing effects of CPDD-0046-50 were evaluated in a substitution self-administration procedure with 0.03 or 0.01 mg/kg cocaine serving as the baseline drug. The procedure was similar to that used with methohexital as the reference compound except that the FR was 30 and the timeout was 10 min in duration. A maximum of 13 injections could be earned in each session.

Twice daily experimental sessions lasted 130 min each. On approximately half of the baseline sessions, completion of the FR requirement resulted in delivery of saline. All animals showed clear and consistent differential responses to saline and cocaine or methohexital before test compounds were substituted.

In test sessions a dose of the test compound was made available for one session. Other conditions were similar to those of the baseline sessions.

RESULTS

CPDD-0045
2-Phenyl-4(5)-[4-((2-pyrimidinyl)-piperazin-1-yl)-methyl]-imidazole dimaleate



Discriminative Stimulus Effects in Rhesus Monkeys

Flumazenil Discrimination. In monkeys receiving 5.6 mg/kg/day of diazepam p.o. and discriminating between 0.32 mg/kg of flumazenil and vehicle, flumazenil produced dose-related increases in the percentage of responses emitted on the flumazenil-associated lever with doses larger than 0.32 mg/kg occasioning greater than 80% flumazenil-appropriate responding.

Under vehicle conditions, the average rates of responding for the two monkeys used in this study were 0.99 ± 0.06 (DU) and 2.40 ± 0.04 (LU) responses per second. Over the doses studied, flumazenil decreased the rate of responding in one monkey to less than 50% of control at a dose of 1.0 mg/kg.

Up to a dose of 32 mg/kg, CPDD-0045 produced a maximum of 6.2% selection of the flumazenil-appropriate lever in one monkey, and no selection of this lever by the other monkey Rates of responding were either unchanged (DU) or decreased modestly (LU) by CPDD-0045.

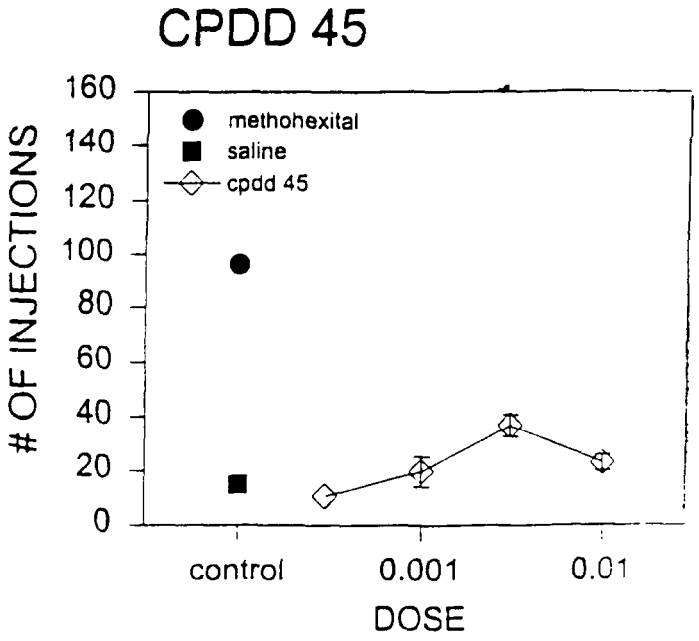
Triazolam Discrimination. In monkeys discriminating between 0.032 or 0.1 mg/kg triazolam and vehicle, triazolam produced dose-related increases in the percentage of responses emitted on the triazolam-appropriate lever. Doses greater than 0.0032 (MA) or 0.01 (FR) occasioned greater than 80% selection of the triazolam-appropriate lever. Following administration of vehicle, the average rates of responding for the two monkeys were 2.40 ± 0.1 (FR) and 2.12 ± 0.03 (MA) responses per second. Rates of responding decreased to less than 60% of control after s.c. injections of 0.1 mg/kg triazolam.

