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Volume 2

Medical Management Treatment Manual

A Clinical Research Guide for Medically Trained Clinicians Providing Pharmacotherapy as Part of the Treatment for Alcohol Dependence

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National Institute on Alcohol Abuse and Alcoholism
COMBINE Monograph Series
Volume 2

Medical Management Treatment Manual

A Clinical Research Guide for Medically Trained Clinicians Providing Pharmacotherapy as Part of the Treatment for Alcohol Dependence

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Copyright Status

This manual was constructed, with permission, from several pre-existing manuals that included medical management as part of their interventions. These manuals are cited below. The Medical Management Subgroup (authors), with the assistance of Kelly Tobin Murray (University of North Carolina, COMBINE Coordinating Center), rewrote and edited sections to provide a focused, cohesive set of guidelines for medical practitioners to follow in delivering Medical Management (MM) treatment. We also acknowledge the individual contributions of Amy Schuhl and Carla Nappi (University of Pennsylvania); and Judith Arroyo, Ph.D. (University of New Mexico). We especially credit the MM clinicians from the COMBINE study, who generously provided the authors with feedback on all aspects of the MM treatment and use of the manual.

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Carroll, K.M., and O'Malley, S. *Compliance Enhancement: A Manual for the Psychopharmacotherapy of Alcohol Dependence.* Unpublished treatment manual, Yale University, 1996.

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Foreword

A major focus of the efforts of the National Institute on Alcohol Abuse and Alcoholism (NIAAA) in treatment research is to develop and test promising medications and behavioral therapies for treating alcohol disorders. This commitment is particularly reflected in NIAAA's multisite clinical trial, COMBINE, which tests two promising medications, naltrexone and acamprosate, alone and combined, in conjunction with two behavioral therapies, Medical Management and Combined Behavioral Intervention. The project involves 11 geographically diverse clinical sites representing both public and private treatment facilities as well as hospital and university outpatient facilities, and a data coordinating center. The cooperative agreement under which this project was established allowed direct collaboration between NIAAA and the researchers, who are among the most senior and experienced treatment scientists in the field.

The two treatment manuals in this series are the result of the collaborative efforts of the COMBINE investigators and are used as guides by therapists in the trial. As used in COMBINE, these manuals summarize the consensus of the investigators on reasonable intervention approaches based on present knowledge and are presented to the alcohol research community as standardized, well-documented intervention tools for alcoholism treatment research. Forthcoming publications from COMBINE will address the relative efficacy of the combinations of interventions. We look forward to offering further refinements of these approaches as COMBINE data are analyzed and published and as further advances are made in alcoholism treatment through ongoing research.

Ting-Kai Li, M.D.
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Overview of COMBINE

Clinical Trial Combining Medication and Behavioral Therapies for the Treatment of Alcoholism

Introduction

This treatment manual and a companion manual in this series are provided to the public to permit replication of the behavioral therapies employed in COMBINE, a multisite clinical trial started in 1997 and funded as a cooperative agreement by the National Institute on Alcohol Abuse and Alcoholism (NIAAA).

The goal of COMBINE is to determine if improvements in treatment outcome for alcohol dependence can be achieved by combining pharmacotherapy and behavioral interventions. COMBINE seeks to evaluate the efficacy of the two most promising medications (naltrexone and acamprosate), both singly and together, when used in conjunction with two behavioral treatments of differing intensities.

One behavioral intervention, Medical Management (MM), employs a series of brief counseling sessions to enhance medication adherence and abstinence from alcohol. The other, Combined Behavioral Intervention (CBI), is a more intensive treatment that combines several successful features from previously evaluated interventions. The brief session therapy (MM) is a type of treatment that might be suitable for delivery in primary care settings. The more intensive therapy (CBI) is suitable for delivery by trained psychotherapists working in specialized alcoholism treatment facilities.

The following sections summarize the nature of the treatments tested in COMBINE, the study design, and considerations for those contemplating use of the manuals. This information has been previously published in greater detail by the COMBINE Research Group. For further information, consult the publications on the study's methods and rationale (COMBINE Research Group 2003*a*); the safety and tolerability of the combined medications (Johnson et al. 2003); and the results of a protocol feasibility study (COMBINE Research Group 2003*b*). The first page of the COMBINE Web site (http://www.cscc.unc.edu/COMBINE) lists topics on the Web site that are accessible to the public.

The COMBINE Interventions

Medication Treatments

Each of the COMBINE medications, naltrexone and acamprosate, has shown efficacy in the treatment of alcohol dependence in placebo-controlled clinical trials conducted in the United States and Europe (Kranzler and Van Kirk 2001; Streeton and Whelan 2001; Mann et al. 2004). In most of these studies, patients received a behavioral treatment to which the active medication or placebo was added. Outcomes typically reported included the

amount of drinking or the proportions of patients remaining abstinent. Naltrexone has been approved as a treatment for alcohol dependence by the U.S. Food and Drug Administration (FDA) since 1994 and is approved in over 30 countries around the world (Litten and Allen 1998). Acamprosate currently is approved for treating alcohol dependence throughout most of Europe and South America, Australia, and parts of Asia and Africa and is now under FDA review in the United States (Mason and Ownby 2000).

A body of laboratory and clinical data suggests that naltrexone and acamprosate act on different neurochemical systems involved in the addictive response and presumably target different aspects of the alcohol dependence syndrome.

Naltrexone acts to block the opioid receptors, causing a reduction in the dopamine levels in the nucleus accumbens and leading to an attenuation in the positive reinforcement effects of alcohol (O'Malley and Froehlich 2003). Naltrexone appears to decrease craving for alcohol as well as decrease the rate of alcohol consumption (O'Malley et al. 2002). Most studies have also observed a decrease in the number of days of heavy drinking (Anton and Swift 2003). Acamprosate interacts with the glutamate receptor in a manner that is still unclear (Harris et al. 2002; Koob et al. 2002). This interaction appears to diminish the negative reinforcement of conditioned craving that follows cessation of drinking by reducing the protracted alcohol withdrawal symptoms (Spanagel and Zieglgansberger 1997; Koob et al. 2002). It is therefore reasonable to hypothesize that the combination of naltrexone and acamprosate might make it easier both to abstain from alcohol and to prevent a slip from turning into a relapse to drinking. Acamprosate may be particularly useful in avoiding initial alcohol consumption and enhancing treatment retention by attenuating symptoms of protracted alcohol withdrawal. Naltrexone may be particularly efficacious in reducing the likelihood of heavy drinking following a slip.

Behavioral Treatments

Modern pharmacotherapy efficacy studies in alcohol dependence generally have employed intensive psychotherapies delivered by trained therapists. However, treatment has increasingly moved toward treating alcoholics within a managed care setting in which the number of sessions is limited, and the sessions usually are provided by staff without specialized training in addiction treatment. It is therefore important to determine if the effects of pharmacotherapy depend on the type of counseling or psychotherapy with which it is combined. The two behavioral approaches tested in COMBINE contrast a treatment feasible for the primary care environment (MM) and one more suitable for use in an alcohol dependence specialty treatment facility (CBI).

Pharmacological and behavioral treatments are not mutually exclusive and indeed may enhance each other. Thus, pharmacotherapies may reduce craving for alcohol and/or the reinforcement experienced from drinking alcohol. Behavioral therapies can teach skills needed to maintain sobriety for extended periods. Several studies have demonstrated that the type of psychosocial intervention can influence the outcome with naltrexone (Anton and Swift 2003).

Medical Management (MM) is a manualized treatment (Pettinati et al. 2000) designed to approximate a primary care approach to alcohol dependence. The treatment, delivered by a medical professional (e.g., nurse or physician), provides strategies to increase medication adherence and supports abstinence through education and referral to support groups (Emrick et al. 1993; Barrett and Morse 1998; Carty et al. 1998). The initial session (40–60 minutes) involves discussion of the alcohol dependence diagnosis and negative consequences

from drinking, a recommendation to abstain, medication information, strategies to enhance medication adherence, and referral to support groups such as Alcoholics Anonymous. In the eight subsequent 15- to 25-minute visits, the clinician assesses the client's drinking, overall functioning, medication adherence, and any medication side effects.

Session structure varies according to the client's drinking status and treatment compliance. When the client does not adhere to the medication regime, the clinician evaluates the reasons and helps the client devise plans to address the problem(s). Clinicians urge clients who drink to attend support groups and offer commonsense recommendations, such as avoiding bars. If the client suffers from medical side effects, the clinician specifies procedures for using concomitant medication to ameliorate them or reduces the dosage of either one or both study agents, resuming the study agents if side effects remit. If a client discontinues medication because he or she cannot tolerate it, the clinician schedules a monthly 15- to 25-minute "medical attention" meeting, during which the clinician employs a similar approach that focuses on the client's drinking and overall health, omitting the medication adherence component.

Combined Behavioral Intervention (CBI) was designed to be a state-of-the-art individual outpatient psychotherapy for alcohol dependence. It merges a variety of well-supported treatment methods into an integrated approach. A manual-guided therapy, CBI nevertheless allows for normal clinical flexibility and individualization of treatment. CBI builds upon features in the manualized therapies of Project MATCH (Kadden et al. 1995; Miller et al. 1992; Nowinski et al. 1995; Project MATCH Research Group 1993) and provides skills training and support-system involvement modeled on a community reinforcement approach to treatment (Azrin et al. 1982; Meyers and Smith 1995). A maximum of 20 sessions is permitted, with the treatment course organized in four phases:

- *Phase 1* emphasizes building motivation for change. It begins with a single session of motivational interviewing (Miller and Rollnick 1991), which is the general clinical style used throughout CBI. This is followed by client assessment feedback in the style of motivational enhancement therapy (Miller et al. 1992).

- *Phase 2* includes a functional analysis of the client's drinking, a review of the client's psychosocial functioning, and a survey of the client's strengths and resources, the results of which will be used in developing an individual plan for treatment and change. The therapist emphasizes the merits of an abstinence goal, and each client is encouraged to become involved in a 12-step or other mutual-help group. Whenever possible, a supportive significant other is identified to participate in the client's treatment sessions as frequently as seems appropriate, ranging from a few to all sessions. The supportive significant other's role is to facilitate the client's compliance and abstinence and to reinforce as many of the CBI modules as the nature of the relationship appears to warrant.

- *Phase 3* draws upon a menu of nine cognitive-behavioral skill-training modules chosen on the basis of the client's needs identified during Phase 2 (cf. Kadden et al. 1995). The modules include (1) assertiveness skills, (2) communication skills, (3) coping with craving and urges, (4) drink refusal and social pressure, (5) job finding, (6) mood management, (7) mutual-help group facilitation, (8) social

and recreational counseling, and (9) social support for sobriety. All modules involve specific behavioral coaching and skill practice.

- *Phase 4* involves maintenance checkups in which the therapist and client review progress to date, renew motivation for change, and reaffirm commitment to an original or revised change plan.

CBI also includes a set of eight optional "pull-out" procedures that can be used at any appropriate point during treatment: (1) sobriety sampling, (2) raising therapist's concerns, (3) implementing case management, (4) handling resumed drinking, (5) supporting medication adherence, (6) responding to a missed appointment, (7) telephone consultation, and (8) crisis intervention.

The number, frequency, and duration of CBI treatment sessions are negotiated between the therapist and client within the bounds of 20 sessions and 16 weeks. Weekly 50-minute outpatient visits are typical but not absolute. All therapy sessions are audiotaped, and random samples are reviewed and rated for quality control purposes.

Study Design

Study Population

The goal recruitment for the trial was 1,375 subjects drawn from 11 clinical research units. Patients met the criteria for alcohol dependence specified in the American Psychiatric Association's *Diagnostic and Statistical Manual, Fourth Edition* (DSM–IV) (American Psychiatric Association 1994).

To be eligible, subjects had to acknowledge a desire to stop drinking and a history of alcohol consumption at or above a certain threshold. Prior to randomization and initiation of study pharmacotherapy, all subjects were required to complete any needed detoxification and abstain from alcohol for 4 days. Subjects had to have been drinking a minimum of 14 drinks (females) or 21 drinks (males) on average per week over a consecutive 30-day period in the 90-day period prior to initiation of abstinence. They also had to have had 2 or more days of heavy drinking (defined as four drinks for females and five drinks for males) in the previous 90 days, with the last drink being within 21 days of randomization to treatment.

Subjects were excluded if they reported recent opiate use, past 6-month opiate abuse or dependence disorder, or active dependence disorder with any substance other than cannabis or nicotine; serious psychiatric disorders requiring specific pharmacological intervention; unstable medical conditions for which either of the study medications was contraindicated (including liver function tests that were more than three times normal); and having received either study medication within the past 30 days.

Participants were recruited from in- and outpatient referrals within the study sites and from community and media sources. Subjects had to have had a breath alcohol level of zero to complete the informed consent and baseline measures. A certificate of confidentiality was obtained by all clinical sites.

Treatment Conditions

After assessment, subjects were randomly assigned to one of nine treatment conditions, as shown in Figure 1, using a permuted block randomization procedure with varying block sizes, which resulted in approximately 153 subjects per cell. Subjects in one cell (termed "cell 9") were to receive no study medication (active or placebo) or MM intervention but only CBI therapy. This cell was included to contrast the

effects of pill-taking (Barlow et al. 2000) on the outcome achievable with CBI alone and was considered a control condition for placebo effects that might result from the pill-taking regimen of 8 pills per day for 16 weeks.

Figure 1. COMBINE Treatment Combinations

Medical Management

	Placebo	Acamprosate
Placebo	1	2
Naltrexone	3	4

Medical Management + Psychotherapy

	Placebo	Acamprosate	No Pills
Placebo	5	6	
Naltrexone	7	8	
No Pills			9

The medications were dispensed to subjects in blister packs with sections divided into morning, noon, and evening doses. Naltrexone was supplied in two tablets to be taken each morning, as 25 milligrams (mg) for the first 3 days, 50 mg for the next 4 days, and 100 mg per day thereafter. Acamprosate was provided in 500-mg pills, as two pills to be taken three times per day, for a total of 3 grams. The two drugs look different, and each has a matched (i.e., identical) placebo. Subjects were given no information about the identity of the medications they received.

All participants randomized into the eight cells, involving either active or placebo medication, were assigned to nine Medical Management appointments at weeks 0, 1, 2, 4, 6, 8, 10, 12, and 16. The subset of participants who also received CBI had a maximum of 20 sessions over a total of 16 weeks of study participation. They also were evaluated for drinking history and craving by research assistants on the days they attended their MM sessions, with longer assessments at weeks 8 and 16. After week 16, all treatments were stopped, but subjects were followed for the next 52 weeks and seen in person on weeks 26, 52, and 68 (following randomization) for drinking history and other assessments.

If necessary, subjects were terminated from the treatment portion of the protocol, primarily for adverse events, serious clinical deterioration, or lack of interest. All subjects who left prematurely underwent an end-of-treatment evaluation and were encouraged to attend research followups.

Assessment

The assessment battery measured the following broad domains: (1) screening and inclusion/exclusion criteria; (2) history/physical, physiological, and laboratory assessments; (3) treatment-related expectancies; (4) drinking-related, psychological, and behavioral outcomes, predictors, mediators, and generalizability measures; and (5) therapy and medication adherence and therapy process measures. Subject compliance was tracked by several methods: attendance records to monitor behavioral intervention participation, counting pills from returned medication cards, and a timeline followback procedure to assess self-reported medication compliance.

Most measures were administered at baseline and again at one or more followup points. Measures considered to be particularly sensitive to subject reactivity (e.g., drinking self-report measures) were placed earlier in the battery. The primary followup assessments occurred at postrandomization weeks 8, 16, 26, 52, and 68. Within-treatment measures of drinking and craving were administered at weekly intervals or at each of the MM visits.

Caveats and Considerations

It is important to understand the conditions under which Medical Management and Combined Behavioral Intervention were delivered in the COMBINE trial. Therapy was conducted in the context of a structured research situation. Both of the manual-guided COMBINE treatments were administered by experienced therapists who had received specialized training in one of the two project interventions. Therapists closely followed the procedures outlined in the manuals. With few exceptions, all sessions were audiotaped to allow both local and project-wide clinical supervisors to observe therapists in action and provide session quality control. Therapists who deviated from protocol or demonstrated weakness in generic counseling skills were "redlined" for further training and monitoring. This manual was written for therapists who had similar training and supervision and may not affect participants the same way if it is given under different quality-control conditions.

Likewise, the manual was designed to standardize the delivery of the therapy within the particular context of the COMBINE project design. For example, all clients received their behavioral treatment(s) after undergoing an extensive baseline assessment battery. Before each therapy session, the client had a breath alcohol test to ensure sobriety. If the client tested positive for alcohol, the session was rescheduled, and arrangements were made to help the client get home safely. Therapists were prohibited from mixing other treatment approaches with the experimental intervention. All therapy was completed within 16 weeks of randomization.

Other standardized features of clinical trials that may also influence the effect of the therapy include inclusion/exclusion criteria, randomized assignment to treatment, and guidelines for dealing with clients who are late for treatment, fail to attend, or deteriorate clinically during the 16-week treatment period. Guidelines regulated and documented the type and amount of therapy the client could receive from sources other than COMBINE. The research and therapy components were kept separate, and all data collection was performed by trained research assistants who did not deliver treatment (although there is anecdotal evidence that some clients may not have grasped the distinctions among the different types of personnel with whom they came into contact).

Although the procedures and principles of the intervention are the result of careful development and are based on models validated in other studies, the COMBINE study and NIAAA staff make no claims or guarantees regarding the effectiveness of the treatments described herein. All manuals of this kind should be regarded as being under development and subject to ongoing improvement based on subsequent research and clinical experience. Information on the efficacy of this approach relative to other approaches and on the types of clients for whom it may be most useful will be available when study results are published, a process expected to begin in 2005. In the interim, it is our hope that the COMBINE treatment manuals will be useful tools for the community, as the Project MATCH therapy manuals have been. (The Project MATCH manuals, previously published by NIAAA, continue to be widely requested by researchers and clinicians from all sectors of the community.) The authors of the COMBINE manuals and NIAAA welcome feedback from users on their experiences with these newest treatment manuals.

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1. Introduction

1.1. Rationale for Medical Management (MM) Treatment

This manual serves as a standardized guide for delivering Medical Management (MM) treatment to patients with alcohol abuse and dependence. MM treatment was designed to be used in conjunction with prescribed medication and to be easily implemented by medically trained practitioners in nonspecialty settings in keeping with the national trend toward integrating substance abuse treatment into medical practice.

Patients who do not take prescribed medication are a common problem, regardless of their disorder. One focus of MM treatment is to help clinicians provide education, support, and strategies to ensure that their alcohol-dependent patients are medication compliant. Medication compliant means taking medications as prescribed. As the medical practitioner, it is important that you familiarize yourself with common reasons why patients skip doses or stop taking their medications (see Chapter 4, "Medication Compliance and Attendance"). This understanding will keep you vigilant in monitoring medication compliance and will assist you in helping patients overcome barriers to correctly following medication instructions.

MM treatment was developed as part of the NIAAA-supported COMBINE study to provide a basic form of clinical intervention supporting effective pharmacotherapy. Thus, medication information in this manual is specific to naltrexone and acamprosate, the two medications provided to patients in COMBINE. The treatment approach is generic, however, so it is possible to use it and substitute other medications and related information.

One of the central questions examined by researchers in the COMBINE study was to compare the effectiveness of pharmacotherapy, delivered in the context of a supportive intervention, such as MM treatment, to pharmacotherapy delivered with MM treatment that has been partnered with an intensive behavioral treatment—Combined Behavioral Intervention (CBI), which includes motivational interviewing, skill building, and detailed discussions of 12-step concepts. If MM treatment were to be delivered in another research or clinical context, modifications to MM treatment to incorporate more intensive techniques could be appropriate and should be considered.

For those interested in more details about COMBINE, see the ***COMBINE Study Fact Sheet*** (Form A–16) included in "Appendix A: Clinician Packet."

REFERENCE
Form A–16: COMBINE Study Fact Sheet

1.2. Treatment Overview

The goal of the MM intervention is to promote the patient's recovery from alcohol dependence.

You can help your patients meet this goal in the following four ways:

- Provide patients strategies for taking their medications and staying in treatment.
- Provide educational materials about alcohol dependence and pharmacotherapy.
- Support their efforts to change drinking habits.
- Make direct recommendations for changing drinking behaviors.

Follow your patients throughout treatment, providing expert assessment, support, and direct advice in their efforts to achieve recovery from alcohol dependence. When talking with your patients, appeal to their reason and common sense, particularly in relation to the overall goal of preserving or restoring their health. In expressing concern for your patients, it is important to be nonjudgmental. Always be friendly, supportive, and optimistic about their recovery.

Your initial MM session occurs after your patient has been evaluated and should last from 40 to 60 minutes. In this session, cover the following points:

- Review the results from his/her evaluation and address any medical concerns.
- Use the results from the evaluation to support the diagnosis of alcohol dependence, provide basic information about the disorder (including prognosis), and advise abstinence.
- Provide a rationale for and information about pharmacotherapy.
- Provide a rationale for evaluating medication compliance at each session.
- Use the patient's history of taking medication to establish an individualized plan that will ensure medication compliance.
- Encourage participation in mutual-support groups (e.g., AA, SMART Recovery).
- Provide pamphlets on alcohol dependence, medications, and mutual-support groups.
- Answer any questions or concerns about treatment.

In followup sessions, follow the procedures below:

- Perform a medical check on the patient's general functioning.
- Take a reading of the blood alcohol concentration (BAC).
- Take the patient's vital signs, and weigh the patient.
- Ask about medication side effects and concurrent medications.
- Perform a brief assessment of the patient's drinking.
- Monitor his/her medication compliance.
- Make recommendations for the patient to follow until the next visit.

These visits typically last about 15 to 25 minutes, though they can be as long as 30 minutes, depending on each patient's medical status, progress in maintaining recovery, and medication compliance between visits.

The treatment adherence checklists to use in the initial and followup sessions are in Appendix B, "Medical Management Training and Session Adherence Checklists." You can also use these checklists when you deliver MM or if you are monitoring adherence, by listening to audiotapes of the MM sessions.

1.3. Pitfalls to Avoid When Using MM Treatment in a Research Context

1.3a. Non–MM Treatment Therapeutic Strategies. Many professional therapies, such as those

listed below, use techniques and strategies that extend beyond the scope of MM treatment:

- Confrontational sessions
- Skills training approaches
- Client-centered counseling
- Family therapy.

Although these methods might complement MM treatment in a clinical setting, they are not part of the MM intervention per se, and most medical staff will not have training to deliver these methods. These approaches were not used by MM clinicians during the COMBINE project (see section 1.1, "Rationale").

1.3b. Nonabstinent Goals. Typically, you should encourage your patients to be abstinent throughout MM treatment if possible. This was also the case in the COMBINE project. Do not tell patients things such as, "Expect slips—they are a natural part of recovery," or "Some reduction in the amount you are drinking is an acceptable goal." However, when patients do drink during treatment, avoid expressing disapproval or disappointment. Praise any improvements or steps they make toward achieving recovery. If a patient does slip, reassure him/her that slips are common and are not signals he/she will not attain recovery.

1.4. Materials

"Appendix A: Clinician Packet" has forms that help you deliver MM treatment; "Appendix B: Medical Management Training and Session Adherence Checklists" has treatment adherence checklists for each session; and "Appendix C: Patient Packet" includes information for the patient to take home and review as necessary. The forms included in each appendix are listed below.

1.4a. Appendix A: Clinician Packet

To Be Used at the Initial MM Session

	Form
A–1	Clinician Report
A–2	Vital Signs and BAC
A–3	Concurrent Medications
A–4	Naltrexone Information Sheet: Clinician Version
A–5	Acamprosate Information Sheet: Clinician Version
A–6	Medication Instructions Summary
A–7	Modified SAFTEE
A–8	SAFTEE Guidelines: Part 1
A–9	SAFTEE Guidelines for Rating Severity of Adverse Events: Part 2
A–10	Menstrual Calendar
A–11	Serious Adverse Event Report
A–12	Serious Adverse Event Followup Report
A–13	Medication Compliance Plan
A–14	Pill Count
A–15	Day 3 Clinician Phone Contact

To Be Used at All MM Followup Sessions

	Form
A–2	Vital Signs and BAC
A–3	Concurrent Medications
A–7	Modified SAFTEE
A–8	SAFTEE Guidelines: Part 1
A–9	SAFTEE Guidelines for Rating Severity of Adverse Events: Part 2

Alcohol Education/Mutual-Support Groups

Form

C–7 Name and Location of AA Pamphlet Relevant to Pharmacotherapy

C–8 Listing of Local Mutual-Support Groups

2. Initial MM Session (40 to 60 minutes)

2.1. Overview of Initial Session

Review the following eight areas with the patient at the initial session:

1. Go over the results from the patient's intake evaluation. Address any medical concerns.
2. Explain the rationale, information, and prognosis on the patient's diagnosis of alcohol dependence. Show how the results from the evaluation support the diagnosis of alcohol dependence. Advise abstinence.
3. Give the rationale and information on medications.
4. Provide the rationale for evaluating medication compliance at each session.
5. Establish the patient's history of medication compliance, suggest strategies for enhancing compliance, and develop an individualized compliance plan.
6. Discuss the benefits of participating in mutual-support groups.
7. Offer pamphlets on alcohol dependence, medications, and mutual-support groups.
8. Solicit and answer the patient's questions or concerns about treatment.