Up to a dose of 32 mg/kg s.c., CPDD-0045 failed to occasion complete triazolam-appropriate responding in either monkey. However, a dose of CPDD-0045 that markedly decreased rates of responding (32 mg/kg) occasioned 47% triazolam-appropriate responding in monkey MA. A retest with the same dose resulted in 55% selection of the triazolam-appropriate lever and a marked rate-decreasing effect. CPDD-0045 decreased rates of responding in both monkeys with a dose of 32 mg/kg decreasing rates to 80% of control in monkey FR and to 15% of control in monkey MA.

Amphetamine Discrimination. In monkeys discriminating between 0.56 or 1.0 mg/kg i.g. amphetamine and saline, CPDD-0045 did not produce any selection of the amphetamine-appropriate lever up to and including doses of 17 mg/kg. Rates of responding were also not affected by administration of these doses of CPDD-0045.

Pentobarbital Discrimination. In monkeys discriminating between 10 mg/kg i.g. pentobarbital and saline, CPDD-0045 did not produce any selection of the pentobarbital-appropriate lever up to and including 17 mg/kg. Rates of responding were not affected by these doses of CPDD-0045.

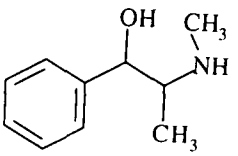
Reinforcing Effects in Rhesus Monkeys



CPDD-0045 was evaluated in five monkeys that were experienced with self-administration of i.v. sodium methohexital and saline. The reference dose of methohexital was 0.1 mg/kg/inj. Four doses of CPDD-0045 were evaluated in one monkey and three doses were evaluated in each of the other four monkeys. At least two observations were made at the tested doses in each monkey. On average, CPDD-0045 maintained very little self-administration behavior in the monkeys (figure 1). There is a slight increase in rates of responding at 0.003 mg/kg/inj, with the suggestion of an inverted U-shaped curve. But even this peak was far-below the amount of behavior maintained by 0.1 mg/kg sodium methohexital. Four of the five monkeys, however, showed high rates of self-administration of CPDD-0045 at at least one dose on at least one occasion. The doses that maintained high rates were repeated as many as 6 times. and most replications resulted in very low rates of responding. There is therefore some indication of variability in the response to CPDD-0045, but no indication of the reason for this variability.

CPDD-0046
(±) Ephedrine.HCl
[racemic ephedrine; racephedrin: Ephetonin]

Discriminative Stimulus Effects in Rhesus Monkeys



Flumazenil Discrimination. In monkeys receiving 5.6 mg/kg/day of diazepam p.o. and discriminating between 0.32 mg/kg of flumazenil and vehicle, flumazenil produced dose-related increases in the percentage of responses emitted on the flumazenil-associated lever with doses of 0.032 or 0.1 occasioning greater than 80% flumazenil-appropriate responding. Under vehicle conditions, the average rates of responding for the two monkeys used in this study were 1.38± 0.05 (DU) and 1.22±0.07 (IG) responses per second. Over the doses studied, flumazenil did not reliably modify rates of responding.

Up to a dose of 32 mg/kg, (±) ephedrine produced a maximum selection of the flumazenil-appropriate lever of 10 % in subject DU and 20% in subject IG. At the same dose, rate of responding was increased to 177% of control in monkey DU and not dramatically altered in monkey IG.

Midazolam Discrimination. In monkeys discriminating between 0.56 mg/kg of midazolam and vehicle, midazolam produced dose-related increases in the percentage of responses emitted on the midazolam-associated lever, with doses of 0.1 (MA) and 1.0 (RO) occasioning greater than 80% drug-lever responding. Under vehicle conditions, the average rates of responding for the two monkeys used in this study were 1.74 ± 0.04 (MA) and 1.57 0.05 (RO) responses per second. Over the doses studied, midazolam did not reliably modify rates of responding.
Up to a dose of 32 mg/kg s.c., (±) ephedrine failed to substitute for midazolam in either monkey. (±) Ephedrine increased rates of responding in monkey RO.