2.2. Guidelines for Reviewing Each Area at the Initial Session

2.2a. Reviewing Results From Patient's Evaluation. You will meet with the patient for the first time after he/she has undergone the intake evaluation. Introduce yourself, describe your role in the treatment plan, and explain how frequently you expect to see the patient over the course of treatment. The forms described in this section are in "Appendix A: Clinician Packet."

If the patient has not had his/her BAC, vital signs, and weight taken, do so prior to giving him/her the first dose of medication. Record this information on ***Vital Signs and BAC*** (Form A–2). If the patient registers a positive

REFERENCE
Form A–2: Vital Signs and BAC

breathalyzer reading, postpone the initial MM treatment visit until he/she can provide a negative reading. However, you or another on-site clinician should explain why the visit will be postponed. If the reading is above the legal limit, make arrangements to have the patient escorted from the facility to another unit capable of retaining the patient, or contact a family member who can take him/her home. Observe the same procedures for the MM

treatment followup visits. (Note: some settings may permit the patient to continue the MM treatment visits as intended if his/her BAC reading is positive, as long as his/her blood alcohol concentration is extremely low.)

After introductions, begin the initial session by reviewing with the patient the results from the evaluation that support his/her diagnosis of alcohol dependence. Begin with the patient's medical status and move into his/her lifetime and current drinking behavior. This discussion will go more smoothly if you review the results of the patient's intake evaluation in a systematic format before you see him/her. The ***Clinician Report*** (Form A–1) is constructed so you can

REFERENCE
Form A–1: Clinician Report

assemble, then quickly review a summary of the patient's results. Record information from the measures listed below on this form prior to the initial session. (Note: It is important that you recognize the difference between this narrow-focused MM treatment report and broader-based reports, such as the one given with Motivational Enhancement Therapy.)

Below is a list of the information to be obtained at the intake evaluation that you should summarize on the ***Clinician Report:***

- Blood pressure, laboratory results (blood and urine), and medical problems identified on the physical exam
- Quantity/frequency of drinking in recent weeks (can use the Timeline Followback or Form–90 from COMBINE)[1]
- Self-report of alcohol-related problems (can use the Drinker Inventory of Consequences [DrInC] from COMBINE)
- Symptoms of alcohol dependence (obtained from a diagnostic interview).

2.2b. Relaying Feedback From the Clinician Report. This section provides suggestions for discussing with patients aspects of the ***Clinician Report;*** tailor your own discussions to your patient's particular situation and level of knowledge about the areas you are covering. Note that not all areas on the form are covered here.

Medical Information

The example below provides a suggestion for explaining to the patient his/her liver enzyme results:

CLINICIAN: Let's begin today by reviewing your physical health and then move on to talking about your drinking. First, let's review together your medical health, including the results of your blood and urine tests.

When we review your medical status, we pay particular attention to your blood tests because some of them tell us how your liver is working. This is what we look for in patients who we know are drinking heavily. Your liver is extremely important to your health. It is involved in producing energy, and it filters and neutralizes impurities and poisons in your bloodstream. Alcohol damages the liver by causing inflammation. In some cases, permanent scars can form, called cirrhosis. Prior to cirrhosis, physical changes in the liver caused by drinking begin as a leakage of chemicals called enzymes

[1] Form–90 is a series of instruments originally published in the Project MATCH manuals. For more information, see Miller, W.R. *Form 90: A Structured Assessment Interview for Drinking and Related Behaviors (Test Manual).* Project MATCH Monograph Series, Volume 5. DHHS Publication No. 96–4004. Bethesda, MD: Dept. of Health and Human Services,1996.

into the blood. When this happens, we see abnormally high values on these blood tests.

Your laboratory results showed the following (*show patient the results).*

(*If the patient's liver function tests are within normal ranges*) Your liver function tests show no significant elevations yet. Although normal results on these tests do not always guarantee that your liver is functioning normally, this is a positive sign that with treatment, you may be able to change your heavy alcohol drinking habits before you do any permanent damage to your body. A healthy liver will also help you make a quicker, more complete recovery.

(*If the patient's liver function tests are abnormal*) This elevated value in the abnormal range on one or more of these blood tests is likely reflecting unhealthy changes in your body that have resulted from your excessive use of alcohol and/or other drugs. It is possible that you can improve your medical status and return these values to normal ranges if you stop drinking. The longer you continue drinking, however, the more difficult it is to reverse the physical damage.

Consequences of Drinking

When reviewing the patient's drinking information, do not focus primarily on the patient's *quantity* of drinking, because some people can drink fairly heavily with few consequences and other people may have serious adverse consequences despite drinking amounts of alcohol that do not cause problems for other people. Since discussions of quantity and frequency may lead to fruitless debates with the patient about safe levels of drinking, focus more on *consequences* of drinking.

The example below provides a suggestion for discussing the consequences of the patient's drinking:

CLINICIAN: I see that you drink very heavily when you drink, and that you have reported several things that are related to having a serious problem with alcohol, such as getting DUIs.

***(If the patient is a binge drinker who may abstain for days or weeks and then drink large amounts)* Although you report going days without drinking, you drink a great deal when you do drink. People who drink this much at one time have what we call high tolerance for alcohol. This is a warning sign, because it means that you have a high blood alcohol level and don't feel drunk, sick, or sleepy—any of which would ordinarily lead you to stop drinking for the night. You need to know that you are not protected like most people from being harmed by drinking; rather, damage is more likely.**

Review the responses on the DrInC in advance and select up to three items that the patient has endorsed for the ***Clinician Report.*** Note that some people will only report a single adverse consequence from drinking, but the consequence may be quite serious (e.g., an arrest for DUI or significant liver disease). In any case, discuss with the patient, as shown in the example below.

CLINICIAN: I see you reported several things that we know are related to having a serious problem with alcohol, such as DUIs. We refer to these experiences as "negative consequences"

because they are harmful events that happened as a direct result of drinking alcohol. Taken together, we use these events as warning signs that drinking for you is destructive to your health and/or well-being.

Diagnostic Information

Inform the patient that according to the diagnostic assessment, he/she has *X* number of symptoms of alcohol dependence. Review each of the symptoms reported with the patient. Provide basic information on what is currently known about alcohol and the disorder. Emphasize that alcohol may be a toxin for some people, and unless the patient stops drinking, the problems he/she has already experienced will continue and new, additional problems are likely to occur in the future, such as hypertension, cancer, heart and brain disease, or decreased life expectancy.

In a nonjudgmental way, emphasize the importance of abstinence. Tell the patient that although any reductions in the amount of his/her drinking will help, the only way to be sure that alcohol is not going to cause any further damage is to stop drinking alcohol entirely.

The example below provides suggestions for discussing the patient's diagnostic information and recommending abstinence:

CLINICIAN: Let's look at the facts. The results of your evaluation point to a clear diagnosis of alcohol dependence. Here is the list of your symptoms: you have a history of excessive drinking, likely coupled with alcohol-related problems; you have made previous unsuccessful attempts to cut down or quit drinking; and you drink more than you intend to drink on a regular basis. Therefore, I strongly suggest that you stop drinking altogether. Let me explain. Alcohol may be a toxin to the body. Consistent heavy alcohol drinking puts you at risk for physical harm and negative social consequences. If you have difficulties in reducing drinking or stopping entirely, this is not a sign of weakness, immoral self-indulgence, or deviance. If your goal is only to "cut down" your amount of drinking, there is a good probability that you will return to heavy drinking. If you continue to drink, your dependence will get worse and it will be even harder to stop. Given your current condition, I cannot guarantee you that there is a level of drinking that will cause you no harm.

That's why abstinence is the safest choice for you. If you stop drinking, you can be sure that you won't have any more problems related to drinking. After some time of no drinking, your ability to think, complete tasks, and get along with others will all likely improve. When you are abstinent, you may discover things about yourself that you have forgotten.

If it is apparent that the patient is unwilling or unable to commit to abstinence, offer a trial of abstinence. The example below provides a suggestion of how to mention this:

CLINICIAN: If you are thinking that lifelong abstinence is too difficult of a goal for you to commit to right now, you could try a brief period of abstinence of say, a month, to find out what it's like to live without alcohol. Would you be willing to try this out? *(You could also suggest other reasons for abstinence, such as experiencing a change, building some*

confidence, or pleasing a spouse or other family members.)

2.2c. Providing Rationale and Information on Medications. Begin by asking your patient what he/she already knows about the medications that will be prescribed, and if necessary, clear up any myths or misinformation. Tell the patient the purpose of the medications being prescribed. Distinguish them from medications used for detoxification. In particular, distinguish these medications from disulfiram (Antabuse), because your patient may have heard that when combined with alcohol, disulfiram makes the user violently sick, and he/she may have negative feelings or images about taking medications to treat alcohol dependence.

Review the ***Concurrent Medications*** form (Form A–3) that the patient completed during the medical exam prior to seeing you at the initial MM session, and inquire about medication that he/she might have started since completing that form. Use the ***Modified SAFTEE*** form (Form A–7) to evaluate the patient's status of current somatic complaints.

Appendix A includes medication information sheets about the medications you will be prescribing—***Naltrexone Information Sheet: Clinician Version*** (Form A–4) and ***Acamprosate Information Sheet: Clinician Version*** (Form A–5). Review with the patient information about these medications, focusing on the following four categories:

1. Efficacy
2. Proposed mechanism of action
3. Potential side effects
4. Dosing.

REFERENCE
Form A–3: Concurrent Medications
Form A–7: Modified SAFTEE
Form A–4: Naltrexone Information Sheet: Clinician Version
Form A–5: Acamprosate Information Sheet: Clinician Version

Appendix C has patient versions of these forms—Forms C–1 and C–2; give them to the patient to review and take home.

Tell the patient that if he/she experiences side effects, there are things he/she can try to manage them before calling you. Go over the ***Patient Instructions for Managing Side Effects*** (Form C–5) and point out the ways to cope with adverse events such as nausea, vomiting, and diarrhea. Advise the patient also to contact you if he/she is concerned with any symptoms in between visits.

REFERENCE
Form C–1 Naltrexone Information Sheet: Patient Version
Form C–2 Acamprosate Information Sheet: Patient Version
Form C–5: Patient Instructions for Managing Side Effects

Show the patient the blister card containing the pills and review the dosing regimen, storage of the medication, and return of the blister cards, empty or containing unused pills. Tell the patient what to do if he/she skips a dose, loses a blister card, or runs out of medications before returning for the next visit, and review what procedures to follow in case of an emergency. Review the information on the ***Medication Instructions Summary*** (Form A–6) while the patient looks over the patient version, ***Medication Instructions Summary*** (Form C–3) as well as the ***Quick Reference Medication Information Grid*** (Form C–4), and answer any questions.

REFERENCE
Form A–6: Medication Instructions Summary
Form C–3: Medication Instructions Summary
Form C–4: Quick Reference Medication Information Grid

Observe the patient taking the morning dose of medication no matter what time of day the session takes place. Do this only at the initial session.

REFERENCE
Form C–6: Sample Medical Emergency Card

If the patient is taking naltrexone (as in the COMBINE study), give him/her two emergency cards (one for his/her wallet and one for a significant other) (***Sample Medical Emergency Card,*** Form C–6). The emergency card is designed to inform medical personnel if the patient seeks medical treatment elsewhere; it states that the patient is taking naltrexone (or may be, depending on the situation) and suggests a treatment plan for naltrexone users. The card includes space on the back for information including the date treatment began and will end, name of medical clinician, and a 24-hour emergency telephone contact.

Emphasize that it takes time for the medications to be effective. Remind the patient that some people feel the medication's effectiveness more slowly than others and that it is important to keep taking the medications as prescribed and to continue trying to maintain abstinence. Encourage the patient's use by telling him/her that the medications are thought to increase abstinence by improving his/her ability to resist drinking, making it easier to choose not to drink.

2.2d. Providing Rationale and Information on Medication Compliance. It is vital that your patient comply with taking the medication as you prescribe it so that you can evaluate how effective the medication is and how the patient is able to tolerate it.

Explain to the patient the importance of consistently taking the medications as prescribed. For example, you could refer to research that showed that subjects who complied with their prescribed naltrexone doses were able to reduce their drinking more than subjects who did not do so (see Pettinati et al. *Journal of Addictive Diseases,* 2000, 19:71–83).

It could help prevent noncompliance if you educate your patient about alcohol dependence, the nature of the medications, and the time course of the medication effects (e.g., the fact that they do not work immediately).

The example below suggests a way to explain the expected time course of the medication's effects:

> **CLINICIAN: For you to get the benefit of these medications to support your treatment goal of abstinence, you must take them consistently and as prescribed. It can take several days to achieve a steady therapeutic level in your blood. And once you have the right amount of medication in your blood, it can still take some time for the medications to have their full effect on helping you change your drinking behaviors.**
>
> **The medications can only help you to maintain abstinence if you take them consistently, as you would with blood pressure medicine or insulin. These medications do not work like aspirin does, which you take only when you feel you need it.**

2.2e. Designing a Patient-Tailored Medication Compliance Plan. Follow the format outlined in the ***Medication Compliance Plan*** (Form A–13) to design a concrete plan for regularly

REFERENCE
Form A–13: Medication Compliance Plan

taking medications to minimize the number of missed doses. This section refers to different areas of this form.

Examine Patient's History of Medication-Taking Practices

Ask the questions on Form A–13 or paraphrase them, as suggested below:

- Have you ever been asked or tried on your own to take pills on a daily basis?
- Have you ever been asked or tried on your own to take four or more pills at one time on a daily basis?
- Have you ever been asked or tried on your own to take pills in the evening or at bedtime on a daily basis?
- Have you ever taken pills from blister cards?
- Do you typically carry your pills with you?
- Have you ever been asked to take prescribed medications until all the pills are gone?

Determine from the patient's answers if he/she had enough opportunities in the past to take several medications at once, in both the morning and evening, and if he/she has a good record of consistently following this regimen.

If you find that the patient has been successful in remembering mundane but necessary day-to-day pill-taking, ask about the strategies he/she found useful for keeping up such a record. If possible, use these routine strategies for taking pills in formulating the ***Medication Compliance Plan*** for adding new medications (see more details about this in "Pill-Taking Strategies," below).

If you find that the patient has not had enough experience taking medication on a regular basis or has a record of taking medications inconsistently, skipping doses, or quitting medication early, discuss examples of the common reasons for medication noncompliance, such as those listed here. This may prompt the patient to say that this could happen to him/her. (See Chapter 4, "Medication Compliance and Treatment Session Attendance," for suggested techniques for dealing with each of these reasons for medication noncompliance.)

Common Reasons for Pill Noncompliance

The list below is similar to the one on the ***Medication Compliance Plan:***

- Forgets to take medications
  - —misplaces one or more doses
  - —misplaces blister card
- Reports troublesome side effects from the medications
- Believes he/she is taking placebo
- Has misconceptions about what the medications will or will not do
  - —expects instant change in drinking
  - —expects elimination of pleasure
- Is uneasy about taking medications
  - —has never liked taking pills, even aspirin
  - —is convinced by members of an AA mutual-support group to stop medications
- Sometimes just wants to drink or "get high"
- Refuses to accept a diagnosis of alcohol dependence
  - —disagrees that he/she has a disorder or that it is serious enough to warrant taking medications
  - —believes he/she is "cured" and no longer needs medications.

Pill-Taking Strategies

If your patient has been successful in taking pills in the past, solicit strategies he/she used to maintain compliance, and write them on the ***Medication Compliance Plan*** (Form A–13).

If your patient has never had a successful routine for pill-taking, assist him/her in tailoring an individualized plan for taking the medication as prescribed. Prompt the patient to think of ideas, or suggest some of the following:

- Take the medications while brushing teeth in the morning and evening.
- Take medications with morning coffee or vitamins.
- Take medications while watching a particular TV show every morning or evening.
- Involve others to witness him/her taking the pills or to administer the medications.
- Place notes or other reminders in prominent places.
- Wear an alarm watch that rings when it is time to take the pills.

Write these suggestions in section II of the ***Medication Compliance Plan*** form, "Personalized Medication Compliance Plan."

Explain that you will routinely go over the success of this plan at the beginning of each visit. Tell the patient to bring back the blister card(s) at each visit because you will use pill counts of the returned blister card(s) to verify his/her medication compliance.

Be sure to tell the patient that if his/her plan proves unsuccessful at any point, you will help revise the plan to develop one he/she feels more comfortable following.

2.2f. Reviewing Benefits of Participating in Mutual-Support Groups. Describe mutual-support groups, such as AA and SMART Recovery, as a way that many people with alcohol dependence find they can secure the alcohol-free lifestyle they know they need to adopt. Mutual-support groups allow the patient to quickly acquire a social network of friends who have found ways of living their lives without alcohol. Mention that the medication treatment is time-limited and that many patients find the importance of mutual-support groups increases when they stop taking the medications.

Let the patient know that he/she is not required to attend a mutual-support group to participate in this treatment. However, tell him/her that it is important for you to keep track of whether or not he/she has attended mutual-support group meetings, so you will be asking about it from time to time. Unless the patient is adamantly opposed, provide a list of telephone numbers, times, and locations of meetings of local mutual-support groups (Form C–8). Choose a location or a specific meeting from those listed and suggest that the patient just try it out and report back later on.

Provide the patient with pamphlets on mutual-support groups. An example of a mutual-support group pamphlet is listed in Appendix C. Feel free to substitute pamphlets available in your region.

The official position of AA is that members should take medications prescribed in good faith. Nonetheless, some AA members (as

REFERENCE
Form C–8: Listing of Local Mutual-Support Groups
Form C–7: Name and Location of AA Pamphlet Relevant to Pharmacotherapy

opposed to the AA organization) may discourage any use of medications to stop drinking. Prepare the patient to cope with some mutual-support group members' objections to psychotropic medications.

The examples below suggest ways to discuss aspects of AA that your patient may find problematic:

> **CLINICIAN:** ***(If the patient is reluctant to attend a meeting for the first time)*** **Attending a mutual-support group is an excellent way of meeting people who don't drink. There are also people there who have been through what you are about to go through and may be able to help you with the hardest parts in ways you can't imagine at this time. Would you be willing to try just one meeting before our next session? Next time we can talk about what you thought of it.**
>
> ***(If the patient has attended a meeting before and was uncomfortable)*** **I know you are saying that your experiences in the past with AA meetings have been disappointing. Who makes up the group really matters, and not all groups are alike. It is likely that you will need to try out several groups before finding one that feels right—kind of like looking for a new restaurant. Would you be willing to let me suggest a group for you to start with? Try the group out and tell me at our next session what you did or did not like about it. Sometimes talking out the problem can help pinpoint the type of group you might feel more comfortable in.**
>
> ***(If the patient is concerned about members disapproving of his/her medications)*** **Some members of mutual-support groups believe that it isn't possible to get over an addiction by taking a pill. If you choose to reveal at a meeting that you are taking medications, you may run into a member who objects and tries to discourage you or other members from taking medications. It is important to remember, however, that the medications you are taking as part of your treatment are tools you will use in your efforts not to drink. They have been shown to help others stop drinking and remain abstinent. Also, these medications are not addicting. And the official policy of AA is supportive of people taking nonaddicting medications prescribed by a doctor. This policy is described in this pamphlet, "The AA Member—Medications and Other Drugs."**

2.2g. Concluding the Initial Session. Follow the steps below to conclude the initial session:

- Summarize the diagnosis and recommendation for abstinence.
- Summarize the dosage regimen the patient will follow until the next visit.
- Remind the patient that he/she is to bring back the blister card at the next visit.
- Ask about remaining questions or concerns.
- Schedule the next visit.
- Tell the patient that in 3 days, you will contact him/her.

3. Followup Sessions (15 to 25 minutes)

3.1. Overview

At each followup session, make these three assessments (they need not be made in this order), explained in detail in the sections below:

1. Perform a brief check on the patient's medical status, including general functioning, BAC, vital signs, weight, concurrent medications, laboratory data (when applicable), medication side effects, and medication compliance.
2. Ask about the patient's drinking status.
3. Make recommendations for the upcoming week(s).

The length of the visit depends on the patient's progress, side effects, and compliance with prescribed medications. Most visits will range from 15 to 25 minutes, but they can be as long as 30 minutes.

3.2. Medical Status, Medication Safety, and Compliance (5 to 10 minutes)

Check out the following areas:

- Take the patient's BAC, vital signs, and weight if this was not done just before this visit, and record the results on the ***Vital Signs and BAC*** form (Form A–2).
- Ask the patient if he/she experienced any medication side effects or adverse events, and inquire if he/she has taken any concurrent medications.
- If the patient has had laboratory tests performed, review the results with him/her; reinforce the concept that improvements in drinking and/or laboratory data are linked with the patient's decision to remain abstinent or drink less.
- Go over the events listed on the ***Modified SAFTEE*** form (Form A–7) to see if the patient has experienced any of these adverse effects (if necessary, use the ***SAFTEE Guidelines, Parts 1 and 2*** [Forms A–8 and A–9] for more information about the events listed on Form A–7).
- If the patient is female and of childbearing potential, inquire about regular use of birth control and her menstrual cycle, and complete the ***Menstrual Calendar*** (Form A–10).
- Use the ***Concurrent Medications*** form (Form A–3) to record any medications the patient is taking in addition to the target pharmacotherapy, including

REFERENCE
Form A–2: Vital Signs and BAC
Form A–7: Modified SAFTEE
Form A–10: Menstrual Calendar
Form A–3: Concurrent Medications
Form A–11: Serious Adverse Event Report

over-the-counter medications and herbal supplements.

- Ask the patient if he/she has any questions or concerns about the pharmacotherapy.
- If the patient describes a serious adverse event, complete the ***Serious Adverse Event Report*** (Form A–11) and process the reporting of these following U.S. Food and Drug Administration (FDA) guidelines and, in the case of research studies, Institutional Review Board (IRB) guidelines.

3.2a. Pill-Taking. If the patient brought the blister card, inspect it for any evidence of missed medications. Even if there are no pills on the card, inquire if he/she took all medications following the prescribed schedule because there could be other reasons for an empty blister card that would indicate noncompliance. If so, you may need to address this in the session.

Record the patient's pill-taking on the ***Pill Count*** sheet (Form A–14). To record accurate information on the ***Pill Count*** sheet, list the number of pills you prescribed to the patient. If

REFERENCE
Form A–14: Pill Count

the patient did not return the blister card, check off "No" in the "Patient Report" section. If the patient brings in the blister card at a later visit, change the "Pills taken" information on the sheet and check "Yes" in the "Patient Report" section.

If the patient took the medication as prescribed, praise him/her for adhering to the treatment regimen. If he/she skipped any doses, inquire about the reasons. Most patients say that they skipped a dose because they forgot to take the medication. Although this is true for some patients unaccustomed to taking medication, some patients say this because it is the easiest reason to explain. If the patient tells you that he/she "forgot" at other sessions, probe further into the circumstances (see Chapter 4, "Medication Compliance and Treatment Session Attendance," for other common reasons for not taking pills). Try to determine why the patient skips his/her doses so that you can provide helpful advice for complying. For example, if the patient tells you he/she didn't take the medication because he/she was drinking, determine if the patient skipped the medications and then drank or if he/she drank first and then missed the dose. If the latter, determine if the patient drank and just forgot to take the medications or if he/she decided to skip a dose after drinking because he/she didn't want to mix alcohol and the medications. Point out that regardless of the specifics, the patient's drinking was related to missing doses.

3.3. Drinking Status (5 to 10 minutes)

Ask the patient about his/her drinking status since the last visit as well as about illegal drug use and attendance at mutual-support groups. In this part of the session, allow for some open-ended discussion of the patient's current concerns about drinking or the medications. Reward any positive steps the patient has made toward achieving recovery. Continue to provide the patient with optimism that he/she can recover.

The examples below suggest questions to ask about different aspects of the patient's drinking status:

CLINICIAN: How have you been since our last visit?

- **What was difficult?**
- **What went well?**
- **How well were you able to keep from drinking?**
- ***(If the patient did drink)*** **What were the circumstances? Remember,**

change occurs in small steps; keep trying, don't get discouraged.

- **How great was your desire to drink?**
- **(*If the patient did drink but found his/her desire to drink was greatly diminished)* Reductions in your desire to drink may be the first sign of change for you.**
- **(*If the patient's desire to drink was strong but he/she didn't drink)* Congratulations on choosing not to drink when you really wanted to. You have taken an important step toward your recovery!**
- **(*If the patient didn't drink)* Did you observe an increase in any other problems (e.g., illegal drug use)?**
- **(*If the patient continued with abstinence)* Congratulations for staying abstinent. You are demonstrating your determination to change. You are making great progress toward your recovery!**

If your patient is also receiving concurrent therapy, provide as much support as possible. Ask if he/she is attending the therapy sessions and if there are any practical problems such as coordinating the schedule of visits so the patient can attend both treatments. If this is a problem, work with the patient to ensure he/she can continue to attend both types of treatment.

3.4. Recommendations/ Troubleshooting for the Four Possible Outcomes (5 to 10 minutes)

The results of the brief assessments described in sections 3.2 and 3.3 dictate how you should spend the remaining time in the session. There are four possible outcomes: the patient is not drinking and is medication compliant; the patient is drinking but is medication compliant; the patient is not drinking and is medication noncompliant; and the patient is drinking and is medication noncompliant. The scenarios below describe ways to handle each outcome.

3.4a. Scenario 1: The Patient Is Not Drinking and Is Medication Compliant. Many patients will take the medications faithfully and discontinue drinking. Some will be compliant early in treatment; others will become compliant midtreatment; some will not reach this point until treatment is almost over. When the patient has achieved this outcome, use the following guidelines:

- Reinforce the patient's ability to follow advice and stick to the plan. Discuss how most patients have trouble achieving abstinence and being medication compliant. Ask the patient to tell you specifically how he/she did so well.
- Address the common but incorrect belief that the patient can stop the medication compliance plan you constructed together at the initial session as soon as he/she feels successful in treatment. Focus on the fact that if the patient completes treatment as prescribed, it may better ensure his/her continued recovery after treatment is over. Explain that even when things have been going well for some time, his/her sessions with you serve as "booster shots" or extra insurance that his/her successful compliance and response to treatment can continue past formal treatment.
- Review the benefits of abstinence in general terms (e.g., improved health, fewer drinking-related problems) and the benefits of the medications.

- Finish the session with positive, supportive statements such as, "It sounds like things are going well. Keep up the good work!"

3.4b. Scenario 2: The Patient Is Drinking but Is Medication Compliant. This is one of the most difficult situations. It can occur early in treatment, at midtreatment, or at the end of treatment. If your client is in this situation early in the treatment process, encourage him/her by saying that the medication has not had a chance to work fully yet. This statement is not effective for patients who start drinking later in treatment.

Encourage these patients to go to mutual-support groups such as Alcoholics Anonymous and SMART Recovery. Although some patients will inform you early on that they have no intention of attending these meetings because of previous negative experiences or a fear of groups, encourage them to try these groups by stressing that a different type of group could be helpful (e.g., going to SMART Recovery instead of AA or attending smaller AA groups, same-sex AA groups, or AA groups in a different location).

The following is a list of additional strategies. Note that these are responses that a primary care clinician (not necessarily an alcoholism treatment specialist) would likely employ in such a situation.

- Review with the patient the data on his/her ***Clinician Report*** from the initial MM session to remind him/her why he/she originally sought treatment.
- Review the benefits of abstinence in general terms (e.g., improved health, fewer drinking-related problems) and the benefits of the medications. Encourage the patient to give abstinence a chance. Tell him/her you know that starting the process of abstaining from alcohol is the most difficult time but that if he/she can get the process started, it should get easier as time goes by.
- Praise any small steps the patient has taken toward abstinence and/or reductions in desire for alcohol. Reassure your patient that recovery is a gradual process and that occasional returns to drinking sometimes occur along the way.
- Review the benefits of any other aspects of the treatment course helpful to maintaining abstinence that the patient seems reluctant to try.
- If the situation occurs early in treatment, remind the patient that the medications work slowly and may not have begun to yield their full effect on reducing drinking.
- If the patient appeals to you for advice on how to become abstinent, find out if he/she has been drinking at home or at a bar or another regular place. If at home, encourage the patient to get the alcohol out of the house. If at a bar or with specific people, suggest not associating with drinking buddies and not going to bars.
- Ask if there is a particular time of the day that the patient drinks. If so, suggest that he/she find some other activity to distract him/her at that time.

3.4c. Scenario 3: The Patient Is Not Drinking but Is Medication Noncompliant. Some patients will discontinue drinking but report difficulties in routinely taking the medications. This can occur early in treatment, at midtreatment, or at the end of treatment. At the point when this happens, do the following:

- Congratulate the patient for not drinking.
- Review the benefits of abstinence in general terms (e.g., improved health, fewer

drinking-related problems) and the benefits of the medications.

- Probe further about why the patient is not taking medications regularly, because this is something you can help the patient change, such as if the noncompliance is related to side effects.
- Tell the patient that he/she may significantly improve his/her chances for sustained improvement by taking the medications.
- Revise and reconstruct the ***Medication Compliance Plan.***

3.4d. Scenario 4: The Patient Is Drinking and Is Medication Noncompliant. Some patients who continue drinking will also frequently report difficulties in routinely taking the medications. This can occur early in treatment, at midtreatment, or at the end of treatment. At the point when this happens, do the following:

- Review the benefits of abstinence in general terms (e.g., improved health, fewer drinking-related problems) and the benefits of the medications. Encourage the patient to give abstinence a chance. Say that you know that beginning the process of abstaining from alcohol is the most difficult time but if he/she can get the process started, it should get easier as time goes by.
- Encourage the patient to give the treatment a chance.
- Explain that although it is very difficult to give up drinking, it is a lot easier to routinely take medications as prescribed. To this end, go over the following:
    - Briefly evaluate reasons that the patient failed to comply with taking medications.
    - Review the common reasons why people fail to regularly take their medications.
    - Reconstruct the ***Medication Compliance Plan*** with the patient and add new ways to circumvent obstacles to medication compliance.

If your review reveals that the patient is no longer motivated to stop or reduce drinking, follow these steps:

- Remind the patient of the specific reasons for which he/she sought treatment (as discussed in the initial session).
- Review the information you gathered about consequences of the patient's recent drinking behavior prior to the initial session.
- Repeat the points you made in the initial session about the general benefits of abstinence.
- Review the benefits of attending as many mutual-help group meetings as possible to maintain abstinence. If the patient had negative experiences before, suggest a different type of group (non–12-step instead of 12-step meeting, and/or a different type of AA meeting [e.g., same-sex, smaller]).
- Find out if the patient has been drinking at home or at a bar or another regular place. If at home, encourage the patient to get the alcohol out of the house. If at a bar or with specific people, suggest not associating with drinking buddies and not going to bars.
- Ask if there is a particular time of the day that the patient drinks. If so, suggest finding some other activity to distract him/her at that time.

- Review the benefits of any other aspects of the treatment course helpful to maintaining abstinence that the patient seems reluctant to try.

3.5. Family Education/ Social Service Referrals

Feel free to encourage the patient to bring a family member or significant other to an MM session to ask questions and discuss medication and/or treatment issues. Depending on the patient's relationship with his/her significant other, this person may help the patient be compliant with MM treatment principles. For example, the patient may benefit from a companion who will remind him/her to take medications and attend MM treatment visits or who will accompany him/her to AA or other kinds of mutual-support group meetings. This session may be up to 15 minutes longer than a normal session.

During the course of treatment, a patient may tell you about a problem such as loss of a place to live, unemployment, or lack of health care. If such a situation arises, make referrals to the appropriate social service agencies as you would likely do in your clinical practice.

3.6. Emergency Crisis Intervention

If your involvement in crisis intervention exceeds two sessions beyond those planned for the patient's MM treatment, it is likely that his/her urgent needs require more attention than MM treatment alone. Use your clinical judgment to determine what action is warranted and whether you should refer him/her for more intensive treatment.

If at any time you feel that the immediate welfare and safety of the patient or another person is in jeopardy (e.g., impending relapse, the patient is acutely suicidal or violent), intervene immediately and appropriately for the protection of those involved.

3.7. Psychosocial Issues

If the patient is concurrently receiving therapy and brings up psychosocial issues at the MM treatment sessions, refer him/her to his/her therapist. If the patient is receiving psychosocial intervention through the MM treatment sessions only, encourage him/her to consider seeing a therapist; start attending AA meetings or, if he/she is attending AA meetings, increase the number of meetings he/she attends; or seek other support mechanisms (e.g., family, friends, minister).

3.8. If Patients Request Additional Treatment

Use MM treatment strategies for dealing with problematic patients, such as suggesting they attend more AA or other kinds of mutual-support group meetings. If your patient requests additional formal help, advise him/her that it is not uncommon for ancillary problems such as marital or parenting issues to arise during the course of treatment, and he/she may eventually resolve or reduce these problems if he/she maintains abstinence. Tell him/her that you will review these ancillary matters again at the end of MM treatment. If the patient is struggling with problems outside the scope of the MM treatment intervention, refer him/her to other formal treatment(s). This can help provide the necessary foundation to support ongoing abstinence.

Address clinical deterioration immediately. Refer the patient to a more intensive, structured treatment program.

3.9. Preparing for the Final MM Treatment Session

As soon as you feel certain that you have effectively involved the patient in the treatment and that he/she has had several productive sessions (this usually happens after six to seven visits), you and your patient need to begin anticipating what will occur at the end of the MM treatment course. Well before the last MM visit, start to plan with the patient how he/she will establish an effective long-term maintenance treatment plan.

4. Medication Compliance and Treatment Session Attendance

4.1. Strategies for Handling Medication Noncompliance

This section reviews the most common reasons for medication noncompliance, as listed on the ***Medication Compliance Plan*** (Form A–13), Part B, "Review Common Reasons for Pill Noncompliance." These reasons rank from the topics that are the easiest to discuss with your patient to the topics that are the most difficult. (Note that the reasons are *not* in order of those most frequently identified with noncompliance.)

REFERENCE
Form A–13: Medication Compliance Plan

4.1a. Forgets to Take or Loses Medications. Even people with life-threatening diseases often forget to take their medications. It is not unusual for people to be distracted by other things in their lives and to either forget to take a dose of medication or forget whether they have already taken it. There are ways to combat forgetfulness, but do not assume that patients will develop these strategies on their own. Once you have established that your patient is actually forgetting, not making excuses to avoid side effects or intentionally not taking a dose, tell him/her about the following ways to incorporate the treatment medications into a preexisting routine:

- Take the medications when brushing teeth in the morning and evening.
- Take medications with morning coffee or vitamins.
- Take medications during a favorite morning and evening TV show.
- Involve others to witness him/her taking the pills or to administer the medications.
- Place notes or other reminders in prominent places such as on a bedside table or bathroom mirror.
- Wear an alarm watch that rings when it is time to take the pills.

If the patient loses or misplaces part of a dose, instruct him/her to take a pill from the extra medication doses if provided. If the patient loses an entire blister card but has additional medication cards available, instruct him/her to start with the appropriate day and time of day (morning or evening) using the next numbered medication card. If the patient has no more blister cards, inform him/her to call you or your staff immediately.

4.1b. Worries About Side Effects. Although it seems logical to assume that the most frequent reason people stop taking their medications is because of side effects, in fact, most of the patients reporting side effects with naltrexone or acamprosate are not the ones who drop out of treatment. This is not to say that side effects are unimportant—but if you explain them properly so the patient has confidence in your ability to manage them, this can greatly improve compliance.

Because most patients believe that the only way to stop unpleasant side effects is to stop taking medications, let your patient know in advance that there are several other strategies he/she can try for reducing side effects as long as he/she keeps you fully informed of what he/she is experiencing. Remind the patient about the ***Patient Instructions for Managing Side Effects*** handout (Form C–5) you gave him/her at the initial session, and provide another copy if necessary. Try the following steps:

REFERENCE
Form C–5: Patient Instructions for Managing Side Effects
Form A–15: Day 3 Clinician Phone Contact

- Inform the patient that most side effects are transient and with proper management will likely dissipate.
- Tell the patient that if he/she keeps you informed about side effects and the level of discomfort, you will adjust the dosage. This adjustment could be in the form of a temporary dose reduction.
- Let the patient know that most people taking these particular medications (acamprosate and/or naltrexone) will not experience any side effects at all.

If your patient is concerned that he/she is not taking enough medication, tell him/her to mention this so you can discuss it. It is a good idea in the first week to call the patient between visits to check on his/her status, both in taking the medication and determining if he/she is experiencing any side effects. Use the ***Day 3 Clinician Phone Contact*** sheet (Form A–15) to document this phone contact.

Remember that for some patients, it may be important to determine whether reported side effects are actually linked to the medications or whether they are caused by other factors in the patients' lives. For example, many patients who have just quit drinking will predictably experience anxiety or sleep or mood disturbances, but they might feel that these discomforts are side effects of the medications they are taking. If you look at the patient's overall situation and help him/her find alternate explanations for what he/she is feeling, it is likely that the patient will continue with medications instead of discontinuing treatment.

Discuss with the patient the severity and "annoyance" of the side effects. One patient may find a side effect to be unbearable that another finds to be simply bothersome. Talk through the pros and cons of continuing medications. Ask the patient directly about weighing the impact of the side effects on his/her life against the impact of a potential relapse. As always, avoid being accusatory or creating the impression that you want the patient to take medications at all costs. However, you can be helpful in assisting the patient to find reasons to continue treatment, when appropriate.

4.1c. Believes He/She Is Taking Placebo (for patients who are enrolled in research trials). If a patient is concerned that he/she is taking a placebo and not the active medications, it is probable that he/she will stop taking the pills. Therefore, routinely (i.e., monthly) ask the patient to "guess" if he/she is taking the active medications or placebo so that you will know what he/she is thinking. If the patient guesses placebo, explore why and address the reasons in the same session or you may lose the patient. Typically, the patient will relate his/her perception to the fact that he/she is still drinking or dramatically craving alcohol. Therefore, it is important to emphasize that the medications' effectiveness takes some time to develop and that in some patients, the medications work more slowly. Regardless of what the patient guesses, if he/she is not reporting side effects, he/she may be silently (or not so silently)

questioning what he/she is taking. If the patient has not reported any side effects, be sure to say that the absence of side effects does not mean that he/she is taking a placebo. Explain that many patients taking acamprosate and many patients taking naltrexone report no side effects at all. Restate that it is important to keep taking the medications as prescribed and to continue trying to achieve full recovery.

4.1d. Has Misinformation About Medications. Medication noncompliance can also occur when patients have mistaken beliefs about what the medications are supposed to do. For example, people starting on antidepressants may quickly decide that the pills are worthless if they haven't been educated to the fact that it will take 10 days or more to begin to see any improvement.

Because the primary drug effect associated with naltrexone and acamprosate is an absence (e.g., a reduction in craving, a reduction of desire to drink more if one slips and has a drink), it may be very difficult for patients to know if the medications are having a therapeutic effect, particularly if they experience no side effects and "feel nothing" when they take the medications. To combat this, inform patients that they may not know when the medication has taken effect, but over time, they will see a change in their drinking behaviors. Patients with alcohol dependence are particularly prone to wanting instant effects from their medications; therefore, warn them that neither naltrexone nor acamprosate will be like this. Discuss their expectations thoroughly so that you know what their beliefs are, and correct mistaken ideas about what the medications will and will not do.

Some patients might refuse or stop taking naltrexone because they fear that it will prevent them from experiencing any positive feelings or natural "highs." Explain that although it is true that naltrexone can sometimes block "runner's high" and the high experienced by some people after eating spicy foods, it certainly does not eliminate pleasure in most people. The brain is much more sophisticated than this—it has at least three different systems for positive reinforcement, and only one of them is opiate mediated; this is the one naltrexone has an effect on. Discuss these issues openly and honestly with your patients; they are much more likely to be treatment compliant if they know you are not trying to take away their fun in life and that you respect the natural human desire for pleasure.

4.1e. Has Never Liked Taking Pills. Some patients are noncompliant because they are not comfortable with taking any medications at all, even aspirin. Try to address this type of concern proactively by reiterating the rationale of why the medications may be helpful in achieving recovery from alcohol dependence.

Give the patient the patient version of the ***Naltrexone*** and ***Acamprosate Information Sheets*** (Forms C–1 and C–2) and the ***Quick Reference Medication Information Grid*** (Form C–4). Encourage the patient to ask you any questions he/she might have that are still unanswered. (See Chapter 5, "Answers to Frequently Asked Medication Questions.")

Some patients may feel uneasy about taking medications because they are influenced by the views held by members of a mutual-support group they attend. In this case, give the patient the pamphlet "The AA Member—Medications

REFERENCE

Form C–1: Naltrexone Information Sheet: Patient Version
Form C–2: Acamprosate Information Sheet: Patient Version
Form C–4: Quick Reference Medication Information Grid
Form C–7: Name and Location of AA Pamphlet Relevant to Pharmacotherapy

and Other Drugs" (see Form C–7) and refer the patient to the section stating that no AA member "plays doctor." Explore with the patient the possibility of his/her participating in and attending specific groups in which members are more tolerant of appropriate use of medication. Reassure the patient about the safety and nonaddicting properties of acamprosate and naltrexone.

4.1f. Desires to Drink or "Get High." Many patients will stop taking their medications for a day or a weekend when they want to drink or "get high." Some patients do this because they have tested out the medications and found that when they drink alcohol after taking the medications, the pleasant feeling is reduced or absent. Other patients may not want to drink and take pills at the same time and resolve the situation by just drinking and not taking pills.

If this is your patient's reason for noncompliance, regardless of whether he/she fits into one of the two situations just described, it is important to ask directly about medication noncompliance, taking a nonjudgmental and commonsense approach to helping the patient resolve the issue.

4.1g. Disagrees About Having an Alcohol Disorder or Feels Like He/She No Longer Needs Medications. Many patients refuse to accept the fact that they have a chronic illness or to believe that the condition is bad enough to require medications. Patients may not always express this attitude—it is often something that they think to themselves because they deny the severity of their condition. This may result in medication noncompliance.

To address this issue, provide the patient with all the information about his/her condition and its treatment. If the patient expresses doubt that his/her condition is serious enough to warrant medication, gently but continually remind the patient of his/her presenting symptoms and of the past consequences of his/her alcohol misuse. Emphasize that having an alcohol dependence problem is not the patient's fault, but also stress that he/she has the responsibility for getting treatment and properly following treatment instructions. Discuss the use of medication as an "aid" rather than a sign of the severity of the problem. After all, most people want to receive state-of-the-art treatment for even a minor problem if they have the option.

Patients who are experiencing a successful recovery, even those who fully comply in the initial phases of treatment, may later decide to stop taking their medications because they feel the problem has been treated and they are now cured and do not need any further "chemical" assistance. They may make this decision on their own—without consulting their medical clinician and typically without knowledge of why continuing medications may be necessary. If your patient has decided prematurely that he/she is "cured," educating him/her about the treatment regimen is the most helpful technique. Explain that feeling ready to stop treatment before it has gone on long enough to work is common with all illnesses (e.g., antibiotics for a bacterial infection). Stress that making the decision to stop medications should be done as a collaborative effort between him/her and you.

4.1h. Takes Medication at Nonprescribed Times and in "Catchup" Doses. If your patient wants to "make up" medications he/she missed as the result of forgetfulness, lack of organization, and so on, support his/her willingness to adhere to the regimen, but inform him/her that taking the medication at other than the scheduled times could cause problems. Review the ***Medication Compliance Plan*** and develop other strategies to help him/her remember to take the prescribed doses if needed.

4.2. Attendance

4.2a. Missed Appointments at Psychosocial Treatment Sessions. Irregular attendance is

typical of patients with alcohol dependence. When pharmacotherapy is part of the primary treatment, a patient who misses office visits can also miss 1 or more weeks of medications. This can be much more serious than missing 1 day or a weekend of medications, and you should address it proactively.

When you next have contact with the patient, cover the following areas:

- Clarify the reasons for the missed appointment.
- Affirm the patient and reinforce his/her commitment in attending the last visit.
- Express your eagerness to see the patient again.
- Briefly mention serious concerns that emerged and your appreciation (as appropriate) that the patient is exploring these.
- Express your optimism about the patient's prospects for change.
- Reschedule the missed appointment.

If the patient offers no reasonable explanation for missing the appointment (e.g., illness, transportation breakdown), explore with him/her whether missing it might reflect any of the following:

- Uncertainty about whether or not treatment is needed (e.g., the patient may state, "I don't really have that much of a problem")
- Failure to accept the alcohol dependence diagnosis
- Frustration or anger about having to participate in treatment (particularly if the patient has been coerced by others into entering the program).

Indicate that it is not surprising, particularly in the beginning phase of treatment, for people to express their reluctance (or frustration, anger, etc.) by not showing up for appointments, being late, and so on. Encouraging the patient to voice these concerns directly may help reduce his/her future missed appointments.

Affirm the patient for being willing to discuss concerns. Then summarize what you have discussed, adding your own optimism about the prospects for positive change, and obtain a recommitment to treatment. Finally, reschedule the appointment.

4.2b. Inactive Status. When a patient misses (unplanned) three or more consecutive scheduled sessions or has not been to a session in a month (whichever comes first), and you have not been able to contact him/her, consider sending a formal note to the patient acknowledging his/her apparent decision not to attend or resume MM treatment sessions and/or take medication. Your note should encourage the patient to return to MM treatment and/or to resume medication at a later time if desired. Urge the patient to have a final evaluation to return unused medications and have a physical exam as a safety check. It is important for safety purposes to have documentation that all attempts were made to conduct a final evaluation on any patient who prematurely discontinues pharmacotherapy.

4.2c. Patients Dissatisfied With Treatment. Patients may report thinking that their treatment is not going to help or may indicate that they want a different treatment. Under these circumstances, you should first reinforce them for being honest about their feelings (e.g., "I'm glad you expressed your concerns to me right away").

You should also confirm, if asked, that patients have the following rights:

- To quit treatment at any time
- To seek help elsewhere
- To decide to work on the problem on their own.

In any event, you should explore the patient's feelings further (e.g., "Whatever you decide is up to you, but it might be helpful for us to talk about why you're concerned").

4.2c.1. When These Concerns Arise During the First Session. If your patient has these concerns at the first session, he/she is probably worried about a suggested approach he/she has not yet tried. It is appropriate to reassure the patient that you will be offering all the help you can.

You cannot guarantee that any particular treatment will work, but you can encourage the patient to give it a good try for the planned period and see what happens. Add that should the problem continue or worsen, you will discuss other possible approaches and options.

4.2c.2. When These Concerns Arise After Two or Three Sessions. If a patient expresses reservations after two or three sessions, consider whether there have been new developments in his/her life, such as the following:

- Have new problems occurred
  - —related or not to drinking?
  - —related or not to the medications?
- Is there input or pressure from someone else for a change in approach or for discontinuation of treatment?
- Is the patient now aware of problems that he/she ignored in the past by drinking?
- Did the ***Medication Compliance Plan*** that you developed at the initial visit fail?
  - —Did the patient properly implement it?
  - —Did the patient try it long enough?

5. Answers to Frequently Asked Medication Questions[2]

5.1. Naltrexone

1. What is naltrexone, and how does it work?

Naltrexone is a medication that blocks the effects of drugs known as opiates, or narcotics (a class that includes morphine, heroin, or codeine). It competes with these drugs for opioid receptors in the brain. Originally used to treat dependence on opiate drugs, it now has also been approved by the U.S. Food and Drug Administration (FDA) as treatment for alcohol dependence. People who are dependent on opiate drugs, such as heroin or morphine, must stop their drug use at least 7 days prior to starting naltrexone. Some people should not take naltrexone, such as those suffering from chronic pain who rely on opioid painkillers or people with liver failure or acute hepatitis.

Although the precise mechanism of action for naltrexone's effect is unknown, reports from successfully treated patients suggest the following three kinds of effects:

1. Naltrexone can reduce a patient's urge or desire to drink.
2. Naltrexone helps patients remain abstinent.
3. Naltrexone can interfere with the patient's desire to continue drinking more if he/she slips and has a drink.

In most clinical trials evaluating the effectiveness of naltrexone, subjects who received naltrexone were significantly more successful in remaining abstinent and in avoiding relapse than were those receiving an inactive placebo pill.

2. Is it possible to become addicted to naltrexone?

No. Naltrexone is not habit forming or a drug of abuse. It does not cause users to become physically or psychologically dependent.

3. What are the side effects of naltrexone?

In a large open-label safety study on naltrexone, conducted by Dupont Pharma in 570 individuals with alcoholism, the most common side effects affected only a small minority of people; they included the following:

- Nausea (10 percent of participants)
- Headache (7 percent of participants)
- Depression (5 to 7 percent of participants)
- Dizziness (4 percent of participants)
- Fatigue (4 percent of participants)
- Insomnia (3 percent of participants)
- Anxiety (2 percent of participants)
- Sleepiness (2 percent of participants).

[2] Adapted from Rounsaville, B.J.; O'Malley, S.; and O'Connor, P. "Guidelines for the Use of Naltrexone in the Treatment of Alcoholism." New Haven, CT: APT Foundation, 1995. Reproduced with the permission of DuPont Pharma.

These side effects were usually mild and of short duration. Patients usually report that they are largely unaware of being on naltrexone. Naltrexone usually has no psychological effects, and users do not feel either "high" or "down." Naltrexone can have toxic effects on the liver. A patient receives blood tests of liver function prior to the onset of treatment and regularly during treatment to determine if he/she should take it at all, if he/she should stop taking it, or if he/she experiences the relatively rare side effect of liver toxicity. Patients should report any side effects to their medical clinician.

4. What will happen if a patient drinks alcohol while taking naltrexone?

Naltrexone does not reduce the effects of alcohol that impair coordination and judgment. Naltrexone may reduce the feeling of intoxication and the desire to drink more, but it will not cause a severe physical response to drinking.

5. Is it all right to take other medications with naltrexone?

Patients should carry a card explaining that they are taking naltrexone, and it should instruct medical staff on pain management. Naltrexone does not reduce the effectiveness of local and general anesthesia used with surgery. However, it does block pain relief from opiate medications. Many pain medications that are not opiates are available. Patients having elective surgery should stop taking naltrexone at least 72 hours beforehand.