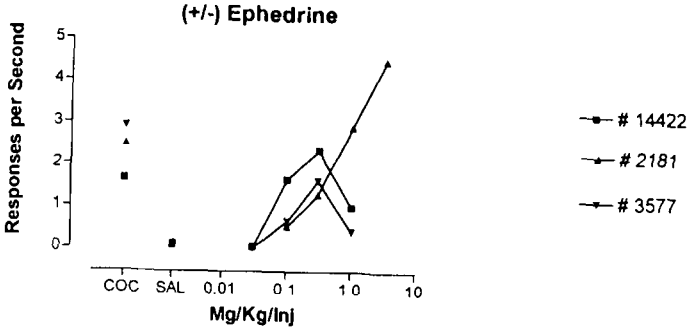
Amphetamine discrimination. Two of the three monkeys trained to discriminate oral amphetamine and given increasing doses of (±) ephedrine showed greater than 80% responding on the amphetamine-appropriate lever. This occurred at a dose of 10 mg/kg (±) ephedrine. However, at a dose of 30 mg/kg (±) of ephedrine, these two monkeys responded only 50% on the drug-appropriate lever. The data are shown in Table 1. At 30 mg/kg, monkeys generally appeared stimulated immediately before the session and refused food immediately after the session.

TABLE 1. Discriminative stimulus effects of amphetamine and (±) ephedrine in monkeys discriminating between amphetamine and vehicle.

			(± ephedrine (mg/kg)			
Subject	Vehicle	Amphetamine	1.0	3.0	10.0	30
8515	0	100	6.5	34.4	13	3
Ou3	0	100	0	40	100	50
8405	0	100	0	1.5	100	50

Pentobarbital discrimination. There was no pentobarbital-appropriate responding by any of the four monkeys tested at 10 and 30 mg/kg.

Reinforcing Effects in Rhesus Monkeys

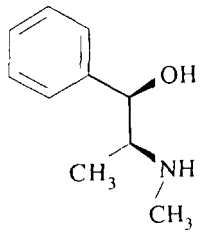


Three doses of (±) ephedrine were studied in two monkeys, and four doses were studied in the third monkey (see figure 2). Each dose was tested at least twice in each monkey with the exception of the largest dose (3.2 mg/kg/inj) in monkey # 2181. This was tested only once. The two monkeys that received only 0.i. 0.3, and 1.0 mg/kg/inj showed an inverted U-shaped curve with a peak rate of responding at 0.3 mg/kg/inj. This peak rate was slightly greater than that maintained by cocaine for one monkey, and slightly less than that maintained by cocaine for the second monkey. The third monkey showed a monotonically increasing rate of responding across the four doses, showing rates considerably above those maintained by cocaine at the 3.2 mg/kg/inj dose. He received this dose on only one occasion because he was profoundly affected by the large amount of drug that he took. This was manifested by agitation. decreased food intake, and repeated lever pressing that was maintained into the evening session, four hrs later, when the responses resulted in saline delivery. This behavior was demonstrated at a slightly lower rate when 1.0 mg/kg/inj was available. The maximum of 13 injections was taken by this monkey at both of these two larger doses.

In this preparation (±) ephedrine had reinforcing effects; it maintained self-administration behavior that closely resembled that maintained by cocaine.

CPDD-0047

(-)-Ephedrine.HCl[1 *R*,2*S*-(-)-2-(methylamino)-1-phenylpropan-1-ol]
(natural product; Ephedral; Sanedrine)



Discriminative Stimulus Effects in Rhesus Monkeys

Flumazenil Discrimination. In monkeys receiving 5.6 mg/kg/day of diazepam p.o. and discriminating between 0.32 mg/kg of flumazenil and vehicle, flumazenil produced dose-related increases in the percentage of responses emitted on the flumazenil-associated lever with a dose of 0.1 mg/kg occasioning greater than 80% flumazenil-appropriate responding in both monkeys. Under vehicle conditions, the average rates of responding for the two monkeys used in this study were 1.38±0.05 (DU) and 1.87 ± 0.10 (LU) responses per second. Over the doses studied, flumazenil did not reliably modify rates of responding.

Up to a dose of 32 mg/kg, (-)-ephedrine did not produce any flumazenil-appropriate responding. However, a dose of 3.2 mg/kg (-)- ephedrine increased rates of responding to 125-155% of control.

Midazolam Discrimination. In monkeys discriminating between 0.56 mg/kg of midazolam and vehicle, midazolam produced dose-related increases in the percentage of responses emitted on the midazolam-associated lever, with doses of 0.1 (MA) and 1.0 (RO) occasioning greater than 80% drug-lever responding. Under vehicle conditions, the average rates of responding for the two monkeys used in this study were 1.74 ± 0.04 (MA) and 1.59 ± 0.04 (RO) responses per second. Over the doses studied, midazolam did not reliably modify rates of responding.

Up to a dose of 32 mg/kg s.c., (-) ephedrine failed to substitute for midazolam in either monkey. However, doses of 3.2 and 10 mg/kg of (-)- ephedrine increased rates of responding to 112-134% of control rates in both monkeys.

Amphetamine Discrimination. Two of the three monkeys trained to discriminate oral amphetamine and given increasing doses of (-) ephedrine showed greater than 80% responding on the amphetamine-appropriate lever. This occurred at a dose of 3.0 or 10 mg/kg (-) ephedrine. The third monkey made 21.5% of its responses on the amphetamine-appropriate lever following administration of 30 mg/kg (-) ephedrine. At 30 mg/kg, monkeys generally appeared stimulated immediately before the session and refused food immediately after the session.

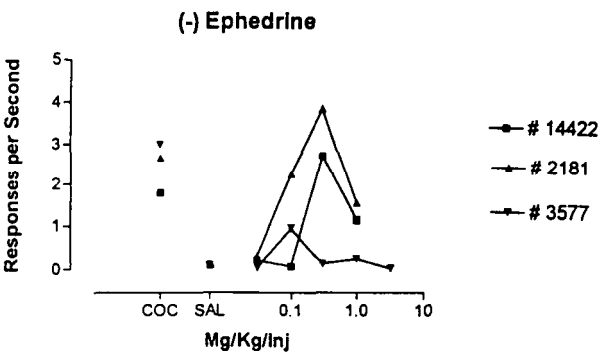
TABLE 2. Discriminative stimulus effects of amphetamine and (-) ephedrine in monkeys discriminating between amphetamine and vehicle.

			(-) ephedrine (mg/kg)				
Subject	Vehicle	Amphetamine	1.0	3.0	10.0	17	30
8515	0	100	0	38.8	2.0		21.5
Ou3	0	100	0	53.3	98		100
8405	0	100	0	95.3	74	100	n.s.

n.s. = not studied

Pentobarbital discrimination. There was no pentobarbital-appropriate responding by any of the four monkeys tested at 10 and 30 mg/kg (-) ephedrine.

Reinforcing Effects in Rhesus Monkeys

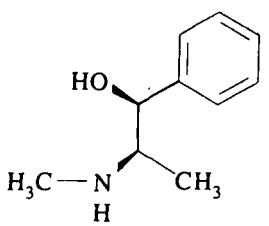


Four doses of (-) ephedrine were studied in two subjects, and five doses were studied in the third subject (see figure 3). Each dose was tested at least twice in each monkey. The two monkeys that received 0.003, 0.1, 0.3, and 1.0mg/kg/inj showed an inverted U-shaped curve with a peak rate of responding at 0.3 mg/kg/inj. This peak rate was slightly greater than that maintained by cocaine for both monkeys. (-) Ephedrine maintained lower rates of responding in the third monkey. The peak rate of responding occurred at 0.1 mg/kg/inj and was well below the rates of responding maintained by cocaine. At other doses, behavior was not maintained above rates maintained by saline.

In this preparation, (-) ephedrine had reinforcing effects; it maintained self-administration behavior that closely resembled that maintained by cocaine in two of the three subjects. In the third subject rates of responding were above those maintained by saline, although below rates maintained by cocaine.