The major active effect of naltrexone is on opiate (narcotic) drugs, which is one class of drugs used primarily to treat pain but is also found in some prescription cough preparations. Naltrexone will block the effect of normal doses of this type of drug. There are many nonnarcotic pain relievers patients can use while on naltrexone.

Otherwise, naltrexone is likely to have little impact on other medications patients commonly use such as antibiotics, nonopioid painkillers (e.g., aspirin, acetaminophen/Tylenol, ibuprofen/Motrin/Advil), and allergy medications. Patients should inform their medical clinician of the medication they are currently taking so that possible interactions can be evaluated. Because the liver breaks down naltrexone, other medications that can affect liver function may affect the dose of naltrexone.

6. What will happen if a patient becomes pregnant while taking naltrexone?

Patients with the biological potential to have a child should be using an effective method of birth control while taking naltrexone. However, if they miss a menstrual period, they should report this to their medical clinician at once and take a pregnancy test.

If a patient becomes pregnant, she will discontinue the medication. The medical clinician should continue to ask after her health throughout her pregnancy as well as the health of her baby after delivery.

7. Should naltrexone be taken with a meal?

There is no information that taking naltrexone with or without meals makes any difference in effect.

8. What happens if a patient stops taking naltrexone suddenly?

Naltrexone does not cause physical dependence, and patients can stop taking it at any time without experiencing withdrawal symptoms.

9. If patients take naltrexone, does it mean that they don't need other treatment for alcohol dependence?

No. Research studies have shown that naltrexone was most effective when it was combined with treatment from professionals and/or mutual-support groups.

10. What is the relationship of naltrexone to AA and other support groups?

There is no contradiction between participating in support groups and taking naltrexone. In fact, one multisite study showed that naltrexone-taking subjects who attended mutual-support groups, such as AA, had better outcomes. It is most likely to be effective for patients whose goal is to stop drinking altogether. If other mutual-support group members caution against taking any medications, patients should refer them to the pamphlet "The AA Member—Medications and Other Drugs," which explicitly states that AA members should not "play doctor" and advise others on medication provided by legitimate, informed medical practitioners or treatment programs.

5.2. Acamprosate[3]

1. What is acamprosate, and how does it work?

Acamprosate is a new, investigative medication for treatment of alcohol dependence approved in several European countries, and it is currently being studied in clinical trials in the United States. It is thought to reduce the urge for alcohol by working directly on certain neurotransmitters in the brain (chemicals that transmit information between nerve cells) whose balance has been disturbed because of regular, heavy drinking.

Although acamprosate can be used in the United States only with permission of the FDA, it has been available in Europe since 1989 and has recently been approved for marketing by prescription in more than 12 European countries, including Belgium, France, Germany, Ireland, Italy, the Netherlands, Spain, Switzerland, and the United Kingdom. It is estimated that more than 1 million patients have been treated with acamprosate since it became available.

2. Is acamprosate addictive?

No. Acamprosate is not habit forming or a drug of abuse. It does not cause users to become physically or psychologically dependent.

3. What are the side effects of acamprosate?

Like virtually all medications, acamprosate can cause side effects, but these are usually minor and go away as patients continue to take the medication. In European controlled clinical trials, the only types of symptoms that were consistently more common in subjects taking acamprosate than in subjects taking placebo were stomach symptoms. These were usually mild, tended to occur when subjects first started taking the medication, and consisted primarily of loose bowel movements or mild diarrhea. Some subjects also had changes in their sex drive—sometimes this was increased and sometimes decreased, but there was no definite pattern. As with many drugs, sometimes people on acamprosate develop skin rashes or itching. In earlier studies, subjects on acamprosate and those on placebo both experienced equal amounts of this type of symptom. Patients should tell their medical clinician of any side effects.

[3] Adapted from Mason, B.J., and Goodman, A.M., *Brief Intervention and Medication Compliance Procedures—Therapist's Manual,* 1997. http://www.alcohol-free.com.

4. What will happen if a patient drinks alcohol while taking acamprosate?

Acamprosate does not change the way the body metabolizes alcohol, so acamprosate will not make patients feel sick if they drink (i.e., it does not work like Antabuse). In addition, there is no evidence of an added effect of alcohol if the patient drinks while taking acamprosate.

5. Is it okay to take other medications with acamprosate?

Because acamprosate is eliminated exclusively by the kidneys, drugs that may be toxic to the kidneys, such as aminoglycoside antibiotics (gentamycin and amikacin), should be avoided. Patients should inform their medical clinician of whatever medication they are currently taking so that possible interactions can be evaluated.

6. What will happen if a patient becomes pregnant while taking acamprosate?

Patients with the biological potential to have a child should be using an effective method of birth control while taking acamprostate. However, if they miss a menstrual period, they should report this to their medical clinician at once and take a pregnancy test.

If a patient becomes pregnant, she will discontinue the medication. The medical clinician should continue to ask after her health throughout her pregnancy as well as the health of her baby after delivery.

Even though acamprosate should not be used during pregnancy, animal studies have not shown any ill effects on either the course of pregnancy or on the offspring, nor is there any evidence from animal studies that acamprosate causes birth defects.

7. Should acamprosate be taken with a meal?

Acamprosate can be taken with food, but food does decrease the amount of medication that the body absorbs. Gastrointestinal symptoms may decrease by taking the medication with food.

8. Is it all right to crush the pills?

Acamprosate pills should not be crushed because they have an enteric coating. Destroying this coating can lead to a worsening of gastrointestinal side effects.

9. What happens if a patient stops taking acamprosate suddenly?

Acamprosate does not cause physiological withdrawal symptoms when it is stopped.

10. What happens if patients miss a dose?

If patients miss a dose of acamprosate, they should not take it simultaneously with the next scheduled dose; there should be a minimum of 2 hours between doses. If this is not feasible, they should not take the skipped dose. Instead, they should wait until their next scheduled dose and take only that dose.

11. If patients take acamprosate, does it mean that they don't need other treatment for alcohol dependence?

No. Research has shown that acamprosate was most effective when it was combined with treatment from professionals and/or mutual-support groups.

12. What is the relationship of acamprosate to AA and other mutual-support groups?

There is no contradiction between participating in support groups and taking acomprosate. It is

most likely to be effective for patients whose goal is to stop drinking altogether. If other mutual-support group members caution against taking any medications, patients should refer them to the pamphlet "The AA Member—Medications and Other Drugs," which explicitly states that AA members should not "play doctor" and advise others on medication provided by legitimate, informed medical practitioners or treatment programs.

6. Medical Attention

6.1. What Is Medical Attention (MA)?

Some patients receiving MM, either with or without psychotherapy, will be unable to continue taking medications after starting them. The most common reasons for this are intolerable side effects and a medical or psychiatric contraindication, such as elevated liver function tests or pregnancy.

In addition, patients may temporarily discontinue pharmacotherapy for various reasons during treatment but may have the goal of restarting medications at some later time during treatment.

Medical attention (MA) is an intervention that has been derived from MM for patients who want to continue seeing their MM practitioner but are not able to take medications. Medical attention consists of medical monitoring (e.g., checking BAC, vital signs, and weight, and administering the SAFTEE), and a discussion of drinking according to the principles of MM.

6.2. Frequency of MA Visits

MA visits should be held as frequently as MM visits in the first month. Thereafter, the frequency of MA visits should be decreased (e.g., to monthly) until patients restart medications or until the end of treatment. MA visits typically will last about 15 minutes, although they can be as brief as 10 or as long as 20 minutes, depending on each patient's medical status and progress in maintaining recovery.

6.3. Treatment Overview

The goal of MA is to promote recovery from alcohol dependence by encouraging patients to continue in their MA visits, supporting patients' efforts to stop drinking, and making recommendations for changing drinking behaviors. MA treatment should be delivered by a medical professional who will follow the patient throughout the treatment. Your role as the medical practitioner is to provide expert assessment, support, and direct advice to patients in their efforts to achieve recovery from alcohol dependence. When talking with the patient, appeal to reason and common sense, particularly in relation to the overall goal of preserving or restoring health. It is important in expressing concern for the client to be nonjudgmental. Always be friendly, supportive, and optimistic about recovery.

MA visits include a medical check on BAC, vital signs, and weight; a review of health status; a brief assessment of drinking; review of attendance at mutual-support recovery groups; and recommendations for the patient to follow until the next visit.

6.4. Pitfalls to Avoid When Using MA in a Research Context

6.4a. Non–MA Therapeutic Strategies. Many professional therapies utilize techniques

and strategies that extend beyond the scope of MA treatment, such as the following:

- Confrontation
- Skills training approaches
- Client-centered counseling
- Family therapy.

Although these methods might complement MA treatment in a clinical setting, they are *not* part of the MA intervention per se, and most medical staff will not have training to deliver these methods. These approaches were not used by MM clinicians during the COMBINE project.

6.4b. Nonabstinent Goals. Typically, patients are encouraged to be abstinent throughout treatment, if possible. This was the case also in the COMBINE project. Do not tell patients in advance things such as, "Expect slips—they are a natural part of recovery," or "Some reduction in the amount you are drinking is an acceptable goal." However, when patients do drink during treatment, it is important to avoid expressing disapproval or disappointment. Praise any improvements or steps toward achieving recovery. If patients do slip, reassure them that slips are common and are not signals that recovery is unattainable.

6.5. Brief Assessment: Functioning and Drinking Status Review (5 minutes)

Ask the patient about his/her drinking status since the last visit. You should also allow for some open-ended discussion so that the patient can tell you his/her current concerns about drinking. Reward any positive steps he/she has made toward achieving recovery. Continue to provide the patient with optimism that he/she can recover.

Before determining the content of the discussion for the rest of the visit, ask the patient any other questions that will provide you with information you feel you need, including whether or not he/she has been attending mutual-support groups.

Below are some questions you could ask during the status review:

CLINICIAN: How have you been since our last visit?

- **What was difficult?**
- **What went well?**
- **How well were you able to keep from drinking?**
- ***(If the patient did drink)* What were the circumstances? Remember change occurs in small steps, keep trying, don't get discouraged.**
- **How great was your desire to drink?**
- ***(If the patient did drink but found that his/her desire to drink was greatly diminished)* Reductions in your desire to drink may be the first sign of change for you.**
- ***(If the patient had a strong desire to drink but did not do so)* Congratulations on not drinking, even though you really wanted to! You have taken an important step toward your recovery!**
- ***(If the patient remained abstinent)* Congratulations on staying abstinent! You are demonstrating your determination to change and are making great progress toward your recovery!**

6.6. Review of Attendance at Mutual-Support Group Meetings

Ask the patient if he/she has been going to mutual-support group meetings. If the patient has gone to meetings, reinforce the importance of this action. If he/she has not gone, provide encouragement to do so.

6.7. Recommendations/ Troubleshooting (5 to 10 minutes)

Because the patient is not taking medications, the recommendations and troubleshooting focus will be on drinking status.

6.7a. The Patient Is Not Drinking. Many patients will attend their MA appointments faithfully and discontinue drinking. Some will do so early in treatment; others will do so midtreatment; some will not reach this point until treatment is almost over. When the patient has achieved this outcome, use the following guidelines:

- Reinforce the patient's ability to follow advice and stick to the plan. Discuss how most patients have trouble initially achieving and maintaining abstinence. Inquire about how, specifically, he/she was able to do so well.
- Review with the patient that when things are going well, it is important to remember that compliance with treatment also means continuing to attend his/her MA appointments and continuing to make the scheduled visits until the end of treatment. Address the common but incorrect belief that the patient can abandon the plan constructed at the initial visit as soon as he/she feels successful in treatment. Focus on the fact that completing treatment as prescribed may better ensure recovery after treatment is over. Explain to the patient that even when things have been going well for some period of time, the visits to you serve as "booster shots" or extra insurance to help his/her successful compliance and response to treatment continue beyond the end of treatment.
- Review the benefits of abstinence (e.g., improved health, fewer drinking-related problems).
- Encourage and reinforce attendance at mutual-support group meetings between appointments.
- Use the last minutes to provide support. End the visit by saying something such as, "It sounds like things are going well. Keep up the good work!"
- If the patient has not been coming to MA sessions, probe further as to why he/she missed appointments and suggest that continuing to come to the MA sessions regularly may help sustain recovery.

6.7b. The Patient Is Drinking. Encouraging patients to go to mutual-support groups such as AA or SMART Recovery is the first-line response in this situation. Although some patients will inform you early on that they have no intention of attending these meetings because of previous negative experiences or a fear of groups, encourage them to try these groups by stressing that a different type of group could be helpful (e.g., going to SMART Recovery instead of AA or attending smaller AA groups, same-sex AA groups, or AA groups in a different location).

The following is a list of additional strategies. Note that these are the types of responses that

a primary care clinician (not an alcoholism treatment specialist) would likely employ in such a situation.

- Review with the patient the data on his/her ***Clinician Report*** (Form A–1) from the initial MM session to remind him/her why he/she originally sought treatment.

REFERENCE
Form A–1: Clinician Report

- Review the benefits of abstinence in general terms (e.g., improved health, fewer drinking-related problems). Encourage the patient to give abstinence a chance. Tell him/her you know that beginning the process of abstaining from alcohol is the most difficult time but that if he/she can get the process started, it should get easier as time goes by.
- Praise any small steps the patient has taken toward abstinence and/or reductions in desire for alcohol. Reassure your patient that recovery is a gradual process and that occasional returns to drinking sometimes occur along the way.
- Review the benefits of any other aspects of the treatment course helpful to maintaining abstinence that the patient seems to be reluctant to try.
- If the patient appeals to you for advice on how to stop drinking, determine if he/she has been drinking at home or at a bar or another regular place. If at home, encourage him/her to remove alcohol from the house. If at a bar or with specific people, suggest that the patient not associate with drinking buddies or stop going to the bar.
- Ask if there is a particular time of the day that the patient drinks. If so, suggest that he/she find some other activity to distract him/her at that time.
- Encourage the patient to attend MA visits and to give treatment a chance. Briefly evaluate the patient's reasons for failing to attend MA appointments, and help the patient construct a plan for circumventing the obstacles to attending these visits.

6.8. Coexisting Medical/Psychiatric Problems

In all cases, evaluate coexisting medical/psychiatric problems, and if clinically appropriate, refer the patient to the appropriate practitioner (e.g., an internist or psychiatrist) for further evaluation and perhaps treatment of the coexisting problem. If the severity of the patient's medical condition warrants it, schedule more frequent visits than ordinarily recommended by the MA protocol.

Appendix A: CLINICIAN PACKET

To Be Used at the Initial MM Session

Form

A–1 Clinician Report
A–2 Vital Signs and BAC
A–3 Concurrent Medications
A–4 Naltrexone Information Sheet: Clinician Version
A–5 Acamprosate Information Sheet: Clinician Version
A–6 Medication Instructions Summary
A–7 Modified SAFTEE
A–8 SAFTEE Guidelines: Part 1
A–9 SAFTEE Guidelines for Rating Severity of Adverse Events: Part 2
A–10 Menstrual Calendar
A–11 Serious Adverse Event Report
A–12 Serious Adverse Event Followup Report
A–13 Medication Compliance Plan
A–14 Pill Count
A–15 Day 3 Clinician Phone Contact

To Be Used at All MM Followup Sessions

Form

A–2 Vital Signs and BAC
A–3 Concurrent Medications
A–7 Modified SAFTEE
A–8 SAFTEE Guidelines: Part 1
A–9 SAFTEE Guidelines for Rating Severity of Adverse Events: Part 2
A–10 Menstrual Calendar
A–14 Pill Count

To Be Used as Needed

Form

A–11 Serious Adverse Event Report
A–12 Serious Adverse Event Followup Report
A–16 COMBINE Study Fact Sheet for the Practitioner**

** The COMBINE Study Fact Sheet provides background clinical information about COMBINE to practitioners using this manual.

Form A–1

Clinician Report

Center	Patient #	Patient Initials	Week

Date: ____ / ____ / ____ (month / day / year)

Staff ID # ____

Note: Attached to this form are copies of the patient's demographic summary, medical history, and source documentation for the sections below.

I. Medical Information

A. The most recent record of your blood pressure was: _____/____ **(from Vitals form)**

B. Your liver enzymes/bilirubin/uric acid are at the following levels: **(from Lab reports)**
[Explain the significance of enzyme/bilirubin elevation, if applicable.]

		Female	**Male**
AST (SGOT): _____	Normal Range	_____ iu/l	_____ iu/l
ALT (SGPT): _____	Normal Range	_____ iu/l	_____ iu/l
GGT (GGTP): _____	Ranges	_____ iu/l	_____ iu/l
Bilirubin: _____	Normal Range	_____ mg/dl	_____ mg/dl
Uric Acid: _____	Normal Range	_____ mg/dl	_____ mg/dl

C. Other abnormal lab values: **(from Lab reports)**

a) _____ c) _____

b) _____ d) _____

D. You have the following drinking-related medical symptom(s)/condition(s): **(from Clin. chart)**

a) _____ c) _____

b) _____ d) _____

Notes:

Clinician Report (*continued*)

Center | Patient # | Patient Initials | Week

Date: month / day / year

Staff ID #

II. Alcohol Use

On average, you drink _____ days/week. (From TLFB; Form 90)

On average, you drink _____ drinks per drinking occasion. (From TLFB; Form 90)

Notes:

III. Consequences of Drinking

[Note: From DrInC-L. Discuss one to three items to which the patient responded "yes." Select the three most clinically relevant items.]

1.

2.

3.

Clinician Report (*continued*)

Center | Patient # | Patient Initials | Week

Date (month / day / year) | Staff ID #

IV. Diagnostic Information

You have the following symptoms of alcohol dependence: [Check either "Yes" or "No" for each symptom listed below.]	**(from Dx Interview) YES**	**NO**
a) When you start drinking, you end up drinking more, or longer, than you planned.	q	q
b) You have tried to, or wanted to, cut down or stop drinking alcohol.	q	q
c) You have spent a lot of time drinking or being hung over.	q	q
d) You have given up important social, occupational, or recreational activities because of alcohol use.	q	q
e) You have continued to drink even though alcohol has caused, or made worse, psychological or physical problems.	q	q
f) You have an increased tolerance to alcohol.	q	q
g) You have experienced withdrawal symptoms when you cut down or stopped drinking.	q	q
h) Your Dx Interview says you meet criteria for alcohol dependence. (At least three symptoms must be checked "YES")	q	q

Notes:

Form A–2

Vital Signs and BAC

Center | Patient # | Patient Initials | Week

Date (month / day / year) | Staff ID #

Instructions: Record the vital signs and BAC at baseline and over the course of treatment.

1. Blood pressure (sitting): _____ mmHg / _____mmHg
   Systolic Diastolic
2. Pulse rate: _____ per minute
3. Breath alcohol concentration: _____._____
4. Weight: _____._____ lbs

Form A–3

Concurrent Medications

Center | Patient # | Patient Initials | Week

Date (month / day / year) | Staff ID #

Instructions: At the baseline visit, the time frame used for asking about concurrent medications is the past 90 days because this is consistent with the time frame used for Form 90 and the SAFTEE. Be sure to also ask about the use of acamprosate or naltrexone in the last 30 days. Also inquire about the use of concomitant medications at each subsequent visit (this form is cumulative).

Week # / Sequence #	Medication	Primary Indication	Started Prior to Tx? Yes	Started Prior to Tx? No	Date Started (mm/dd/yy)	Ongoing at End of Tx? Yes	Ongoing at End of Tx? No	Date Stopped (mm/dd/yy)	Notes
/			❑	❑	/ /	❑	❑	/ /	
/			❑	❑	/ /	❑	❑	/ /	
/			❑	❑	/ /	❑	❑	/ /	
/			❑	❑	/ /	❑	❑	/ /	
/			❑	❑	/ /	❑	❑	/ /	
/			❑	❑	/ /	❑	❑	/ /	
/			❑	❑	/ /	❑	❑	/ /	
/			❑	❑	/ /	❑	❑	/ /	

If medications are used for an adverse experience, list the event on the SAFTEE.

Form A–4

Naltrexone Information Sheet: Clinician Version[1]

1. What is naltrexone, and how does it work?

Naltrexone is a medication that blocks the effects of drugs known as opiates, or narcotics (a class that includes morphine, heroin, or codeine). It competes with these drugs for opioid receptors in the brain. Originally used to treat dependence on opiate drugs, it now has also been approved by the U.S. Food and Drug Administration (FDA) as treatment for alcohol dependence. People who are dependent on opiate drugs, such as heroin or morphine, must stop their drug use at least 7 days before starting naltrexone. Some people should not take naltrexone, such as those suffering from chronic pain who rely on opioid painkillers or people with liver failure or acute hepatitis.

Although the precise mechanism of action for naltrexone's effect is unknown, reports from successfully treated patients suggest the following three kinds of effects:

- Naltrexone can reduce the patient's urge or desire to drink.
- Naltrexone helps patients remain abstinent.
- Naltrexone can interfere with the patient's desire to continue drinking more if he/she slips and has a drink.

In most clinical trials evaluating the effectiveness of naltrexone, subjects who received naltrexone were significantly more successful in remaining abstinent and in avoiding relapse than were those receiving an inactive placebo pill.

2. Is it possible to become addicted to naltrexone?

No. Naltrexone is not habit forming or a drug of abuse. It does not cause users to become physically or psychologically dependent.

3. What are the side effects of naltrexone?

In a large open-label safety study on naltrexone, conducted by Dupont Pharma in 570 individuals with alcoholism, the most common side effects affected only a small minority of people; they included the following:

- Nausea (10 percent of participants)
- Headache (7 percent of participants)
- Depression (5 to 7 percent of participants)
- Dizziness (4 percent of participants)
- Fatigue (4 percent of participants)
- Insomnia (3 percent of participants)

[1] Adapted from Rounsaville, B.J.; O'Malley, S.; and O'Connor, P. "Guidelines for the Use of Naltrexone in the Treatment of Alcoholism." New Haven, CT: APT Foundation, 1995. Reproduced with the permission of DuPont Pharma.

Naltrexone Information Sheet: Clinician Version (*continued*)

- Anxiety (2 percent of participants)
- Sleepiness (2 percent of participants).

These side effects were usually mild and of short duration. The side effects, predominantly nausea, have been severe enough to cause 5 to 10 percent of people starting it to stop the medication. Patients usually report that they are largely unaware of being on naltrexone. Naltrexone usually has no psychological effects, and users do not feel either "high" or "down." Naltrexone can have toxic effects on the liver. A patient receives blood tests of liver function prior to the onset of treatment and regularly during treatment to determine if he/she should take it at all, if he/she should stop taking it, or if he/she experiences the relatively rare side effect of liver toxicity. Patients should report any side effects to their medical clinician.

4. What will happen if the patient drinks alcohol while taking naltrexone?

Naltrexone does not reduce the effects of alcohol that impair coordination and judgment. Naltrexone may reduce the feeling of intoxication and the desire to drink more, but it will not cause a severe physical response to drinking.

5. Is it all right to take other medications with naltrexone?

Patients should carry a card explaining that they are taking naltrexone, and it should instruct medical staff on pain management. Naltrexone does not reduce the effectiveness of local and general anesthesia used with surgery. However, it does block pain relief from opiate medications. Many pain medications that are not opiates are available. Patients having elective surgery should stop taking naltrexone at least 72 hours beforehand.

The major active effect of naltrexone is on opiate (narcotic) drugs, which is one class of drugs used primarily to treat pain but is also found in some prescription cough preparations. Naltrexone will block the effect of normal doses of this type of drug. There are many nonnarcotic pain relievers patients can use while on naltrexone.

Otherwise, naltrexone is likely to have little impact on other medications patients commonly use, such as antibiotics, nonopioid painkillers (e.g., aspirin, acetaminophen/Tylenol, ibuprofen/Motrin/Advil), and allergy medications. Patients should inform their medical clinician of the medication they are currently taking so that possible interactions can be evaluated.

Because the liver breaks down naltrexone, other medications that can affect liver function may affect the dose of naltrexone.

6. What will happen if a patient becomes pregnant while taking naltrexone?

Patients with the biological potential to have a child should be using an effective method of birth control while taking naltrexone. However, if they miss a menstrual period, they should report this to their medical clinician at once and take a pregnancy test.

If a patient becomes pregnant, she will discontinue the medication. The medical clinician should continue to ask about her health throughout her pregnancy and also about the health of her baby after delivery.

Naltrexone Information Sheet: Clinician Version (*continued*)

7. Should patients take naltrexone with a meal?

There is no information that taking naltrexone with or without meals makes any difference in effect.

8. What happens if the patient stops taking naltrexone suddenly?

Naltrexone does not cause physical dependence, and patients can stop taking it at any time without experiencing withdrawal symptoms.

9. If patients take naltrexone, does it mean that they don't need other treatment for alcohol dependence?

No. Research studies have shown that naltrexone was most effective when it was combined with treatment from professionals and/or mutual-support groups.

10. What is the relationship of naltrexone to AA and other mutual-support groups?

There is no contradiction between participating in support groups and taking naltrexone. In fact, one multisite study showed that naltrexone-taking subjects who attended mutual-support groups, such as AA, had better outcomes. It is most likely to be effective for patients whose goal is to stop drinking altogether. If other mutual-support group members caution against taking any medications, patients should refer them to the pamphlet "The AA Member—Medications and Other Drugs," which explicitly states that AA members should not "play doctor" and advise others on medication provided by legitimate, informed medical practitioners or treatment programs.