CPDD-0048

(+) ephedrine.HCl [1S,2R-(+)-2-(methylamino)-1-phenylpropan-l-ol]
(enantiomer of natural product)



Discriminative Stimulus Effects in Rhesus Monkeys

Flumazenil Discrimination. In monkeys receiving 5.6 mg/kg/day of diazepam p.o. and discriminting between 0.32 mg/kg flumazenil and vehicle, flumazenil produced dose-related increases in the percentage of responses emitted on the flumazenil-associated lever with a dose of 0.1 (LU) or 0.32 (DU) mg/kg asioning greater than 80% drug-lever responding. Under control (vehicle) conditions, the average rate of responding for the two monkeys used in this study were 1.87 ± 0.10 (LU) and 1.38 ± 0.05 (DU) responses per second. Over the doses studied, flumazenil did not reliably modify rates of responding.

Up to a dose of 32.0 mg/kg, (+) ephedrine did not produce any flumazenil-appropriate responding in either monkey. However, 32.0 mg/kg of (+) ephedrine increased rates of responding in both monkeys to 150-156% of control rates.

Midazolam Discrimination. In monkeys discriminating between 0.56 mg/kg midazolam and vehicle, midazolam produced dose-related increase in the percent of responses emitted on the midazolam-associated lever with doses of 0.1 (MA) or 0.32 (RO) mg/kg occasioning greater than 80% drug-lever responding. Under control conditions, the average rates of responding for the two monkeys used in this study were 1.72 ± 0.04 (MA) and 1.59 ± 0.04 (RO) responses per second. Over the doses studied, midazolam did not reliably modify rates of responding.

Up to a dose of 32.0 mg/kg, (+) ephedrine failed to substitute for midazolam in either monkey. However, (+) ephedrine modestly increased rates of responding in monkey RO (113% of control).

Amphetamine Discrimination. One of the three monkeys showed 100% selection of the amphetamine-appropriate lever when given a dose of 30 mg/kg (+) ephedrine. One of the three monkeys did not select the amphetamine-appropriate lever at any dose of (+) ephedrine. The third monkey, 8405, showed a maximum selection of the amphetamine-appropriate lever of 45% following administration of 30 mg/kg (+) ephedrine. This monkey was visibly stimulated and refused food after administration of 30 mg/kg (+) ephedrine. The generalization data are shown in the following table.

TABLE 3. Discriminative stimulus effects of amphetamine and (+) ephedrine in monkeys discriminating between amphetamine and vehicle.

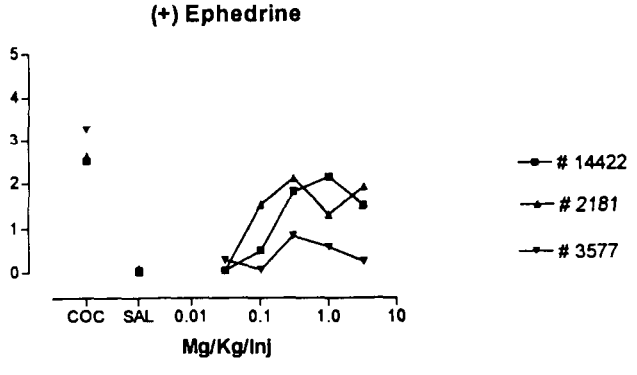
			(+) ephedrine (mg/kg)				
Subject	Vehicle	Amphetamine	1.0	3.0	10.0	17	30
8515	0	100	0	0	3	0	0
Ou3	0	100	n.s.	0	51.5	48.	100
8405	0	100	0	0	16.5	38	45

n.s. = not studied

Pentobarbital discrimination. There was no pentobarbital-appropriate responding by any of the four monkeys tested at 10 and 30 mg/kg (+) ephedrine.