Form A–5

Acamprosate Information Sheet: Clinician Version[2]

1. What is acamprosate, and how does it work?

Acamprosate is a new, investigative medication for treatment of alcohol dependence already approved in several European countries and currently being studied in clinical trials in the United States. It is thought to reduce the urge for alcohol by working directly on certain neurotransmitters in the brain (chemicals that transmit information between nerve cells) whose balance has been disturbed because of regular, heavy drinking.

Although acamprosate can be used in the United States only with permission of the U.S. Food and Drug Administration, it has been available in Europe since 1989 and has recently been approved for marketing by prescription in more than 12 European countries, including Belgium, France, Germany, Ireland, Italy, the Netherlands, Spain, Switzerland, and the United Kingdom. It is estimated that more than 1 million patients have been treated with acamprosate since it became available.

2. Is acamprosate addictive?

No. Acamprosate is not habit forming or a drug of abuse. It does not cause users to become physically or psychologically dependent.

3. What are the side effects of acamprosate?

Like virtually all medications, acamprosate can cause side effects, but these are usually minor and subside as patients continue to take the medication. In European controlled clinical trials, the only types of symptoms that were *consistently* more common in subjects taking acamprosate than in subjects taking placebo were stomach symptoms. These were usually mild, tended to occur when subjects first started taking the medication, and consisted primarily of loose bowel movements or mild diarrhea. Some subjects also had changes in their sex drive—sometimes this was increased and sometimes decreased, but there was no definite pattern. As with many drugs, sometimes people on acamprosate develop skin rashes or itching. In earlier studies, subjects on acamprosate and those on placebo both experienced equal amounts of this type of symptom. Patients should tell their medical clinician of any side effects.

4. What will happen if the patient drinks alcohol while taking acamprosate?

Acamprosate does not change the way the body metabolizes alcohol, so acamprosate will not make patients feel sick if they drink (i.e., it does not work like Antabuse). In addition, there is no evidence of an added effect of alcohol if the patient drinks while taking acamprosate.

5. Is it possible to take other medications with acamprosate?

Because acamprosate is eliminated exclusively by the kidneys, drugs that may be toxic to the kidneys, such as aminoglycoside antibiotics (gentamycin and amikacin), should be avoided. Patients should inform their medical clinician of whatever medication they are currently taking so that possible interactions can be evaluated.

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[2] Adapted from Mason, B.J., and Goodman, A.M. *Brief Intervention and Medication Compliance Procedures—Therapist's Manual,* 1997. http://www.alcohol-free.com.

Acamprosate Information Sheet: Clinician Version (*continued*)

6. What will happen if a patient becomes pregnant while taking acamprosate?

Patients with the biological potential to have a child should be using an effective method of birth control while taking acamprosate. However, if they miss a menstrual period, they should report this to their medical clinician at once and take a pregnancy test.

If a patient becomes pregnant, she will discontinue the medication. The medical clinician should continue to ask about her health throughout her pregnancy and also about the health of her baby after delivery.

Even though acamprosate should not be used during pregnancy, animal studies have not shown any ill effects on either the course of pregnancy or on the offspring, nor is there any evidence from animal studies that acamprosate causes birth defects.

7. Should acamprosate be taken with a meal?

Acamprosate can be taken with food, but food does decrease the amount of medication that the body absorbs. Gastrointestinal symptoms may decrease by taking the medication with food.

8. Is it all right to crush the pills?

Acamprosate pills should not be crushed because they have an enteric coating. Destroying this coating can lead to a worsening of gastrointestinal side effects.

9. What happens if patients stop taking acamprosate suddenly?

Acamprosate does not cause physiological withdrawal symptoms when it is stopped.

10. What happens if patients miss a dose?

If patients miss a dose of acamprosate, they should not take it simultaneously with the next scheduled dose; there should be a minimum of 2 hours between doses. If this is not feasible, they should *not* take the skipped dose. Instead, they should wait until their next scheduled dose, and take *only* that dose.

11. If patients take acamprosate, does it mean that they don't need other treatment for alcohol dependence?

No. Research has shown that acamprosate was most effective when it was combined with treatment from professionals and/or mutual-support groups.

12. What is the relationship of acamprosate to AA and other mutual-support groups?

There is no contradiction between participating in support groups and taking acamprosate. It is most likely to be effective for patients whose goal is to stop drinking altogether. If other mutual-support group members caution against taking any medications, patients should refer them to the pamphlet "The AA Member—Medications and Other Drugs," which explicitly states that AA members should not "play doctor" and advise others on medication provided by legitimate, informed medical practitioners or treatment programs.

Form A–6

Medication Instructions Summary: General Review of Most Frequently Asked Questions

1. How often should I take the medications?

Take four pills in the morning, two at midday, and two in the evening.

2. Can I take medications with meals?

Because one of the medications is best taken on an empty stomach to help with absorption, it is best to take the medications about 1 hour before a meal or 2 hours after a meal. However, if you experience or are concerned about stomach problems, take the medications with meals. Discuss this with the clinician prescribing your medications.

3. What should I do if I miss a dose? Should I take two doses at once?

No. Do not take a double dose of either medication. Allow at least 2 hours between doses.

4. If I miss a morning dose, should I take the morning dose or the midday dose at midday?

If you miss the morning pills, take them as soon as you remember. If you remember near the time for the midday dose, take the four morning pills, wait 2 hours, and then take the midday dose. Allow at least 2 hours between doses.

5. Why are there three extra lines of medication in the blister card for each week?

The blister cards have 10 days worth of medication. This includes doses for 7 days of medication plus a few extras in case you find yourself without medications. For example, if you drop a pill down the sink or are unable to come in for your scheduled session, you may need an extra pill.

6. What should I do if I lose a dose?

If you lose one or more pills, replace it with medication from the corresponding extra medications. For example, if you needed to replace a lost morning dose, go down the morning columns (the first four columns of pills) on the blister card to find the first line of extra medication (eighth row of pills), and take those pills.

7. Can I crush, cut, or chew the medications?

No; because one of the pills has a protective coating to reduce stomach problems, it is best to take the pills whole.

8. What should I do with the blister card?

Return the blister card empty or with unused medications at the next visit. Return it even if you did not take all of the pills that were recommended.

Medication Instructions Summary: General Review of Most Frequently Asked Questions (*continued*)

9. Can I remove the medications from the blister card and take them with me?

It is best to keep the pills in their original packaging until you actually take the dose. Although you will be asked about whether you took your medication at each visit, the blister card is another way to keep track of pill-taking. If you take the pills out of the blister card, you might lose them or may not be able to remember if you took those pills. If you absolutely must take the pills out of the blister card, try to remember which pills you removed as well as if you did actually take that dose.

10. Does it matter where I store the medications?

Do not store the medications in a car, because high temperatures affect them.

Modified SAFTEE (version used in COMBINE study)

Center ☐☐ Patient # ☐☐☐☐☐☐☐ Patient Initials ☐☐☐ Week ☐☐ Sequence ☐☐ Date ☐☐ / ☐☐ / ☐☐☐☐ (month / day / year) Staff ID # ☐☐☐

Instructions: Complete at all visits for patients who are assigned to MM. For further instructions, see ***SAFTEE Guidelines*** **Parts 1** and **2** (Forms A–8 and A–9).

Question	Event	Date of Onset	Duration (Days)	Pattern IS IN CO	Severity MN MI MO S	Drug Related N DR TO K O X	Action Taken N IS C SU DC O R I
A. General Inquiry Have you had any physical or health problems since your last visit? Have you noticed any changes in your physical appearance since your last visit? Have you cut down on the things you usually do because you have not felt well physically since your last visit?	1 _____ 2 _____ 3 _____ 4 _____ 5 _____ 6 _____ 7 _____ 8 _____ 9 _____ 10 _____	1 _____ 2 _____ 3 _____ 4 _____ 5 _____ 6 _____ 7 _____ 8 _____ 9 _____ 10_____	1_____ 2_____ 3_____ 4_____ 5_____ 6_____ 7_____ 8_____ 9_____ 10_____	☐ ☐	☐ ☐	☐ ☐	☐ ☐
				IS=Isolated IN=Intermittent CO=Continuous	MN=Minimal MI=Mild MO=Moderate S=Severe	N=No DR=Dose-response TO=Timing of onset K=Known drug effect O=Other (specify) X=Don't know	N=None IS=Increased surveillance C=Contra active RX SU=Suspend RX DC=Discontinue RX O=Other R=Dose reduction I=Dose increased

Modified SAFTEE (*continued*)

Center	Patient #	Patient Initials	Week	Sequence	Date	Staff ID #
					month / day / year	

Question	Event	Date of Onset	Duration (Days)	Pattern	Severity	Drug Related	Action Taken
				IS IN CO	MN MI MO S	N DR TO K O X	N IS C SU DC O R I
B. Specific Events Have you had any of the following problems since your last visit?	Prev /Rec Y N						
1. Nausea……..	❒ ❒ ❒	1 _____	1 _____	❒ ❒ ❒	❒ ❒ ❒ ❒	❒ ❒ ❒ ❒ ❒ ❒	❒ ❒ ❒ ❒ ❒ ❒ ❒ ❒
2. Vomiting……..	❒ ❒ ❒	2 _____	2 _____	❒ ❒ ❒	❒ ❒ ❒ ❒	❒ ❒ ❒ ❒ ❒ ❒	❒ ❒ ❒ ❒ ❒ ❒ ❒ ❒
3. Diarrhea……..	❒ ❒ ❒	3 _____	3 _____	❒ ❒ ❒	❒ ❒ ❒ ❒	❒ ❒ ❒ ❒ ❒ ❒	❒ ❒ ❒ ❒ ❒ ❒ ❒ ❒
4. Abdominal pain…….	❒ ❒ ❒	4 _____	4 _____	❒ ❒ ❒	❒ ❒ ❒ ❒	❒ ❒ ❒ ❒ ❒ ❒	❒ ❒ ❒ ❒ ❒ ❒ ❒ ❒
5. Decreased appetite…...	❒ ❒ ❒	5 _____	5 _____	❒ ❒ ❒	❒ ❒ ❒ ❒	❒ ❒ ❒ ❒ ❒ ❒	❒ ❒ ❒ ❒ ❒ ❒ ❒ ❒
6. Increased appetite……	❒ ❒ ❒	6 _____	6 _____	❒ ❒ ❒	❒ ❒ ❒ ❒	❒ ❒ ❒ ❒ ❒ ❒	❒ ❒ ❒ ❒ ❒ ❒ ❒ ❒
7. Headache……...	❒ ❒ ❒	7 _____	7 _____	❒ ❒ ❒	❒ ❒ ❒ ❒	❒ ❒ ❒ ❒ ❒ ❒	❒ ❒ ❒ ❒ ❒ ❒ ❒ ❒
8. Dizziness……...	❒ ❒ ❒	8 _____	8 _____	❒ ❒ ❒	❒ ❒ ❒ ❒	❒ ❒ ❒ ❒ ❒ ❒	❒ ❒ ❒ ❒ ❒ ❒ ❒ ❒
9. Fatigue……...	❒ ❒ ❒	9 _____	9 _____	❒ ❒ ❒	❒ ❒ ❒ ❒	❒ ❒ ❒ ❒ ❒ ❒	❒ ❒ ❒ ❒ ❒ ❒ ❒ ❒
10. Nervousness/anxiety….	❒ ❒ ❒	10_____	10_____	❒ ❒ ❒	❒ ❒ ❒ ❒	❒ ❒ ❒ ❒ ❒ ❒	❒ ❒ ❒ ❒ ❒ ❒ ❒ ❒
11. Insomnia……..	❒ ❒ ❒	11_____	11_____	❒ ❒ ❒	❒ ❒ ❒ ❒	❒ ❒ ❒ ❒ ❒ ❒	❒ ❒ ❒ ❒ ❒ ❒ ❒ ❒
12. Somnolence……...	❒ ❒ ❒	12_____	12_____	❒ ❒ ❒	❒ ❒ ❒ ❒	❒ ❒ ❒ ❒ ❒ ❒	❒ ❒ ❒ ❒ ❒ ❒ ❒ ❒
13. Depression*……	❒ ❒ ❒	13_____	13_____	❒ ❒ ❒	❒ ❒ ❒ ❒	❒ ❒ ❒ ❒ ❒ ❒	❒ ❒ ❒ ❒ ❒ ❒ ❒ ❒
14. Itching……...	❒ ❒ ❒	14_____	14_____	❒ ❒ ❒	❒ ❒ ❒ ❒	❒ ❒ ❒ ❒ ❒ ❒	❒ ❒ ❒ ❒ ❒ ❒ ❒ ❒
15. Rash……..	❒ ❒ ❒	15_____	15_____	❒ ❒ ❒	❒ ❒ ❒ ❒	❒ ❒ ❒ ❒ ❒ ❒	❒ ❒ ❒ ❒ ❒ ❒ ❒ ❒
16. Decreased libido……..	❒ ❒ ❒	16_____	16_____	❒ ❒ ❒	❒ ❒ ❒ ❒	❒ ❒ ❒ ❒ ❒ ❒	❒ ❒ ❒ ❒ ❒ ❒ ❒ ❒
17. Increased libido……	❒ ❒ ❒	17_____	17_____	❒ ❒ ❒	❒ ❒ ❒ ❒	❒ ❒ ❒ ❒ ❒ ❒	❒ ❒ ❒ ❒ ❒ ❒ ❒ ❒
18. Missed menses……	❒ ❒ ❒	18_____	18_____	❒ ❒ ❒	❒ ❒ ❒ ❒	❒ ❒ ❒ ❒ ❒ ❒	❒ ❒ ❒ ❒ ❒ ❒ ❒ ❒
19. Significant lab abnormalities (describe)	❒ ❒ ❒	19_____	19_____	❒ ❒ ❒	❒ ❒ ❒ ❒	❒ ❒ ❒ ❒ ❒ ❒	❒ ❒ ❒ ❒ ❒ ❒ ❒ ❒
20. Other (describe)……	❒ ❒ ❒	20_____	20_____	❒ ❒ ❒	❒ ❒ ❒ ❒	❒ ❒ ❒ ❒ ❒ ❒	❒ ❒ ❒ ❒ ❒ ❒ ❒ ❒
21. Other (describe)……..	❒ ❒ ❒	21_____	21_____	❒ ❒ ❒	❒ ❒ ❒ ❒	❒ ❒ ❒ ❒ ❒ ❒	❒ ❒ ❒ ❒ ❒ ❒ ❒ ❒
* Requires additional specification				IS=Isolated IN=Intermittent CO=Continuous	MN=Minimal MI=Mild MO=Moderate S=Severe	N=No DR=Dose-response TO=Timing of onset K=Known drug effect O=Other (specify) X=Don't know	N=None IS=Increased surveillance C=Contra active RX SU=Suspend RX DC=Discontinue RX O=Other R=Dose reduction I=Dose increased

Modified SAFTEE (*continued*)

Center | Patient # | Patient Initials | Week | Sequence | Date (month / day / year) | Staff ID #

Specific Event Number (# from part B)	Description

Form A–8

SAFTEE Guidelines: Part 1[3]

The ***Modified SAFTEE*** (Form A–7) is designed to collect information on adverse health events that the patient experiences during a specified time period of a clinical trial. Clinicians should use the ***SAFTEE*** to report patients' adverse health events regardless of whether these events are suspected to be drug related. This ensures that clinicians report unanticipated events as well as "known or expected" events. The ***Modified SAFTEE*** has three general health questions (part A) that ask if the patient has had any health problems since the last visit, has noticed any changes in appearance, or has stopped doing certain activities because of not feeling well.

Preferred Events Terms

The ***Modified SAFTEE*** also has a section on what specific events, or problems, the patient has noticed since the last visit (part B). Form A–7 lists 18 terms, which are on the ***SAFTEE*** list of 76 preferred-event terms, below. For consistency, raters are asked to use these terms to record the reported event rather than their own terms or the patient's words. Alternate terms should be used only when a specific protocol requires it and should be standard across all the sites using the same protocol. For events marked by an asterisk(*), additional specifications are needed.

Alphabetical List of Preferred Terms

Abdominal pain
Accidental injury*
Akathisia
Akinesia
Anxiety/nervousness
Appetite decrease
Appetite increase
Attempted suicide
Blurred vision
Breast pain/swelling
Changes in color (urine)
Chest pain
Concentration difficulty
Confusion
Constipation
Coughing
Cramps
Decreased libido
Dental problems*
Depression
Difficulty falling asleep
Difficulty swallowing
Difficulty urinating
Discharge (nipples)
Dizziness/faintness
Drowsiness
Dry mouth
Dyskinesia* (specify where)
Dystonia* (specify where)
Earache
Early morning awakening
Edema* (specify where)
Eye irritation
Fever
Flatulence
Genital discomfort*
Gum problems*
Hair problems*
Headache*
Hypersalivation

[3] From Nassima Ait-Daoud, M.D., and Bankole Johnson, M.D., Ph.D., at the University of Texas, San Antonio Health Science Center.

SAFTEE Guidelines: Part 1 (*continued*)

Increased frequency (urination)
Increased libido
Increased thirst
Insomnia
Headache
Intercurrent illness*
Interrupted sleep
Irregular heartbeat
Irritability
Itching (specify where)
Loss of consciousness*
Medical or surgical procedure*
Memory problem
Mouth ulcer
Muscle/bone/joint pain*
Nasal congestion
Nausea
Perceptual problems
Poor hearing
Premenstrual tension
Rapid heartbeat
Rash/skin irritation*
Rigidity (muscle)
Sexual dysfunction
Shortness of breath
Sore throat
Sore tongue*
Stomach/abdominal discomfort
Stool discoloration
Somnolence
Tinnitus
Tiredness/fatigue
Tremor
Vomiting
Weight gain
Weight loss
Wheezing

Examination Procedures

When administering the ***Modified SAFTEE***, ask the patient each question and then allow sufficient time for a response. When the patient responds positively, record necessary information about that event.

For the initial visit, the assessment interval is 90 days prior to the visit; this covers the period on Form 90.

For subsequent visits, ask the patient only about events that he/she experienced since the last visit. Remind the patient of the time interval between each session to focus him/her on the appropriate period.

Completion of the Recording Form

If the patient mentions an event while answering one of the three general health questions in part A and describes it again while responding to the list of symptoms in part B, check the "Prev/Rec" box in part B.

Choose one of the following categories for every event the patient mentions:

- **Date of onset**: record the month and day that the event first occurred since the last assessment. For the initial assessment, record any event that occurred 90 days prior to the visit.

SAFTEE Guidelines: Part 1 (*continued*)

- **Duration**: record any event in increments of days. Events that last less than 1 day should be recorded as 1 day (e.g., an event that lasts 15 minutes on 1 occasion should be recorded as 1 day; an event that lasts 15 minutes on 3 different days should be recorded as 3 days). The duration should not be greater than the interval between the assessments. For the first assessment, the duration should not be greater than 90 days.
- **Pattern**: show whether the event occurred on a continuous ("CO"), intermittent ("IN"), or isolated ("IS") basis.
- **Severity**: assess the intensity of the event by referencing the ***SAFTEE Guidelines for Rating Severity of Adverse Events*** (Form A–9), through observation, and/or through the patient's report of subjective distress. Check "MN" for "Minimal," "MI" for "Mild," "MO" for "Moderate," and "S" for "Severe."
- **Drug related**: assess the relationship of drug to event. This category provides the opportunity to indicate the reasons for suspecting a drug-related effect. If no such effect is suspected, check "N" for "No." "DR" for "Dose-response" indicates that the intensity of the event is related to the dosage level. Check "TO" for "Timing of onset" if the onset of the event has some regular relationship to drug administration (e.g., it always occurs 1 hour after taking the drug). "K" for "Known drug effect" is another reason for suspecting a drug relationship. Check "O" for "Other" if other reasons are possible.
- Action taken: show the clinician's response to a particular event: "N" for "None," "IS" for "Increased surveillance," "C" for "Contra active RX," "SU" for "Suspended RX," "DC" for "Discontinued RX," "O" for "Other," "R" for Dose reduction," and "I" for "Dose increased."

SAFTEE Guidelines for Rating Severity of Adverse Events: Part 2[4]

An adverse event is defined as any side effect, complaint, new intercurrent illness, exacerbation of a previous illness, or injury that the patient experiences while involved in treatment. The event, if minimal, mild, moderate, or severe, should be documented on part B of the ***Modified SAFTEE*** (Form A–7) and described using standard medical terminology. If serious/life threatening, complete the ***Serious Adverse Event Report*** (Form A–11) and provide all required information. In addition, document any hospitalizations, or surgical or diagnostic procedures.

Common Symptom Severity Indicators

Severity:	*Minimal*	*Mild*	*Moderate*	*Severe*

1. Nausea

Minimal	Single occurrence lasting less than 2 hours; no change in eating habits
Mild	Multiple occurrences or duration of longer than 2 hours; no change in eating habits
Moderate	Intake significantly less than minimum daily requirement, but able to eat
Severe	No significant nutritional intake

2. Vomiting

Minimal	Stomach contractions, retching, or heartburn without emesis
Mild	One episode in any 24-hour period
Moderate	Two to 5 episodes in 24 hours, or 1 episode per day on 5 days or less
Severe	Six to 10 episodes in 24 hours, or more than 1 episode on more than 5 days

3. Diarrhea

Minimal	Loose but not watery stools, without cramping or incontinence
Mild	Diarrhea without cramping or incontinence, or 2 or fewer episodes per day
Moderate	Diarrhea with cramping, no incontinence, or 3 or more episodes per day
Severe	Diarrhea with incontinence and cramping, or 6 or more episodes per day

4. Abdominal Pain

Minimal	Single occurrence of abdominal pain that is not distressing and does not limit activities
Mild	Multiple occurrences of abdominal pain that are not distressing and do not limit activities

[4] From Robert Swift, M.D., Ph.D., at Brown University Medical School, Providence, Rhode Island.

SAFTEE Guidelines for Rating Severity of Adverse Events: Part 2 (*continued*)

Moderate	Single or multiple occurrences of abdominal pain that cause distress but do not limit activities
Severe	Abdominal pain or cramping of sufficient severity to limit activities

5. Change in Appetite

Minimal	Hunger increased or decreased without change in food intake or weight
Mild	Hunger increased or decreased with change in food intake and pretreatment weight stable, or less than 5-percent reduction or increase
Moderate	Hunger increased or decreased; change in food intake and 5- to 10-percent weight loss or gain present without intention to diet or gain weight
Severe	Hunger increased or decreased; weight loss or gain of more than 10 percent of pretreatment weight without intention to diet or gain weight

6. Headache

Minimal	Single occurrence of headache that is not distressing and does not limit activities
Mild	Multiple occurrences of headache that are not distressing and do not limit activities
Moderate	Single or multiple occurrences of headache that cause distress but do not limit activities
Severe	Headache with pain of sufficient severity to limit activities

7. Dizziness

Minimal	Occasional transient subjective dizziness, lasting less than 1 minute per occurrence; no impairment of function and no objective findings
Mild	Subjective dizziness lasting more than 1 minute; no impairment of function and no objective findings
Moderate	Dizziness with impairment of function or limitation of activities; nystagmus or increased body sway noted on exam
Severe	Dizziness with impairment of function, falling, or syncope

8. Fatigue

Minimal	Subjective fatigue without increased need for rest; able to perform all activities of daily living (ADLs)
Mild	Subjective fatigue with increased need for rest; able to perform all ADLs
Moderate	Subjective fatigue with increased need for rest; able to perform ADLs only with effort
Severe	Unable to perform ADLs; able to meet basic needs only with assistance

SAFTEE Guidelines for Rating Severity of Adverse Events: Part 2 (*continued*)

9. Nervousness/Anxiety

Minimal	Occasional nervousness/anxiety that does not cause distress or limit activities
Mild	Occasional nervousness/anxiety that is distressing but tolerable, but does not limit activities
Moderate	Occasional or persistent nervousness/anxiety that is distressing but tolerable and limits activities
Severe	One or more panic attacks or persistent nervousness/anxiety that are intolerable

10. Insomnia

Minimal	Sleep that is not restful but without change in amount or pattern of sleep
Mild	More than three occasions of unexplained difficulty falling asleep or of increased nocturnal awakenings, but without change in amount of sleep
Moderate	More than three occasions of unexplained difficulty falling asleep and nocturnal awakenings with significant reduction in sleep, but without daytime impairment of function
Severe	More than three occasions of unexplained difficulty falling asleep and nocturnal awakenings with significant reduction in sleep, with daytime impairment of function

11. Somnolence

Minimal	Occasional subjective tiredness but without change in daily activities
Mild	Persistent subjective tiredness but without change in daily activities
Moderate	Persistent subjective tiredness; requiring resting or napping less than 2 hours during the day
Severe	Persistent tiredness that significantly limits daily activities, requiring napping or resting more than 2 hours daily; falling asleep during work, school, or other activities

12. Depression

Minimal	Occasional depressed mood that does not cause distress or limit activities
Mild	Occasional depressed mood that is distressing but tolerable, but does not limit activities
Moderate	Occasional or persistent depressed mood that is distressing but tolerable and is associated with change in activities
Severe	Suicidal ideation or persistent depression that is intolerable and is associated with change in activities

SAFTEE Guidelines for Rating Severity of Adverse Events: Part 2 (*continued*)

13. Itching

Minimal	Localized itching without need to scratch
Mild	Localized itching with scratching
Moderate	Generalized itching that is tolerable, does not interfere with sleep or activities
Severe	Generalized itching that is intolerable, interferes with sleep and/or activities

14. Skin Rash

Minimal	Localized erythema or localized macular/papular eruption lasting less than 48 hours and without symptoms
Mild	Localized erythema or localized macular/papular eruption lasting longer than 48 hours and without symptoms
Moderate	Erythema or macular/papular eruption with pruritis or other associated symptoms involving more than one site on the body
Severe	Generalized (most of body affected) symptomatic macular, papular, or urticarial or atypical eruption with or without mucous membrane involvement and with or without exfoliative dermatitis or ulcerating dermatitis

15. Change in Libido

Minimal	Occasional increase or decrease in libido that does not engender distress or concern; no change in sexual activity or performance
Mild	More persistent libido increase or decrease that does not engender distress or concern; no changes in sexual activity or performance
Moderate	More persistent libido increase or decrease that does engender distress or concern; change in sexual activity or performance reported
Severe	Significant increase or total lack of interest in sex that is distressing or of concern; associated with changes in sexual activity or performance

16. Missed Menses

Minimal	Single occurrence of delayed menses (one cycle) that is otherwise regular
Mild	Single occurrence of absent menses (one cycle) that is otherwise regular
Moderate	Multiple occurrences of delayed or absent menses
Severe	Total amenorrhea

Form A–10

Menstrual Calendar

Center | Patient # | Patient Initials

Date (month / day / year) | Staff ID #

Instructions: Record the pattern of a woman's menstrual cycle in a calendar format to indicate any irregularities and/or missed periods as the result of early pregnancy. Record initially at baseline during the physical exam and continue through the protocol (the form is cumulative).

Instructions for Completing the Menstrual Cycle Chart

- Perform a pregnancy test prior to randomization on all female patients unless they are menopausal (no period for more than 1 year) or have had a hysterectomy or tubal ligation.
- Find the correct month. Put an "**X**" in the box of the **first** day of the last period and put **X**s in the following boxes through the **last** day of bleeding.
- At baseline, do the same for the two prior menstrual cycles.
- At each visit, put an "**S**" in the box of the day(s) where there has been any spotting since the last visit.
- If it has been 35 or more days since the first day of the patient's last period, do a pregnancy test at the visit. Also perform a pregnancy test if the patient has experienced any irregular spotting or bleeding between periods. Consider doing a pregnancy test every 4 weeks for any patient who does not have a consistent bleeding pattern (21- to 35-day cycles).
- **If the patient's pregnancy test is positive, discontinue the medications**. Pregnant women can continue to receive the counseling components of the treatment. In addition, refer the patient to an appropriate medical care provider regarding her pregnancy.

Year	Month	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
	January																															
	February																															
	March																															
	April																															
	May																															
	June																															
	July																															
	August																															
	September																															
	October																															
	November																															
	December																															

Form A–10

Menstrual Calendar (*continued*)

Center | Patient # | Patient Initials

Date (month / day / year) | Staff ID #

Instructions: Complete at each MM visit. This form is cumulative.

Week # / Sequence #	MM Session Date (mm/dd/yy)	Birth Control		Type of Birth Control (See Codes at Bottom of Page)	Date of Last Menstrual Period	Pregnancy Test		Pregnancy Test Results		Notes
		Yes	No		(mm / dd / yy)	Yes	No	Pos.	Neg.	
/	/ /	q	q		/ /			q	q	
/	/ /	q	q		/ /			q	q	
/	/ /	q	q		/ /			q	q	
/	/ /	q	q		/ /			q	q	
/	/ /	q	q		/ /			q	q	
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/	/ /	q	q		/ /			q	q	
/	/ /	q	q		/ /			q	q	

Methods of Birth Control: **1**=oral contraceptives **2**=hormonal (levonorgestrel) or surgical implants **3**=barrier plus spermicide **4**=abstinence **5=**other **6=**NA **(**menopausal—no period for > 1 year, hysterectomy, tubal ligation).

Form A–11

Serious Adverse Event Report

Center	Patient #	Patient Initials	Week	Sequence
				0 1

Date: ___ / ___ / ____ (month / day / year)

Staff ID #: ____

Instructions: Complete this form whenever a patient has an experience that is known with certainty or suspected with good reason to constitute a threat to life or to cause severe or permanent damage. A serious adverse event is characterized by one or more of the following: it requires inpatient or prolonged hospital-ization; it results in persistent or significant disability/incapacity; it results in death; it is life-threatening; or it is a congenital anomaly/birth defect. Drug misuse, drug overdose, and malignant tumors should also be regarded as serious, even if they do not result in the outcomes mentioned above. If there is a question about whether an event should be defined as serious, reference the FDA definition of a serious adverse event in the Federal Register. Once completed, notify the appropriate agencies within 48 hours.

1. a. Gender: **F**emale q **M**ale q b. Age: ____
2. Start of treatment: _____/_____/_____ (month day year)
3. Onset date of SAE: _____/_____/_____ (month day year)
4. Serious adverse experience (describe sign/symptom): _____
5. Action taken (check all that apply):

Yes	**No**			
q	q	a) Medication		
q	q	b) Dose reduced		
q	q	c) Drug temporarily stopped	(Date stopped:	____/____/_____)
q	q	d) Drug permanently stopped	(Date stopped:	____/____/_____)
q	q	e) Hospitalized		month day year
q	q	f) Other	Specify: _____	

6. Why was the event serious? (**check one**):
   - q 1) Fatal event
   - q 2) Life-threatening event
   - q 3) Disabling/incapacitating
   - q 4) Inpatient hospitalization
   - q 5) Hospitalization prolonged
   - q 6) Congenital anomaly
   - q 7) Cancer
   - q 8) Result of an overdose
7. Relationship to drug (**check one**):
   - q 1) Not related
   - q 2) Possibly related
   - q 3) Not assessable

Form A–12

Serious Adverse Event Followup Report

Center	Patient #	Patient Initials	Week	Sequence

Date: ___ ___ / ___ ___ / ___ ___ ___ ___ (month / day / year)

Staff ID#: ___ ___ ___

Instructions: Indicate date and any specific followup events or other clinical information relevant to the SAE reported on Form A–11.

Signature:_____

Form A–13

Medication Compliance Plan

Center | Patient # | Patient Initials | Week

Date: month / day / year

Staff ID#

I. Examine Patient's History of Medication/Vitamin-Taking Practices

A. Determine Patient's Experience With Pill-Taking

For each item below, check one response (Y/N). If "Yes," indicate in the next column if patient was successful (Y/N) at taking the pills under the conditions specified. If "No," that is, patient has not had the experience for longer than 1 week, check last column (N/A).

		Patient Response		Was Patient Successful		
		Y	N	Y	N	N/A
1.	Were you ever instructed or have you ever tried independently to take a pill(s) on a daily basis?	q	q	q	q	q
2.	Were you ever instructed or have you ever tried independently to take four or more pills at one time on a daily basis?	q	q	q	q	q
3.	Were you ever instructed or have you ever tried independently to take pills later in the day or at bedtime on a daily basis (in contrast to morning daily doses)?	q	q	q	q	q
4.	Were you ever instructed or have you ever tried independently to take pills from blister cards?	q	q	q	q	q
5.	Do you typically carry pills on or with you?	q	q	q	q	q
6.	Do you usually take prescribed medications/vitamins until all pills are gone?	q	q	q	q	q

Notes:

Medication Compliance Plan (*continued*)

Center | Patient # | Patient Initials | Week

Date (month / day / year) | Staff ID#

B. Review Common Reasons for Pill Noncompliance (optional—to be used when appropriate per patient; strongly suggest use with all patients at initial session)

Ask the patient, "Have you experienced or could you see yourself not taking your medications during this treatment because of any of the following reasons?" (**Circle all that apply**)

1. Forgets to take or loses medications
2. Worries about side effects
3. Believes he/she is taking placebo
4. Has misinformation about medications (e.g., expects instant changes in drinking)
5. Has never liked taking pills—even aspirin
6. Desires to drink or "get high"
7. Tires of taking pills every day
8. Disagrees about having an alcohol disorder
9. Feels like he/she no longer needs medications

Tell the patient, "If any of these situations occur during treatment, please talk to me about it."

Notes:

C. Discuss Successful Pill-Taking Strategies

List any pill-taking strategies that the patient uses/has used and indicate how successful they are/were. If the patient has no prior experience with pill-taking, have him/her think of strategies for remembering to take pills and list them here:

Medication Compliance Plan (*continued*)

Center | Patient # | Patient Initials | Week

Date (month / day / year) | Staff ID#

D. Summary and Recommendation

Based on patient responses on section A and notes, check the number that best applies.

___1. Experienced and successful with daily pill-taking. May not need a new plan.

___2. Experienced but has **NOT** been successful with daily pill-taking. May require a comprehensive plan with continual re-evaluation.

___3. No experience with daily pill-taking. Requires a basic plan for pill-taking.

II. Personalized Medication Compliance Plan

Record date: _____ (month) / _____ (day) / 20 _____ (year) Note: This plan can be revised as needed.

Pill Count (version used in COMBINE study)

Center	Patient #	Patient Initials	Week	Sequence	Date	Staff ID #
					month / day / year	

Instructions: If the blister card is not returned, check "No" for Patient Report. If the blister card is returned at a later date: 1) make any necessary changes based on the blister card and 2) for Patient Report, put a line through "No" and check "Yes."

Day of Week	1. M/Tu/W/Th/F/Sa/Su	2. M/Tu/W/Th/F/Sa/Su	3. M/Tu/W/Th/F/Sa/Su	4. M/Tu/W/Th/F/Sa/Su	5. M/Tu/W/Th/F/Sa/Su
Date	___/___/_____ mm dd yy	___/___/_____ mm dd yy	___/___/_____ mm dd yy	___/___/_____ mm dd yy	___/___/_____ mm dd yy
Enter # of Pills prescribed (PP) Pills taken (PT)	**NALT:** **ACAM:** PP: ____ PP: _____ PT: ____ PT: _____	**NALT:** **ACAM:** PP: ____ PP: _____ PT: ____ PT: _____	**NALT:** **ACAM:** PP: ____ PP: _____ PT: ____ PT: _____	**NALT:** **ACAM:** PP: ____ PP: _____ PT: ____ PT: _____	**NALT:** **ACAM:** PP: ____ PP: _____ PT: ____ PT: _____
Comments					
Patient Report	Pkg. return: Yes q No q	Pkg. return: Yes q No q	Pkg. return: Yes q No q	Pkg. return: Yes q No q	Pkg. return: Yes q No q
Day of Week	6. M/Tu/W/Th/F/Sa/Su	7. M/Tu/W/Th/F/Sa/Su	8. M/Tu/W/Th/F/Sa/Su	9. M/Tu/W/Th/F/Sa/Su	10.M/Tu/W/Th/F/Sa/Su
Date	___/___/_____ mm dd yy	___/___/_____ mm dd yy	___/___/_____ mm dd yy	___/___/_____ mm dd yy	___/___/_____ mm dd yy
Enter # of Pills prescribed (PP) Pills taken (PT)	**NALT:** **ACAM:** PP: ____ PP: _____ PT: ____ PT: _____	**NALT:** **ACAM:** PP: ____ PP: _____ PT: ____ PT: _____	**NALT:** **ACAM:** PP: ____ PP: _____ PT: ____ PT: _____	**NALT:** **ACAM:** PP: ____ PP: _____ PT: ____ PT: _____	**NALT:** **ACAM:** PP: ____ PP: _____ PT: ____ PT: _____
Comments					
Patient Report	Pkg. return: Yes q No q	Pkg. return: Yes q No q	Pkg. return: Yes q No q	Pkg. return: Yes q No q	Pkg. return: Yes q No q

11. Any change to prescribed dose schedule? Yes q No q

11a. If yes, date change started: ___/____/____ mm dd yy

11b. Date ended: ___/___/_____ mm dd yy

11c. Describe change:_____

11d. Reason for change to Rx dose schedule: _____

Form A–15

Date Entered_____
Staff Initials_____

Day 3 Clinician Phone Contact

Center | Patient # | Patient Initials | Week

Date (month / day / year) | Staff ID #

Instructions: Complete this for all patients on the third day of Week 1. Complete also on the third day after a dose reduction. If you do not reach the patient on the third day, call on the fourth or fifth day.

1. Reason that patient was called:
   - q Week 1, day 3 phone contact
   - q Other:

2. Did you reach the patient? q Yes q No
   a) If no, did you reach the patient on day 4? q Yes q No
   b) If no, did you reach the patient on day 5? q Yes q No

3. Is the patient taking the prescribed medications?
   - q a) Yes, as prescribed
   - q b) Yes, but not as prescribed
   - q c) No — Date stopped: __/__/____

4. Is the patient drinking? q Yes q No

5. Which of the following symptoms, if any, is the patient having? (**Check all that apply**)
   - q a) No side effects
   - q b) Nausea
   - q c) Vomiting
   - q d) Diarrhea
   - q e) Headache
   - q f) Anxiety
   - q g) Rash
   - q h) Other (specify)

6. What did you recommend? (**Check all that apply**)
   - q a) No change
   - q b) Dose reduction
   - q c) Pepto-Bismol®
   - q d) Vistaril®
   - q e) Change in time of dosing
   - q f) Tylenol
   - q g) Take with food
   - q h) Other (specify)

Form A–16

COMBINE Study Fact Sheet for the Practitioner

Study Title

Combining Medications and Behavioral Interventions

Study Purpose

To examine the potential toxicity and acceptability of the administration of naltrexone and acamprosate both alone and in combination in approximately 1,375 alcohol-dependent patients.

Study Duration

The majority of COMBINE patients will receive 16 weeks of Medical Management (MM) and pharmacotherapy in a double-blind, placebo-controlled trial in one of three categories: (1) the combination of naltrexone and acamprosate; (2) each medication alone plus placebo; or (3) just placebo. One-half of the patients will also be given the Combined Behavioral Intervention (CBI). A small cohort (approximately 150 patients) will not receive pharmacotherapy but will receive CBI.

MM Session Schedule

Nine sessions total: Weeks 0, 1, 2, 4, 6, 8, 10, 12, 16.

Procedure for Dispensing Medications

A medical professional will dispense medications at MM sessions.

At the initial MM session, the MM clinician observes the patient taking his/her first dose of medication. The patient should receive the morning dose at the initial MM session no matter what time the appointment takes place. If the session is held in the morning, the patient is to take all three doses that day. If the initial MM session is held in the afternoon, the patient is to take the evening dose that evening, and the clinician should tape over the Day 1 afternoon dose on the blister card.

Note: The clinician may instruct patients to take their medication with meals.

Three days after the first MM session, the MM clinician should call the patient to inquire whether he/she is taking and/or tolerating the medication and then complete the ***Day 3 Clinician Phone Contact*** form (Form A–15). At all MM sessions, the clinician should support and encourage the patient in taking the medication. If the patient is having difficulty tolerating the run-up dose because of nausea and/or vomiting, the clinician should first encourage the patient to use Pepto-Bismol®. If the patient has already tried that without success, the clinician should proceed with the dosage reduction strategy outlined in the "Procedure for Reducing Dosage" section included in this fact sheet.

Emergency Cards

Patients will be given emergency cards to carry in their wallets stating that they are in a study involving investigative medications including naltrexone. The card includes suggestions on how medical practitioners should treat the patient in cases of cardiopulmonary resuscitation or if anesthesia is required; phone numbers for the patient's physician, pharmacy, and 24-hour emergency assistance; and treatment beginning and ending dates. The patient's significant other will also be given an emergency card.

COMBINE Study Fact Sheet (*continued*)

Medication Packaging

Blister cards

Dosage Form

All study patients will take four tablets in the morning, two tablets at midday, and two tablets in the evening of some combination of active medication or placebo.

Note: Patients should be advised not to crush acamprosate pills because this can reduce the pill's bioavailability and increase the gastrointestinal (GI) side effects.

Timing of Doses

If a patient misses a dose of acamprosate, he/she should *not* take it simultaneously with the next scheduled dose; there should be a minimum of 2 hours between doses. If this is not feasible, the clinician should instruct the patient not to take the skipped dose but to wait until the next scheduled dose and take only that dose.

If a patient misses the morning dose, the clinician should instruct him/her to replace the midday dose with the morning dose.

It is permissible to administer naltrexone BID when evidence of side effects dictates twice-a-day dosing.

Procedure for Handling Side Effects

The clinician should handle side effects by doing the following:

1. Listen to patient complaints seriously.
2. Rule out any serious concomitant medical disorders.
3. Rule out serious drug-related adverse experiences as evidenced by such symptoms as yellow eyes, light-colored stools, dark urine, or severe abdominal pain.
4. Ask the patient if he/she has recently used alcohol or other drugs. Rule out alcohol, opiate, or other drug use and/or withdrawal as contributors to presenting complaints.
5. Ascertain what strategies the patient has used to manage the presenting symptom(s) and the degree of relief obtained, if any. Refer the patient to ***Patient Instructions for Managing Side Effects*** (Form C–5).
6. Reassure the patient that adverse drug experiences tend to be transient and resolve within 12 to 72 hours.
7. Tell the patient that the first steps in dealing with adverse experiences should be to take an over-the-counter medication such as Pepto-Bismol (for GI side effects) or acetaminophen (for headache); adjust the time of the dosing (e.g., take naltrexone at night); and/or take the medication with meals. If this is unsuccessful or insufficient, try the dose reduction strategy as detailed under "Procedure for Reducing Dosage," below. The following step, if necessary, should be to use prescription medication (i.e., hydroxyzine) (see step #8).

COMBINE Study Fact Sheet (*continued*)

8. Use hydroxyzine (Vistaril®) as a treatment for several side effects; prescribe it for a maximum of the equivalent of 10 days dosage. If the patient discontinues Vistaril and side effects reappear, prescribe Vistaril again; however, the patient must be off Vistaril for at least 3 days before taking it again.

Procedure for Reducing Dosage

The clinician should do the following for patients reporting nausea, vomiting, diarrhea, dizziness, nervousness, anxiety, and insomnia:

1. Tell the patient that the doses of one medication will be reduced initially, and if this is not sufficient, the dose of the other medication will be reduced.
2. Tell the patient to take only one acamprosate in the morning and one in the afternoon, rather than taking two in the morning and two in the afternoon.
3. Reduce the patient's dose of naltrexone before reducing the acamprosate dose if the patient's bilirubin level increases by 50 percent over baseline values and is still within allowable limits for patient to stay in the study. If the patient continues to suffer from side effects when the naltrexone dosage has been reduced to 50 mg, reduce the dosage to 25 mg. However, if the patient cannot tolerate the 25 mg dose of naltrexone, discontinue all study medications.
4. Reduce the patient's dose of naltrexone to 25 mg for all side effects, including elevated bilirubin, if he/she cannot be maintained on the 50 mg dose. Attempt to increase the dose of naltrexone whenever possible, but if the patient cannot tolerate the increase, he/she can remain on a maintenance dose of 25 mg of naltrexone.
5. Call the patient 3 days after making a dosage reduction. If the patient is doing better, he/she can stay with this dosage regimen. If the patient still experiences symptoms, tell him/her to take only one naltrexone in the morning rather than two. Complete the ***Day 3 Clinician Phone Contact*** form (Form A–15).
6. At the next MM visit, encourage the patient to start increasing the medication dosage, beginning with naltrexone. If the patient is able to tolerate it, increase the acamprosate dose 3 days later. If the patient is unable to tolerate a second dose increase, recommend going back to the reduced dosage level. If the patient is reluctant to go back to the full dose, assure him/her that if the side effects return at the full dose, he/she may go back to the lower dose.

Procedure for Retitration

Acamprosate will not be titrated. These procedures refer to naltrexone only. Patients who have been off study medications for 4 or more weeks may be retitrated at the discretion of the clinician. Although patients who have been off medication for less than 4 weeks probably do not need retitration, the procedure may be used anyway.

If a patient is removed from study medication for any length of time, the retitration would be 2 days at 50 mg naltrexone per day, and then the patient will resume the usual dose of 100 mg of naltrexone a day. This will occur at the discretion of the study medical clinician; if a patient did not experience any side effects while taking the study medication previously, the medical clinician may decide not to retitrate.

COMBINE Study Fact Sheet (*continued*)

Patients who are retitrating will be instructed to take only 1 pill of naltrexone per day for the 2 days of 50 mg dosing.

If the patient is not tolerating the study medication, he/she could be retitrated on 25 mg of naltrexone (half of 1 pill) at the discretion of the medical clinician.

Management of Adverse Effects

The clinician should manage adverse effects by doing the following:

Diarrhea

1. Suggest that the patient take Pepto-Bismol® if he/she has not already done so. If this does not work in 1 to 2 days, proceed to #2.
2. Reduce the dose of the study medication as described in the section "Procedure for Reducing Dosage."

Nausea

1. Suggest that the patient take Pepto-Bismol if he/she has not already done so. If this does not work in 1 to 2 days, proceed to #2.
2. Reduce the dose of the study medication as described in the section "Procedure for Reducing Dosage."
3. If the patient continues to experience nausea for 3 days after the doses of both medications have been reduced, offer a prescription for hydroxyzine pamoate (Vistaril®), 25 mg to 50 mg, after checking for allergies; instruct the patient to take Vistaril 30 minutes before taking the next dose of the study medication. Patients can take up to 50 mg of Vistaril per day, either all in the morning, all in the evening, or half in the morning and half in the evening. Some patients will do better taking the Vistaril in the morning because they may experience worse nausea in the morning. However, Vistaril can be sedating in some people, so balance these two considerations in deciding about the timing of the Vistaril dosing. Note on the ***Concurrent Medications*** form (A–3) if you have prescribed Vistaril.
4. If steps #1 through #3 are not successful, hold all doses of study medication, and proceed with the steps under "Vomiting."

Vomiting

1. Discontinue study medication until the patient is no longer nauseated.
2. When the patient has a morning on which he/she experiences no nausea, check for allergies and, if possible, prescribe 25 mg or 50 mg of Vistaril to be taken 30 minutes before taking a dose of study medication (see #3 in the "Nausea" section for further details about Vistaril dosing).
3. Reduce the dose of the study medication as described in the section "Procedure for Reducing Dosage."

Dizziness, Nervousness, Anxiety, Insomnia

Prescribe 25 mg or 50 mg of Vistaril.

COMBINE Study Fact Sheet (*continued*)

Headaches

Advise the patient to take over-the-counter medications such as acetaminophen.

Dermatologic Symptoms

1. If the patient experiences localized rash or pruritis, no intervention is required; explore other etiology.
2. If the patient experiences generalized erythema and/or macular or maculopapular rash and/or pruritis, without other etiologic explanation:
   a) Discontinue vitamin B supplements.
   b) Try symptomatic treatment with oral antihistamines (e.g., hydroxyzine hydrochloride [Atarax®], 25 mg t.i.d.) and topical corticosteroids (e.g., triamcinolone acetonide cream) for up to 1 week.
      (i.) If rash/pruritis improves or disappears, continue the study drug.
      (ii.) If rash/pruritis worsens, the rash is atypical (i.e., other than maculopapular), the rash is urticarial, or if there is mucous membrane involvement, in the absence of another etiologic explanation, discontinue study drug and refer the patient to a dermatologist for evaluation and possible biopsy. (Note: Code as an adverse event, and prepare other appropriate documentation.)

Procedure for Handling Abnormal Lab Values

The clinician should handle abnormal lab values as follows:

Elevated Liver Enzymes: A patient with an ALT/AST greater than five times the normal rate will need to have ALT/AST repeated within 1 to 2 weeks; if it is still greater than five times the normal rate after that, stop the patient's medication. If the repeat values are less than five times the normal rate but are still elevated, monitor the patient using clinical judgment. A study physician will evaluate the patient if he/she has a total bilirubin above 50 percent baseline level but is still within normal range to determine whether he/she should discontinue study medication.

If a patient's bilirubin levels increase by 50 percent over the baseline values but still remain within the normal range, reduce the naltrexone dose first, rather than run the risk that the patient's bilirubin levels will continue to rise and meet the threshold for the patient's withdrawal from the study medications altogether. As when handling the patient's side effects, reduce the naltrexone dose to 25 mg if the patient cannot tolerate the 50 mg dosage. However, if the patient cannot tolerate the 25 mg dose of naltrexone, discontinue all study medications.

Patients whose total bilirubin is greater than 10 percent above the upper limit of normal will be taken off the study medication immediately.

COMBINE Study Fact Sheet (*continued*)

Renal insufficiency: A study physician will evaluate patients whose serum creatinine level is 1.3 or 1.4 to ascertain whether they should discontinue study medication. However, if a patient has a creatinine cut-off of 1.5, he/she should be removed from the study medication.

GGT: If a patient's GGT is elevated, the responsible medical clinician will determine the course of action, which may include more frequent monitoring of liver function tests.