Reinforcing Effects in Rhesus Monkeys

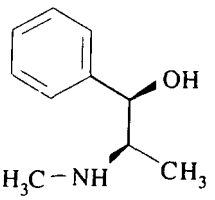
Five doses of (+) ephedrine were studied in all three subjects: 0.03, 0.1, 0.3, 1.0 and 3.2 mg/kg/inj (see figure 4). Each dose was tested at least twice in each monkey. The three monkeys showed a dose-effect curve that was generally inverted U-shaped with a peak rate of responding at 0.3 mg/kg/inj for two monkeys and 1.0 mg/kg/inj for the third monkey. This peak rate was slightly less than that maintained by cocaine for two monkeys. (+) Ephedrine maintained lower rates of responding in the third monkey, well below the rates of responding maintained by cocaine.



In this preparation (+) ephedrine had reinforcing effects; it maintained self-administration behavior that closely resembled that maintained by cocaine in two of the three subjects. In the third subject rates of responding were above those maintained by saline, although below rates maintained by cocaine.

CPDD-0049

(-)pseudoephedrine((-)-ephedrine; 1R,2R-(-)-2-[methylamino]-1-phenylpropan-l-ol)



Discriminative Stimulus Effects in Rhesus Monkeys

Amphetamine Discrimination. One of the three monkeys given increasing doses of (-) pseudoephedrine showed generalization between 10 mg/kg (-) pseudoephedrine and amphetamine. The other two monkeys did not show any generalization between the two compounds up to doses of 30 mg/kg (-) pseudoephedrine. The data are shown in Table 4. Monkeys were not visibly stimulated but occasionally refused food after administration of 30 mg/kg (-) pseudoephedrine.

TABLE 4. Discriminative stimulus effects of amphetamine and (-) pseudoephedrine in monkeys discriminating between amphetamine and vehicle.

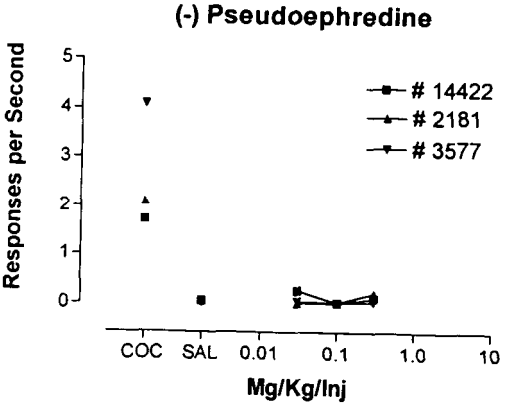
			(-) pseudoephedrine (mg/kg)				
Subject	Vehicle	Amphetamine	1.0	3.0	10.0	17	30
8515	0	100	0	0	0	0	0
Ou3	0	100	0	51.5	96	n.s.	0
8405	0	100	0	0	0	16.5.	33

n.s. = not studied

Pentobarbital discrimination. There was no pentobarbital-appropriate responding by any of the four monkeys tested at 10 and 30 mg/kg (-) pseudoephedrine.

Reinforcing Effects in Rhesus Monkeys

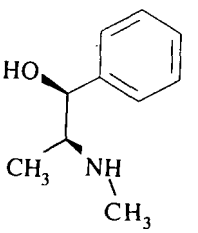
Three doses of (-) pseudoephedrine were studied in each of three subjects (see figure 5). Each dose was tested at least twice in each monkey. Larger doses could not be tested because of difficulty putting this base into solution at requisite concentrations. None of the doses tested maintained behavior above that maintained by saline in any of the three monkeys,



In this preparation, (-) pseudoephedrine had no reinforcing effects at the doses tested.

CPDD-0050

(+) pseudoephedrine. HCl (1S,2S-(+)-2(methylamino)-1-phenylproan-l-ol); (+)-·ψ ephedrine; d-isoephedrine; Galpseud, Novafed, Rhinalair, Otrinol, Sinufed, Sudafed



Discriminative Stimulus Effects in Rhesus Monkeys

Flumazenil Discrimination. In monkeys receiving 5.6 mg/kg/day of diazepam p.o. and discriminating between 0.32 mg/kg flumazenil and vehicle, flumazenil produced dose-related increases in the percentage of responses emitted on the flumazenil-associated lever with a dose of 0.1 (LU) or 0.32 (DU) mg/kg occasioning greater than 80% drug-lever responding. Under control (vehicle) conditions, the

average rate of responding for the two monkeys used in this study were 1.22 ± 0.07 (LU) and 1.38 ± 0.05 (DU) responses per sec. Over the doses studied, flumazenil did not reliably modify rates of responding.