Week 16 Lab Results

The clinician providing feedback for Week 16 lab results should contact the patient after treatment has ended, relaying the lab results by phone if the patient is not available in person.

Procedure for Adding Concurrent Medications

Patients should be regularly reminded to report any concurrent medications they are taking, including over-the-counter preparations, vitamins, and so on. Because acamprosate is eliminated exclusively by the renal route, patients should avoid nephrotoxic drugs, such as aminoglycoside antibiotics, during this study as well as diuretics, which affect elimination of acamprosate. Patients can intermittently take nonsteroidal anti-inflammatory drugs, which also affect the elimination of acamprosate, but they should avoid these drugs when possible. Because naltrexone is an opiate antagonist, patients should avoid narcotics and other opioid drugs during the study, as well as Mellaril®, which has been associated with an adverse interaction with naltrexone.

If a patient begins to take a concurrent medication on the disallowed list, he/she should be discontinued from study medication immediately.

Drugs not allowed as concomitant medications

- Cis-retinoic acid (Accutane®)
- Alphamethyl Dopa (Aldomet®)
- Anorexics (e.g., over the counter, amphetamines, phenylpropanolamine, Dexatrim®)
- Antiarrhythmics (e.g., quinidine, digoxin [Lanoxin®], disopyramide [Norpace®])
- Anticoagulants (e.g., coumadin [Warfarin®])
- Anticonvulsants (e.g., valproic acid [Depakote®], gabapentin [Neurontin®], phenytoin [Dilantin®], carbamazepine [Tegretol®])
- Antidepressants (e.g., fluoxetine [Prozac®], sertraline [Zoloft®], paroxetine [Paxil®], trazodone [Desyrel®], desipramine [Norpramin®])
- Antipsychotics (e.g., haloperidol [Haldol®], risperidone [Risperdal®], olanzepine [Zyprexa®], fluphenazine [Prolixin®], perphenazine [Trilifon®])
- Antiretrovirals (Combivir®, Epivir®, Norvir®, Retrovir®)
- Buprenorphine (Buprenex®)

COMBINE Study Fact Sheet (*continued*)

- Bupropion (e.g., Wellbutrin®, Zyban®)
- Buspirone (Buspar®)
- Chemotherapeutic agents for cancer
- Cholestyramine
- Disulfiram (Antabuse®)
- Duradrin
- Flexeril
- Herbal supplements with GABA properties (e.g., Kava, GABA, or DHEA) or antidepressant properties (e.g., St. John's Wort, L-Tryptophan, 5-HTP)
- Herbal supplements containing ephedra
- Methotrexate
- Monoamine oxidase inhibitors (e.g., phenelezine [Nardil®], tranylcypromine [Parnate®])
- Mood stabilizers (e.g., lithium [Eskalith®, Lithobid®])
- Opioid analgesics (e.g., morphine, codeine, oxycodone [Percodan®, Percocet®], hydrocodone [Vicodan], propoxephine [Darvon], tramadol [Ultram®])
- Ondansetron (Zofran®)
- Oral corticosteroids (e.g., prednisone, dexamethasone)
- Psychostimulants (e.g., amphetamines [Dexadrine®], methylphenidate [Ritalin®])
- Reserpine
- Robaxin
- Sedatives (antihistamines are okay) (e.g., barbiturates, benzodiazepines, hypnotics [Ambien®]).

Drugs allowed as concomitant medications

- Acyclovir
- Allopurinol
- Antiasthma agents (e.g., inhalers, B-agonists, theophylline), antibiotics
- Anti-inflammatory drugs (e.g., aspirin, ibuprofen [Motrin®, Advil®], naproxen [Naprosyn®, Aleve®])
- Aspirin (81 mg/day regimen for cardiac disease)
- Colchicine
- Inhaled steroids

COMBINE Study Fact Sheet (*continued*)

- Lipitor®: permitted if on a stable dose (3 months). Lipitor should not be started and the dose should not be changed during the trial.
- Melatonin
- Nicotine replacement therapy (e.g., gum, inhaler, or patch [no Zyban®])
- Proton pump inhibitors (pantoprazole)
- Sildenafil.

Drugs allowed as concomitant medications for chronic use only (consistent use for 1 month prior to randomization and dose stabilized, or if the medication is started postrandomization)

- Antianginal agents: nitrates
- Antihypertensives (e.g., doxazosin [Cardura®], terazosin [Hytrin®], Tenormin®, diltiazem [Cardizem®], lisinopril [Zestril®], enalapril [Vasotec®], metoprolol [Lopressor®])
- Calcium channel blockers (e.g., nifedipine, verapamil, nimodipine)
- Clonidine (Catapres®)
- Diuretics (e.g., hydrochlorothiazide [Diuril®, Dyazide®], spironolactone [Aldactone®])
- H2 Blockers (e.g., ranitidine [Zantac®] [No cimetidine])
- Hormones and oral contraceptives (estrogen [Premarin®], progesterone)
- Insulin
- Oral hypoglycemic agents
- Thyroid supplements.

Drugs allowed as concomitant medications for episodic use only

- Analgesics, nonnarcotic (e.g., aspirin, acetaminophen [Tylenol®], ibuprofen [Motrin®, Advil®])
- Antacids (e.g., magnesium hydroxide-aluminum hydroxide [Maalox®, Mylanta®], calcium [Tums®])
- Antidiarrheal preparations (not opioid-based)
- Antihistamines (e.g., diphenhydramine [Benadryl®], hydroxyzine [Vistaril®], Claritin®, cetrizine [Zyrtec®])
- Antimigrain (e.g., Imitrex®, no Fiorinal®)
- Antinausea agents
- Cough/cold preparations (nonnarcotic cough suppressants)
- Laxatives.

COMBINE Study Fact Sheet (*continued*)

Procedure for Managing Patients Who Request Treatment Outside COMBINE

The clinician should follow the steps below for problematic patients:

1. Employ MM strategies, such as suggesting the patient attend more AA or Al-Anon meetings.
2. Advise patients requesting additional formal help that it is common for ancillary problems such as marital or parenting issues to arise during the course of treatment and that such problems might eventually be resolved or reduced if they maintain abstinence. Review these matters again at the end of the patient's treatment, but focus primarily on MM-related concerns (i.e., medication compliance, side effects, and support for abstinence).
3. The project coordinator (PC) and principal investigator (PI) should be involved if clinical deterioration is an issue.
4. If a patient's ancillary problems persist, refer the patient to the PC so he/she can provide the patient with referral sources.
5. If the patient is struggling with concrete problems such as housing, unemployment, or financial matters, make a case management referral to other formal treatment(s). (This is consistent with the MM model because such referrals would help provide the necessary foundation to support the patient's ongoing abstinence.)

Patients who become involved in formal adjunctive treatment will not be removed from the treatment protocol. However, the clinician should document this involvement in the Research Records.

Procedure for Handling Emergent Psychiatric Symptoms

This is site-specific, based on good clinical practice protocols designed to ensure patient safety at each institution.

Procedure for Handling Increased Drinking

Based on the treatment goals of total abstinence and decreased drinking, patients who require a more intensive treatment setting at any point after randomization will be categorized as "treatment failure." Such patients will be discontinued from further study participation. The clinician will document the reason for premature discontinuation of such patients as "needed more intensive treatment" in the Research Records.

Medication Noncompliance

If the patient takes any dose not as prescribed, the clinician should document it as noncompliance in the Research Records.

Treatment Noncompliance

Inactive Status

A patient will be designated "inactive" if he/she misses three consecutive scheduled sessions or does not attend a visit in 1 month (whichever comes first), regardless of the reasons for missing the sessions. Also, a patient who directly expresses his/her unwillingness to reschedule subsequent treatment sessions will be declared "inactive."

COMBINE Study Fact Sheet (*continued*)

When a patient is designated inactive in MM, the MM clinician will send him/her a formal note confirming his/her decision not to attend or resume MM sessions and/or take trial medication. The note will include a message encouraging the patient to return to MM and/or resume trial medication at a later time if desired. The clinician will send a followup letter 2 weeks later, reiterating this message.

When a patient is designated inactive in both CBI and MM, the MM clinician will send a formal note confirming the patient's decision not to attend or resume MM sessions and/or take trial medication (the CBI therapist will send a separate note). The note will include a message encouraging the patient to attend future MM sessions and/or to resume trial medication if desired. The MM clinician will send a followup letter 2 weeks later, reiterating this message.

The clinician should document in the Research Records the patient's inactive status as such:

1. The patient discontinues study medications but continues to go to MA sessions.
2. The patient discontinues medications and MA.

Note whether it was the clinician's or the patient's decision to discontinue study medications or MA and indicate reasons for discontinuation of study medication. Indicate also if patient continued or not with CBI, where applicable.

Preparing for the Final MM Session

As soon as the clinician feels he/she has engaged the patient in the treatment and has had several productive visits (e.g., six to seven visits), the clinician needs to begin to anticipate, with the patient, what will occur at the end of the research treatment period. Before the final visit, the clinician should discuss with the patient what type of treatment, if any, the patient may want to pursue following completion of the research treatment trial. The clinician should inform the patient that he/she cannot continue treatment with the clinician after the scheduled treatment ends. Since the MM clinician in a double-blind study will not know which active medication, if any, the patient has taken, it is difficult for this clinician to clearly recommend a particular course of treatment in the future. Thus, the clinician should ask the patient about his/her thoughts about continuing treatment (or not), and then use best clinical judgment in discussing this issue and in recommending future treatment. The clinician should consider the patient's current clinical condition and wishes when making this recommendation.

If the patient is assigned to both MM and CBI, the clinician and therapist should coordinate the referral process prior to the last session and not provide contradictory information to the patient.

Reasons for Discontinuation of Study Medications

Below is a list of reasons why the clinician should stop the patient's medications:

1. The patient has a severe and/or serious adverse experience or severe intercurrent medical/psychological/surgical event.

COMBINE Study Fact Sheet (*continued*)

2. There was an appearance of an exclusion criterion not considered attributable to study medication (e.g., pregnancy).
3. The patient's AST/ALT is greater than five times normal after the test has been repeated.
4. The patient's total bilirubin is greater than 10 percent of the upper limit of normal.
5. The patient's serum creatinine level is 1.5 or greater.

Reasons for Premature Study Discontinuation

[Note: An effort must be made to have all patients who prematurely discontinue study participation undergo an end-of-treatment evaluation (Visit 9).]

Below is a list of reasons why patients could leave the study before they finish treatment:

1. The patient required more intensive treatment during the active treatment phase, so his/her status is considered "treatment failure."
2. The patient had reasons other than "treatment failure" (e.g., work commitments do not permit keeping appointments, relocates).
3. The investigator decides to discontinue patient participation prematurely for a reason other than "treatment failure."

APPENDIX B
MEDICAL MANAGEMENT TRAINING AND SESSION ADHERENCE CHECKLISTS

Form B–1

MM Practitioner Qualifications, Training, and Supervision

Practitioner Qualifications

To be an MM practitioner, the person should be medically trained and have a working knowledge of the following areas: the pharmacotherapies to be used, medication compliance, and alcohol dependence. Prior education on substance dependence and/or exposure to substance abuse patients is important, but the MM practitioner is not required to be a specialist in counseling, therapy, or substance abuse treatment. Depending upon the medical training the MM practitioner has, he/she may need supervision and should have access to physician consultation about medication side effects, changes in dosing, significant lab values, and any medical concerns.

In the COMBINE study, pharmacists, physicians, nurse practitioners, physician's assistants, and nurses delivered the MM intervention. MM clinicians were required to be certified in providing the MM intervention prior to giving treatment in the main study. There was on-site supervision for the duration of the study. Also, each site regularly submitted audiotapes of MM sessions the practitioners conducted, and a centralized intervention-training center for COMBINE at the University of New Mexico provided written feedback on their delivery.

Practitioner Training

Besides staying focused on the medical and health-related issues, the MM practitioner needs to express warmth and support while conveying his/her expertise and knowledge (i.e., have a good bedside manner). To this end, the MM practitioner undergoes training comprising the following three segments:

1. *Preparation.* The practitioner needs to learn and understand the general and treatment-specific MM procedures, documentation requirements, and overall purpose of the intervention.
2. *Practice.* The practitioner needs to practice delivering the MM intervention to a variety of clinical cases. In COMBINE, the practitioners also trained by using two scenarios that were based on typical cases. Each of the case scenarios included an initial visit and four followup visits. These role-playing episodes ensured that the practitioners had experience coping with patients who had side effect issues, had problems with medication compliance, were resistant to treatment, and had problems with maintaining abstinence; the episodes also ensured the practitioners had opportunities for providing support for patients who were doing well.
3. *Certification.* To be certified to provide MM intervention, the practitioner must meet standards showing that he/she has mastered the style (e.g., warmth, informative, authoritative [see the six dimensions in the "Practitioner Supervision" section following]) and the skills to complete the key elements of the intervention that are consistent with the MM manual.

MM Practitioner Qualifications, Training, and Supervision (*continued*)

Practitioner Supervision

Ideally, the MM practitioner should receive ongoing clinical supervision. Supervisors can accomplish this by audiotaping the practitioner in session with patients, then reviewing tapes either selected at random or selected to address a specific issue. A coding system was developed in COMBINE to monitor MM treatment adherence; the clinical supervisor can also use it for providing feedback to the MM practitioner. The coding system consists of the six dimensions outlined below. Each dimension is rated on a 1-to-7 Likert scale, with 7 representing an exemplary performance on that dimension. The acceptable scoring range on any of the dimensions is 5 through 7, with 6 considered the target for overall proficiency.

The Six Dimensions of the COMBINE Coding System

1. Informative

The practitioner communicates correct information to the patient appropriately and effectively and in a way that it is clear, concise, and understandable. This includes educational information (e.g., effects of alcohol, how the liver functions, expectations for treatment participation, importance of medication compliance, managing side effects), the patient's clinical feedback (e.g., lab results, consequences of drinking, dependence criteria), and the practitioner's advice (i.e., recommendations for abstinence, suggestions for strategies to increase medication compliance, and encouragement for AA or other mutual-support group attendance). Practitioners receive lower ratings for providing inaccurate, inappropriate, misleading, or unclear information. Practitioners receive higher ratings for providing exceptionally clear and well-timed information.

2. Direction

The practitioner maintains appropriate control of the session and follows the recommended sequencing. That is, the practitioner provides appropriate structure, moves smoothly through treatment procedures, and brings the patient back on task when conversation drifts away to tangential topics. Practitioners receive lower ratings when the overall flow of the session is disjointed, confusing, or lacks cohesion. Practitioners receive higher ratings when the direction of the session moves in a logical flow that builds a case for the treatment.

3. Authoritativeness

The practitioner conveys his/her professionalism, expertise, and confidence in his/her competence to provide effective treatment to his/her patients. The practitioner stands firm in his/her vision of the overall goal of abstinence and advocates for medication compliance, expresses optimism for his/her patient's recovery, and offers straightforward suggestions and strategies that are useful and appropriate. Practitioners receive lower ratings when they lack a sense of expertise, consistently defer to the patient or other professionals, or collude with the patient in an inappropriate manner. Practitioners receive higher ratings when they are able to convey a vision of recovery, even in the face of discouraging news from the patient.

MM Practitioner Qualifications, Training, and Supervision (*continued*)

4. Warmth

The practitioner comes across as warm, friendly, engaged, compassionate, helpful, and concerned. Practitioners receive lower ratings when they are judgmental or appear cold and disinterested. Practitioners receive higher ratings when they respond consistently and genuinely in providing praise, support, or concern.

5. Following Protocol Requirements

The practitioner follows the protocol when he/she delivers treatment procedures as prescribed in the MM manual. The adherence checklists are used to track this dimension (see Appendix B for checklists). Ratings are decreased in 0.5-point increments for key components the practitioner does not deliver. Ratings are increased in the same 0.5-point increments if the practitioner does an exceptional job of covering those key components.

6. Avoiding Nonprotocol Items

The practitioner should avoid doing things that are not a part of the MM intervention or protocol. In research trials, nonprotocol events should be strictly avoided. In clinical settings, nonprotocol procedures may or may not be allowable within the MM practitioner's overall approach, depending upon the practitioner's training and the treatment plan. To this end, the MM practitioner should be clear with the patient about what non-MM elements may or may not occur during MM visits. Practitioners receive lower ratings when they provide some form of psychotherapy or counseling beyond the expectations of the MM intervention. They may also receive lower ratings when there are excessive interruptions during the session (e.g., phone calls, knocks on the door). Practitioners receive higher ratings when they are able to confine the content of the session to the elements that are part of the MM intervention, as specified in the MM manual.

Considerations for Research

The MM intervention, originally designed in a research setting, can easily be used in other research settings. It is important to create a standard intervention delivery, which can be achieved with a well-developed training and certification process for practitioners. In addition, ongoing monitoring of practitioner performance through observation (primarily audiorecording and coding of sessions), feedback to practitioners, and supervision/coaching/ training to resolve performance issues is essential to maintaining intervention standards. Procedures to "decertify" an individual practitioner and a mechanism for recertification should be in place for situations in which the practitioner's performance levels fall below the acceptable range (e.g., if dimension ratings consistently fall below 5).

Common Pitfalls

As the result of coding sessions and reviewing practitioner performance, some common problem areas have emerged. These are listed with suggestions for addressing them.

MM Practitioner Qualifications, Training, and Supervision (*continued*)

Providing patient feedback. Practitioners incorrectly use the feedback portion of the initial MM visit as a way to verify assessment data rather than as a time to proactively educate patients about their disorder and motivate them for treatment. For example, a practitioner may ask the patient to answer the same questions he/she answered on an assessment sheet or affirm his/her earlier responses. This can lead to disagreements about the responses, which decreases the practitioner's authoritative position. The most effective way of delivering the assessment information at the initial MM visit is to present a statement that explains the source of the information and then to immediately present the information in the same way that medical results would typically be communicated to patients.

Delivering a logical and coherent intervention. There is structure built into the MM intervention for both the initial and followup visits that is designed to build and maintain a strong case for both abstinence and medication compliance. The recommended flow ensures a logical progression toward the overall goals of the intervention. Practitioners often struggle with adhering to that flow. The result is a lack of cohesion that is often confusing to the patient and may reduce the impact of the intervention.

Maintaining a limited focus. This intervention is designed to be used in a private practice setting as well as in a medical clinic. Depending upon the situation, a practitioner may be expected to confine the session to MM principles and not venture into psychotherapy or extended problem-solving. It is important for the MM practitioner to determine if the patient's multiple problems are primarily a result of excessive drinking. After successful treatment, many patients find that some of their psychological and social problems dissipate with abstinence. However, this is not always the case. Sometimes a patient needs more specialized services, and either the MM practitioner will provide them or the MM practitioner will make a referral and work collaboratively with another specialized professional. That is, some practitioners may have training and experience that includes addiction counseling–based interventions. Clearly, if counseling or other therapies are added to MM visits, this will change the amount of time needed as well as the nature of the MM intervention. However, many practitioners will not have this expertise, and they may need strategies for confining MM visits to a limited focus.

Length of MM visits. The length of the MM visits will be determined largely by the setting in which they are conducted. The availability of support staff to complete portions of the MM visit, such as taking vital signs, affects how much time a practitioner needs to spend with a patient. In a research setting, the time may also be affected by the amount and type of data collected during the visit. MM visits that are less than 15 minutes are too short to cover all the key elements in the MM intervention. These visits often seem rushed and can convey a lack of caring by the practitioner. MM visits that are longer than 25 minutes may happen when the patient has complicated medical/medication problems. However, most visits that last longer than 25 minutes either suffer from a lack of structure and focus on the part of

MM Practitioner Qualifications, Training, and Supervision (*continued*)

the practitioner or include various types of nonprotocol items (see "The Six Dimensions of the COMBINE Coding System" section).

Promoting abstinence. Although the MM intervention is abstinence-based, taking too strong a stand on this may result in the loss of some patients. Practitioners need to maintain their relationship with patients, staying "on their side" while at the same time making recommendations for abstinence. Sometimes, framing the progress of the patient in relationship to abstinence is a way for a practitioner to be successful at negotiating abstinence without becoming pushy or judgmental. Nonetheless, this is always a formidable task for the practitioner.

Form B–2

Instructions for Use of MM Treatment Adherence Checklists

MM treatment adherence checklists are intended to serve as guidelines for the MM practitioner to follow in conducting initial and followup sessions. They are also intended to be the means of tracking practitioner adherence to MM treatment as outlined in the MM manual.

The adherence checklists cover all phases of MM intervention. Each checklist includes space to mark the week of treatment and the date of treatment. The practitioner should use the checklist appropriate to the session he/she is conducting and only check items that he/she covers in each session.

Form B–3

PATIENT ID #_____ **WEEK #_____**

MM CLINICIAN ID #_____ **DATE_____**

MM Initial Session, Advance Preparation

Review *Clinician Report* Form Information Checklist

	Medical Information: Double-check lab report, and record any other drinking-related medical symptoms as noted on physical examination or lab reports.
	Alcohol Use: Record the number of drinking days per week and average number of drinks per drinking day.
	Consequences of Drinking: Record one to three negative consequences acknowledged by the patient. Select items with the highest score or impact to discuss as examples of drinking-related problems.
	Diagnostic Information: Review symptoms of alcohol dependence.

Prepare Chart Material Checklist

	1. Vital Signs and BAC (Form A–2)
	2. Concurrent Medications (Form A–3)
	3. Modified SAFTEE (Form A–7)
	4. ***Menstrual Calendar*** (Form A–10) (put NA, if not applicable)
	5. Naltrexone Information Sheet: Patient Version (Form C–1), Acamprosate Information Sheet (Form C–2), Medication Instructions Summary (Form C–3)
	6. Medication Compliance Plan (Form A–13)
	7. Support group materials
	8. Medical Emergency Cards (Form C–6)
	9. Patient Instructions for Managing Side Effects (Form C–5)
	10. Determine if the patient is seeing a second clinician for therapy.

Form B–4

PATIENT ID #_____ **WEEK #_____**

MM CLINICIAN ID #_____ **DATE_____**

MM Initial Session: Introduction Checklist

	1.	Introduce yourself and your role.
	2.	Take vital signs, BAC, and weigh patient. (If done by other staff, note NA.)
	3.	Give structuring statement.
	4.	Go over ***Concurrent Medications*** form (Form A–3) (wherever appropriate in the session); ask specifically about NSAID use.
	5.	Administer the ***Modified SAFTEE*** (Form A–7) wherever appropriate in the session. For women, get birth control information and complete the ***Menstrual Calendar*** (Form A–10).

MM Initial Session: Feedback Checklist

	1.	Give structuring statement. *[Explain four areas you will cover: physical effects, amount of drinking, drinking-related problems, and symptoms of alcohol dependence.]*
	2.	Explain briefly what the liver does, and how alcohol can affect it (i.e., fat deposits, inflammation, scarring, and destruction of liver).
	3.	Review blood pressure reading, liver enzymes, any abnormal lab values, and other drinking-related medical symptoms. *[State your medical opinion of how alcohol is affecting the patient physically.]*
	4.	Review drinking pattern date (from TLFB or Form 90). [For example, on average, patient has been drinking ___ days per week, and on days when patient drinks, he/she has had an average of ___ drinks. State that this level of drinking has negative impact on patient.]
	5.	Review consequences of drinking by selecting three good examples of items marked on the DrInC. *[State your impression of the patient's negative consequences.]*
	6.	Review the specific dependence criteria that the patient met. *[Repeat that together these symptoms confirm alcohol dependence and that this diagnosis applies to the patient.]*
	7.	Pull together the physical, drinking, problem, and dependence feedback and draw your conclusions about problem severity.
	8.	Make your medical recommendation that the patient stop drinking.
	9.	If the patient resists long-term abstention, recommend a trial period of abstinence. *[Put NA if patient already agreed to abstinence above.]*

Form B–5

PATIENT ID #_____ WEEK #_____

MM CLINICIAN ID #_____ DATE_____

MM Initial Session: Medication Compliance Checklist

	1.	Provide rationale for pharmacotherapy. Explain that these medications have been found to work to help people to maintain abstinence (e.g., they seem to reduce the urge or desire to drink).
	2.	Distinguish from other types of drugs (disulfiram [Antabuse]), addicting drugs, medications used in detoxification. Address any misconceptions.
	3.	Provide medication information sheets (Forms C–1, C–2, C–3).
	4.	Explain what is known about how the medication works. *[Explain possible side effects and their likelihood. Explain that these medications take some time to take effect—don't expect to feel immediate effects.]*
	5.	Administer ***Modified SAFTEE*** (Form A–7) prior to giving the patient initial dose of medication.
	6.	Observe patient take the morning dose (allow 20 minutes to watch for negative reaction).
	7.	Explain dosing (check separately):
____		a. Typical dose is four pills in morning, two pills at midday, two pills in evening.
____		b. Pills can be taken with food if desired.
____		c. Explain what to do about missed doses, lost medication, and so on.
____		d. There must be at least 2 hours between doses.
____		e. Pills cannot be crushed.
____		f. Give patient handout ***Patient Instructions for Managing Side Effects*** (Form C–5).
	8.	Explain emergency procedures and provide emergency contact cards (Form C–6) (one for patient and one for significant other).
	9.	Provide basic rationale for compliance and monitoring. *[Taking the dosage as prescribed increases the effectiveness of medications. Advise the patient at each MM session that you will be following up on medications taken.]*
	10.	***Medication Compliance Plan*** (Form A–13): Review history of taking pills (check separately):
____		a. Discuss possible problems in taking medications properly, where applicable.
____		b. Decide level of need for plan for pill-taking.
____		c. Decide on strategies to remember pills.
____		d. Record the personal medication compliance plan.
____		e. Tell patient that the plan will be revised, if needed.
	11.	Advise patient to return blister cards at each visit, even if all pills are not taken.