Up to a dose of 32.0 mg/kg, (+) ephedrine did not produce any flumazenil-appropriate responding in either monkey and did not systematically alter rates of responding.

Midazolam Discrimination. In monkeys discriminating between 0.56 mg/kg midazolam and vehicle, midazolam produced dose-related increase in the percent of responses emitted on the midazolam-associated lever with a dose of 0.1 mg/kg occasioning greater than 80% drug-lever responding. Under control conditions, the average rates of responding for the two monkeys used in this study were 1.74 ± 0.04 (MA) and 1.59 ± 0.04 (RO) responses per second. Over the doses studied, midazolam did not reliably modify rates of responding.

Up to a dose of 32.0 mg/kg, (+) ephedrine failed to substitute for midazolam in either monkey and did not systematically alter rates of responding.

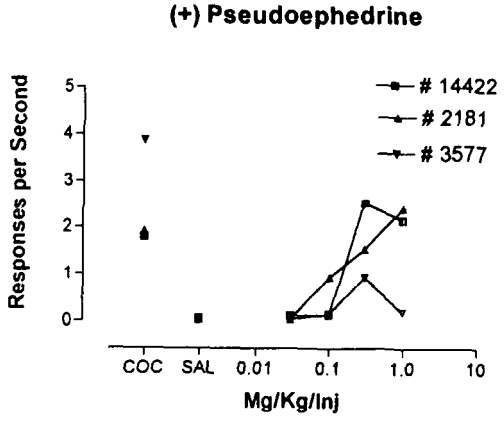
Amphetamine Discrimination. At doses up to and including 30 mg/kg, (+) pseudoephedrine produced increased selection of the amphetamine-appropriate lever in two of the monkeys. The maximum choice of the amphetamine-appropriate lever was 80% and 100% for these monkeys. The third monkey did not make more than 5% of its responses on the amphetamine-appropriate lever following administration of this range of doses of (+) pseudoephedrine The data are shown in Table 5. Monkeys were not visibly stimulated but occasionally refused food after administration of 30 mg/kg (+) pseudoephedrine.

TABLE 5. Discriminative stimulus effects of amphetamine and (+) pseudoephedrine in monkeys discriminating between amphetamine and vehicle.

			(+) pseudoephedrine (mg/kg)				
Subject	Vehicle	Amphetamine	1.0	3.0	10.0	17	30
8515	0	100	0	1.5	0	5	0
Ou3	0	100	0	66.7	66.5	80	50
8405	0	100	2	1.5	20	41.5	100

Pentobarbital discrimination. There was no pentobarbital-appropriate responding by any of the four monkeys tested at 10 and 30 mg/kg (-) ephedrine.

Reinforcing Effects in Rhesus Monkeys



Four doses of (+) pseudoephedrine were studied in each of three monkeys (see figure 6). Each dose was tested at least twice in each monkey. This drug maintained rates of responding that had an inverted-U shape in two of the monkeys. The peak rare of responding was at 0.3 mg/kg/inj in both of these subjects. In the third monkey, rates increased across each of the tested doses, producing a maximum at 1.0 mg/kg/inj. In one monkey (# 14422), rates of responding were similar to those maintained by cocaine. In a second monkey (# 2181) rates were high, but below the very high rates maintained by cocaine in this monkey for this evaluation. Larger doses of (+) pseudoephedrine might have produced higher rates of responding. In the third monkey (# 3577) rates maintained by (+) pseudoephedrine were not as high as those maintained by cocaine, but the shape of the curve indicated that the drug was serving as a reinforcer at one dose.

In this preparation (+) pseudoephedrine had reinforcing effects: it maintained self-administration behavior that closely resembled that maintained by cocaine in two of the three subjects. In the third subject rates of responding were above those maintained by saline, although below rates maintained by cocaine.

REFERENCES

Acteo, M.D.; Bowman, F.; Butelman, E.; English, J.A.; Harris, L.; Jacobson, A.E.; Mattson, M.V.; Medzihradsky, F.; Patrick, G.; Rowlett, J.K.; Smith, C.B.; Winger, G.; Woods, J.H.; and Woolverton, W.L. Zipeprol: preclinical assessment of abuse potential. ***Drug Alc Depend*** 42:93-104, 1996.

English, J.A.; Rowlett, J.K.; Woolverton, W.L.; Patrick, G.A.; Hawkins, W.T.; Winger, G.; and Woods, J.H. Progress report from the testing program for stimulant and depressant drugs (1995). In L.S. Harris (Ed.), *Proceedings, College on Problem of Drug Dependence* , National Institute on Drug Abuse Monograph #162, Washington DC.: U.S. Government Printing Office, 1996, pp. 452-468.

Jacobson, A.E. (1988) Biological evaluation of compounds for their physical dependence potential and abuse liability. XII. Drug Testing Program of the Committee on Problems of Drug Dependence (1988). In L.S. Harris (Ed.), *Proceedings, Committee on Problems of Drug Dependence,* National Institute on Drug Abuse Monograph #90, Washington D.C.: U.S. Government Printing Office, 1988, pp. 392-420.

Jacobson, A.E. (1988) Biological evaluation of compounds for their physical dependence potential and abuse liability. XI. Drug Testing Program of the Committee on Problems of Drug Dependence (1987). In L.S. Harris (Ed.), *Proceedings, Committee on Problems of Drug Dependence,* National Institute on Drug Abuse Monograph #81, Washington D.C.: U.S. Government Printing Office, 1988, pp. 466-484.

Jacobson, A.E. Biological evaluation of compounds for their physical dependence potential and abuse liability. XIV. Animal Testing Committee of the Committee on Problems of Drug Dependence (1990). In L.S. Harris (Ed.), *Proceedings, Commitee on Problems of Drug Dependence,* National Institute on Drug Abuse Monograph #105, Washington, DC.: U.S. Government Printing Office, 1991, pp. 622-639.

Jacobson, A.E. Biological evaluation of compounds for their physical dependence potential and abuse liability. XIX. Drug Evaluation Committee of the College on Problems of Drug Dependence (1995). In L.S. Harris (Ed.), *Proceedings, College on Problems of Drug Dependence,* (National Institute on Drug Abuse Monograph #162, Washington D.C.: U.S. Government Printing Office, 1996, pp. 363-376.

Jacobson, A.E. Biological evaluation of compounds for their physical dependence potential and abuse liability. XX. Drug Evaluation Committee of the College on Problems of Drug Dependence (1996). In L.S. Harris (Ed.), *Proceedings, College on Problems of Drug Dependence,* National Institute on Drug Abuse Monograph #174, Washington D.C.: U.S. Government Printing Office, 1997, pp. 323-337.

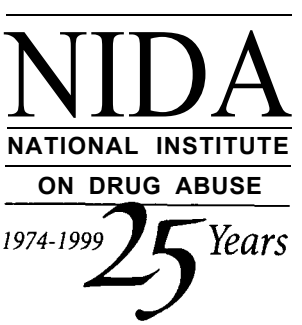
Johanson, C.E. Stimulant depressant report. In L.S. Harris (Ed.), *Proceedings, Committee on Problems of Drug Dependence,* National Institute on Drug Abuse Monograph #67, Washington D.C.: U.S. Government Printing Office, 1986, pp. 98-104.

ACKNOWLEDGEMENTS: This research was supported, in part, by the College on Problems of Drug Dependence and USPHS Grants Da-09163 (GW), DA 09157(CPF), and DA09 139 (WLW).

AUTHOR INDEX

SUBJECT INDEX

'U.S. Government Printing Office: 1999 – 450-790/10189



NIH Publication No. 99-4395
Printed March 1999