Form B–6

PATIENT ID #_____ WEEK #_____

MM CLINICIAN ID #_____ DATE_____

MM Initial Session: Wrap-Up Checklist

	1.	Summarize diagnosis briefly and recommend abstinence.
	2.	Recommend mutual-support groups as an aid to change.
	3.	Provide literature on local mutual-support groups. [*Problem-solve obstacles to attendance as necessary.*]
	4.	If patient is also seeing a therapist, support the patient in his/her effort.
	5.	Document the number of pills prescribed on the ***Pill Count*** form (Form A–14).
	6.	Schedule next session.
	7.	Advise patient that you will call in 3 days.

Form B–7

PATIENT ID #_____ **WEEK #_____**

MM CLINICIAN ID #_____ **DATE_____**

Brief Checklist for MM Initial Session

_____ Introduce yourself and your role, check vital signs, give overview and timeline of intervention.

_____ Conduct *baseline* ***Modified SAFTEE*** (Form A–7) (reference last 90 days).

_____ Complete ***Concurrent Medications*** form (Form A–3) (reference last 90 days).

_____ Complete ***Menstrual Calendar*** (Form A–10) (indicate NA if not appropriate).

_____ Provide feedback from initial evaluation (***Clinician Report*** [Form A–1]) (vital signs, lab results, drinking-related symptoms, drinking pattern and consequences, dependence criteria).

_____ Provide information (importance of the liver and how it works, effects of alcohol, diagnostic information, reasons for abstinence).

_____ Give professional opinion about severity of the problem.

_____ Recommend abstinence.

_____ Ask patient for commitment to abstinence. If patient is unwilling to commit to long-term abstinence, restate the rationale for and seek agreement to abstinence for duration of treatment.

_____ Explain purpose and function of medications, and provide information sheets on naltrexone and acamprosate (Forms C–1 and C–2).

_____ Discuss likelihood of side effects and give ***Patient Instructions for Managing Side Effects*** (Form C–5).

_____ Explain proper medication use (extra doses, 2 hours between doses, don't crush, can take with food, morning dose always first) and give first dose (allow 20 minutes for observation).

_____ Give ***Medical Emergency Cards*** (Form C–6) and explain emergency procedures.

_____ Provide rationale for and complete ***Medication Compliance Plan*** (Form A–13).

_____ Briefly review diagnosis, recommendation, and plan.

_____ Encourage AA/mutual-support group attendance; give list of local meetings.

_____ Schedule next visit and discuss Day 3 phone call (***Day 3 Clinician Phone Contact*** form [Form A–15]).

Form B–8

PATIENT ID #_____ WEEK #_____

MM CLINICIAN ID #_____ DATE_____

MM Followup Sessions: Part 1 Checklist

	1.	Take patient's vital signs, BAC, and weigh patient (if done by other staff, note NA).
	2.	Ask the patient how he/she has been since the last visit, what was difficult, what went well. *[Note: If the patient has not done any drinking since the last visit, ask specific questions, such as, "How were you able to keep from drinking?"]*
	3.	Medical Status
____		a. Record concurrent medication use on the ***Concurrent Medications*** form (Form A–3) (ask specifically about NSAID use).
____		b. Administer ***Modified SAFTEE*** (Form A–7).
____		c. Complete ***Menstrual Calendar*** (Form A–10) and get current birth control information (put NA if applicable).
____		d. Complete ***Serious Adverse Event Report*** (Form A–11) if necessary.
____		e. Report current laboratory results, when appropriate.
	4.	Ask whether patient returned blister card. Praise patient for medications taken. *[Examine the blister card and ask if the medications missing were actually taken.]*
	5.	Inquire about any skipped doses (even if pills appear taken). Query relation of skipped doses to any drinking.
	6.	Determine what treatment scenario is applicable, check which applies, and complete appropriate Followup Visit Checklists:
____		***Abstinent and Medication Compliant*** (Form B–9)
____		***Nonabstinent and Medication Compliant*** (Form B–10)
____		***Abstinent and Medication Noncompliant*** (Form B–11)
____		***Nonabstinent and Medication Noncompliant*** (Form B–12)
	7.	If patient is in therapy with another clinician, ask about it.
	8.	Document the number of pills prescribed on the ***Pill Count*** sheet (Form A–14).

Form B–9

PATIENT ID #_____ WEEK #_____

MM CLINICIAN ID #_____ DATE_____

Abstinent and Medication Compliant

	1. Reinforce the patient's ability to stick to the plan. Praise progress. Ask how the patient did it.
	2. Remind the patient it is necessary to continue to take all medications and attend sessions until the end of treatment.
	3. Review benefits of abstinence.
	4. Provide support.
	5. Reinforce or inquire about AA or other mutual-support group attendance. Note here as "not willing to consider" ("NWTC") if the patient is adamantly opposed.
	6. Conclude visit on a positive note, with general encouragement and praise.

Form B–10

PATIENT ID #_____ WEEK #_____

MM CLINICIAN ID #_____ DATE_____

Nonabstinent and Medication Compliant

	1. Reinforce the patient for taking medication.
	2. Review with the patient the ***Clinician Report*** (Form A–1) to remind the patient why he/she sought treatment.
	3. Praise small steps of progress.
	4. Review the benefits of abstinence (in general terms).
	5. Remind the patient that medications work gradually over time.
	6. Review the benefits of other aspects of treatment (other therapy/mutual-support groups).
	7. Reinforce or inquire about AA or other mutual-support group attendance. Note here as "not willing to consider" ("NWTC") if patient is adamantly opposed.
	8. Conclude visit on a positive note, with general encouragement and praise.

Form B–11

PATIENT ID #_____ WEEK #_____

MM CLINICIAN ID #_____ DATE_____

Abstinent and Medication Noncompliant

	1.	Reinforce the patient for remaining abstinent.
	2.	Review general benefits of abstinence, and how medications help abstinence.
	3.	Probe why the patient did not take medications regularly; problem-solve.
	4.	Emphasize that taking medications faithfully can improve chances of staying abstinent.
	5.	Return to Medication Compliance Plan (Form A–13).
—		a. Review common reasons for noncompliance (Section B on Form A–13).
—		b. Reconstruct Medication Compliance Plan.
	6.	Reinforce or inquire about AA or other mutual-support group attendance. Note here as "not willing to consider" ("NWTC") if patient is adamantly opposed.
	7.	Conclude visit on a positive note, with general encouragement and praise.

Form B–12

PATIENT ID #_____ WEEK #_____

MM CLINICIAN ID #_____ DATE_____

Nonabstinent and Medication Noncompliant

	1. Reinforce the patient for any progress you see (including coming in for session).
	2. Review the benefits of abstinence, and review reasons for stopping (from initial session).
	3. Encourage the patient to give treatment a chance.
	4. Emphasize that taking medication faithfully can improve chances of staying abstinent.
	5. Return to Medication Compliance Plan (Form A–13).
_____	a. Review common reasons for noncompliance (Section B on Form A–13).
_____	b. Reconstruct Medication Compliance Plan.
	6. If patient is no longer motivated to stop or reduce drinking, then:
_____	a. Remind the patient of the reasons for stopping; refer to ***Clinician Report*** form Form A–1).
_____	b. Remind the patient of the benefits of abstinence.
_____	c. Discuss AA attendance.
_____	d. Discuss other aspects of treatment that might help increase abstinence.
	7. Reinforce or inquire about AA or other mutual-support group attendance. Note here as "not willing to consider" ("NWTC") if patient is adamantly opposed.
	8. Conclude visit on a positive note, with general encouragement and optimism.

Form B–13

PATIENT ID #_____ WEEK #_____

MM CLINICIAN ID #_____ DATE_____

Brief Checklist for MM Followup Sessions

_____ Review ***Vital Signs and BAC*** (Form A–2) with patient.

_____ Conduct brief assessment of drinking, medication compliance, and general function.

_____ Complete ***Concurrent Medication*** form (Form A–3).

_____ Conduct ***Modified SAFTEE*** (reference time since last visit) (Form A–7) (complete ***Serious Adverse Event Report*** [Form A–11] as needed).

_____ Complete ***Menstrual Calendar*** (Form A–10) (indicate NA if not applicable).

_____ Review new lab results if appropriate; compare with earlier results.

_____ Check blister card for missed doses or trouble with medication compliance (revise ***Medication Compliance Plan*** [Form A–13], as necessary).

_____ Reinforce and praise progress.

Session Type

__1. Abstinent/medication compliant __2. Nonabstinent/medication compliant

__3. Abstinent/nonmedication compliant __4. Nonabstinent/nonmedication compliant

Options for Review and Problem-Solving; Opportunities for Praise and Reinforcement

_____ Benefits of abstinence

_____ Patient's reasons for seeking treatment

_____ How the medications work

_____ Importance of medication compliance

_____ Suggestions of strategies for abstaining from alcohol

_____ Suggestions for improving medication compliance

Wrap-Up

_____ Inquire about and encourage AA/mutual-support group attendance.

Form B–14

PATIENT ID #_____ **WEEK #_____**

MM CLINICIAN ID #_____ **DATE_____**

Brief Checklist for Medical Attention Visits

_____ Review ***Vital Signs and BAC*** (Form A–2) with patient.

_____ Conduct brief assessment of drinking and general function.

_____ Complete ***Concurrent Medication*** form (Form A–3). Ask specifically about NSAIDs.

_____ Conduct ***Modified SAFTEE*** (Form A–7) (reference time since last visit; complete ***Serious Adverse Event Report*** [Form A–11] as needed).

_____ Complete ***Menstrual Calendar*** (Form A–10) (indicate NA if not applicable).

_____ Review new lab results if appropriate; compare with earlier results.

Options for Review and Problem-Solving; Opportunities for Praise and Reinforcement

_____ Benefits of abstinence

_____ Patient's reasons for seeking treatment

_____ Suggestions of strategies for abstaining from alcohol

_____ Reinforce need to continue coming to MA/MM appointments

_____ Reinforce and praise progress

_____ Plans for resuming the medications (if appropriate).

Wrap-Up

_____ Inquire about and encourage AA/mutual-support group attendance.

_____ Provide support.

Appendix C: PATIENT PACKET

Medication Education

Form

C–1 Naltrexone Information Sheet: Patient Version
C–2 Acamprosate Information Sheet: Patient Version
C–3 Medication Instructions Summary
C–4 Quick Reference Medication Information Grid
C–5 Patient Instructions for Managing Side Effects
C–6 Sample Medical Emergency Card

Alcohol Education/Mutual-Support Groups

C–7 Name and Location of AA Pamphlet Relevant to Pharmacotherapy
C–8 Listing of Local Mutual-Support Groups

Form C–1

Naltrexone Information Sheet: Patient Version[1]

1. What is naltrexone, and how does it work?

Naltrexone is a medication that blocks the effects of drugs known as opiates, or narcotics (a class that includes morphine, heroin, or codeine). It competes with these drugs for opioid receptors in the brain. Originally used to treat dependence on opiate drugs, it now has also been approved by the U.S. Food and Drug Administration (FDA) as treatment for alcohol dependence. If you are dependent on opiate drugs, such as heroin or morphine, you must stop your drug use at least 7 days prior to starting naltrexone. Some people should not take naltrexone, such as those suffering from chronic pain who rely on opioid painkillers or people with liver failure or acute hepatitis.

Although the precise mechanism of action for naltrexone's effect is unknown, reports from successfully treated patients suggest the following three kinds of effects:

1. Naltrexone can reduce your urge or desire to drink.
2. Naltrexone helps you remain abstinent.
3. Naltrexone can interfere with your desire to continue drinking more if you slip and have a drink.

In most clinical trials evaluating the effectiveness of naltrexone, subjects who received naltrexone were significantly more successful in remaining abstinent and in avoiding relapse than were those receiving an inactive placebo pill.

2. Is it possible to become addicted to naltrexone?

No. Naltrexone is not habit forming or a drug of abuse. It does not cause users to become physically or psychologically dependent.

3. What are the side effects of naltrexone?

In a large open-label safety study on naltrexone, conducted by Dupont Pharma in 570 individuals with alcoholism, the most common side effects affected only a small minority of people; they included the following:

- Nausea (10 percent of participants)
- Headache (7 percent of participants)
- Depression (5 to 7 percent of participants)
- Dizziness (4 percent of participants)
- Fatigue (4 percent of participants)
- Insomnia (3 percent of participants)
- Anxiety (2 percent of participants)
- Sleepiness (2 percent of participants).

[1]Adapted from Rounsaville, B.J.; O'Malley, S., and O'Connor, P. "Guidelines for the Use of Naltrexone in the Treatment of Alcoholism." New Haven, CT: APT Foundation, 1995. Reproduced with the permission of DuPont Pharma.

Naltrexone Information Sheet: Patient Version (*continued*)

These side effects were usually mild and of short duration. The side effects, predominantly nausea, have been severe enough to cause 5 to 10 percent of people starting it to stop the medication. Patients usually report that they are largely unaware of being on naltrexone. Naltrexone usually has no psychological effects, and users do not feel either "high" or "down." Naltrexone can have toxic effects on the liver. You will receive blood tests of liver function prior to the onset of treatment and regularly during treatment to determine if you should take it at all, if you should stop taking it, or if you experience the relatively rare side effect of liver toxicity. You should report any side effects to your medical clinician.

4. What will happen if I drink alcohol while taking naltrexone?

Naltrexone does not reduce the effects of alcohol that impair coordination and judgment. Naltrexone may reduce your feeling of intoxication and the desire to drink more, but it will not cause a severe physical response to drinking.

5. Is it all right to take other medications with naltrexone?

You should carry a card (Form C–6) explaining that you may be on naltrexone, which instructs medical staff on pain management. Naltrexone does not reduce the effectiveness of local and general anesthesia used with surgery. However, it does block pain relief from opiate medications. Many pain medications that are not opiates are available. If you are having elective surgery, you should stop taking naltrexone at least 72 hours beforehand.

The major active effect of naltrexone is on opiate (narcotic) drugs, which is one class of drugs used primarily to treat pain but is also found in some prescription cough preparations. Naltrexone will block the effect of normal doses of this type of drug. There are many nonnarcotic pain relievers you can use while on naltrexone.

Otherwise, naltrexone is likely to have little impact on other medications you may commonly use such as antibiotics, nonopioid painkillers (e.g., aspirin, acetaminophen/ Tylenol®, ibuprofen/Motrin®/Advil®), and allergy medications. You should inform your medical clinician of the medication you are currently taking so that possible interactions can be evaluated.

Because the liver breaks down naltrexone, other medications that can affect liver function may affect the dose of naltrexone.

6. What will happen if I become pregnant while taking naltrexone?

If you have the biological potential to have a child, you should be using an effective method of birth control while taking naltrexone. However, if you miss a menstrual period, report this to your medical clinician at once and take a pregnancy test.If you become pregnant, you will discontinue the medication. Your medical clinician should continue to ask about your health throughout your pregnancy and also about the health of your baby after delivery.

7. Should I take naltrexone with a meal?

There is no information that taking naltrexone with or without meals makes any difference in effect.

Naltrexone Information Sheet: Patient Version (*continued*)

8. What happens if I stop taking naltrexone suddenly?

Naltrexone does not cause physical dependence, and you can stop taking it at any time without experiencing withdrawal symptoms.

9. If I take naltrexone, does it mean that I don't need other treatment for alcohol dependence?

No. Research studies have shown that naltrexone was most effective when it was combined with treatment from professionals and/or mutual-support groups.

10. What is the relationship of naltrexone to AA and other mutual-support groups?

There is no contradiction between participating in support groups and taking naltrexone. In fact, one multisite study showed that naltrexone-taking subjects who attended mutual-support groups, such as AA, had better outcomes. It is most likely to be effective for you if your goal is to stop drinking altogether. If other mutual-support group members caution against taking any medications, you should refer them to the pamphlet "The AA Member—Medications and Other Drugs," which explicitly states that AA members should not "play doctor" and advise others on medication provided by legitimate, informed medical practitioners or treatment programs.

Form C–2

Acamprosate Information Sheet: Patient Version[2]

1. What is acamprosate, and how does it work?

Acamprosate is a new, investigative medication for treatment of alcohol dependence already approved in several European countries and currently being studied in clinical trials in the United States. It is thought to reduce the urge for alcohol by working directly on certain neurotransmitters in the brain (chemicals that transmit information between nerve cells) whose balance has been disturbed because of regular, heavy drinking.

Although acamprosate can only be used in the United States with permission of the U.S. Food and Drug Administration, it has been available in Europe since 1989 and has recently been approved for marketing by prescription in more than 12 European countries, including Belgium, France, Germany, Ireland, Italy, the Netherlands, Spain, Switzerland, and the United Kingdom. It is estimated that more than 1 million patients have been treated with acamprosate since it became available.

2. Is acamprosate addictive?

No. Acamprosate is not habit forming or a drug of abuse. It does not cause users to become physically or psychologically dependent.

3. What are the side effects of acamprosate?

Like virtually all medications, acamprosate can cause side effects, but these are usually minor and go away as patients continue to take the medication. In European controlled clinical trials, the only types of symptoms that were *consistently* more common in subjects taking acamprosate than in subjects taking placebo (a sugar pill) were stomach symptoms. These were usually mild, tended to occur when subjects first started taking the medication, and consisted primarily of loose bowel movements or mild diarrhea. Some subjects also had changes in their sex drive—sometimes this was increased and sometimes decreased, but there was no definite pattern. As with many drugs, sometimes people on acamprosate develop skin rashes or itching. In earlier studies, subjects on acamprosate and those on placebo both experienced equal amounts of this type of symptom. You should tell your medical clinician of any side effects.

4. What will happen if I drink alcohol while taking acamprosate?

Acamprosate does not change the way the body metabolizes (breaks down) alcohol, so acamprosate will not make you feel sick if you drink (i.e., it does not work like Antabuse). And there is no evidence of an added effect of alcohol if you drink while taking acamprosate.

5. Is it possible to take other medications with acamprosate?

Because acamprosate is eliminated exclusively by the kidneys, drugs that may be toxic to the kidneys, such as aminoglycoside antibiotics (gentamycin and amikacin), should be avoided. Inform your medical clinician of whatever medication you are currently taking so that possible interactions can be evaluated.

[2]Adapted from Mason, B.J., and Goodman, A.M. *Brief Intervention and Medication Compliance Procedures—Therapist's Manual,* 1997. http://www.alcohol-free.com.

Acamprosate Information Sheet: Patient Version (*continued*)

6. What will happen if I become pregnant while taking acamprosate?

If you have the biological potential to have a child, you should be using an effective method of birth control while taking acamprosate. However, if you miss a menstrual period, report this to your medical clinician at once and take a pregnancy test.

If you become pregnant, you will discontinue the medication. Your medical clinician should continue to ask about your health throughout your pregnancy and also about the health of your baby after delivery.

Even though acamprosate should not be used during pregnancy, animal studies have not shown any ill effects on either the course of pregnancy or on the offspring, nor is there any evidence from animal studies that acamprosate causes birth defects.

7. Should I take acamprosate with a meal?

Acamprosate can be taken with food, but food does decrease the amount of medication that the body absorbs. Gastrointestinal symptoms may decrease by taking the medication with food.

8. Is it all right to crush the pills?

Acamprosate pills should not be crushed because they have an enteric coating. Destroying this coating can lead to a worsening of gastrointestinal side effects.

9. What happens if I stop taking acamprosate suddenly?

Acamprosate does not cause physiological withdrawal symptoms when it is stopped.

10. What happens if I miss a dose?

If you miss a dose of acamprosate, do not take it simultaneously with the next scheduled dose; there should be a minimum of 2 hours between doses. If this is not feasible, do *not* take the skipped dose. Instead, wait until your next scheduled dose, and take *only* that dose.

11. If I take acamprosate, does it mean that I don't need other treatment for alcohol dependence?

No. Research has shown that acamprosate was most effective when it was combined with treatment from professionals and/or mutual-support groups.

12. What is the relationship of acamprosate to AA and other mutual-support groups?

There is no contradiction between participating in support groups and taking acamprosate. It is most likely to be effective for you if your goal is to stop drinking altogether. If other mutual-support group members caution against taking any medications, you should refer them to the pamphlet "The AA Member—Medications and Other Drugs," which explicitly states that AA members should not "play doctor" and advise others on medication provided by legitimate, informed medical practitioners or treatment programs.

Form C–3

Medication Instructions Summary: General Review of Most Frequently Asked Questions

1. How often should I take the medications?

Take four pills in the morning, two at midday, and two in the evening.

2. Can I take medications with meals?

Because one of the medications is best taken on an empty stomach to help with absorption of the medication, it is best to take the medications about 1 hour before a meal or 2 hours after a meal. However, if you experience or are concerned about stomach problems, take the medications with meals. Discuss this with the clinician prescribing your medications.

3. What should I do if I miss a dose? Should I take two doses at once?

No. Do not take a double dose of either medication. Allow at least 2 hours between doses.

4. If I miss a morning dose, should I take the morning dose or the midday dose at midday?

If you miss the morning pills, take them as soon as you remember. If you remember near the time for the midday dose, take the four morning pills, wait 2 hours, and then take the midday dose. Allow at least 2 hours between doses.

5. Why are there three extra lines of medication in the blister card for each week?

The blister cards have 10 days worth of medication. This includes doses for 7 days of medication plus a few extras in case you find yourself without medications. For example, if you drop a pill down the sink or are unable to come in for your scheduled session, you may need an extra pill.

6. What should I do if I lose a dose?

If you lose one or more pills, replace them with medication from the corresponding extra medications. For example, if you needed to replace a lost morning dose, go down the morning columns (the first four columns of pills) on the blister card to find the first line of extra medication (eighth row of pills) and take those pills.

7. Can I crush, cut, or chew the medications?

No; because one of the pills has a protective coating to reduce stomach problems, it is best to take the pills whole.

8. What should I do with the blister card?

Return the blister card empty or with unused medications at the next visit. Return it even if you did not take all of the pills that were recommended.

9. Can I remove the medications from the blister card and take them with me?

It is best to keep the pills in their original packaging until you actually take the dose. Although you will be asked about whether you took your medication at each visit, the blister card is another way to keep track of pill-taking. If you take the pills out of the blister

Medication Instructions Summary (*continued*)

card, you might lose them or not be able to remember if you took those pills. If you absolutely must take the pills out of the blister card, try to remember which pills you removed as well as if you did actually take that dose.

10. Does it matter where I store the medications?

Do not store the medications in a car because high temperatures affect them.

Quick Reference Medication Information Grid

How do the medications work?	1. Take away or reduce the desire to drink 2. Help maintain abstinence 3. Reduce the urge to keep drinking if a slip occurs.
Are they addictive?	No
Are there any possible side effects?	Nausea, loose bowel movements, headache, dizziness, fatigue, insomnia, anxiety, depression, sleepiness, increased or decreased sex drive, skin rashes, and itching
What happens if I drink while taking the medications?	1. Decreased feeling of intoxication 2. Decreased desire to drink more 3. No effect.
What other medications should I avoid while taking the medications?	Opioid (narcotic) pain relievers and drugs that are toxic to the kidney (e.g., gentamycin, amikacin).
What happens if I get pregnant while taking the medications?	Tell your medical clinician at once. You will no longer be able to take the medications. Your medical clinician, however, will continue to ask for information on your health throughout your pregnancy and also on the health of your baby after delivery.
Should I take my pills with a meal?	Medication can be taken with food.
What happens if I stop taking the medications suddenly?	Nothing
Are these medications the only treatment I need for alcohol dependence?	No. Counseling and/or participation in mutual-support groups are highly recommended.
If I miss a dose, should I take two doses at once?	No. You should not take a double dose of medication. Allow at least 2 hours between doses. If this is not possible, then skip the missed dose.
If I miss a morning dose, should I take the morning dose or the midday dose at midday?	If you miss the morning pills, always take them as soon as you remember. Even if it is time for the midday dose, remember to take the four morning pills if at all possible, and then take the remaining doses, with at least 2 hours between doses.
Why are there three extra lines of medication in the blister card for each week?	The blister cards have 10 days worth of medication. This includes doses for 7 days (1 week) of medication plus some extras. These extras are provided in the event that you find yourself without medications. For example, if you drop a pill down the sink or are unable to come in for your scheduled session, you may take some of the extra pills.
What should I do if I lose a dose of the medications?	If you drop or lose one or more pills, replace them with medication from the corresponding extra set(s) of medications. For example, if you needed to replace a lost morning dose, go down the morning columns (the first four columns of pills) on the blister card to find the first line of extra medication (eighth row of pills) and take those pills.

Form C–5

Patient Instructions for Managing Side Effects

Most people do not experience side effects from the medication you are taking. Occasionally, some people experience symptoms related to giving up drinking that can be confused with side effects from the medication. These symptoms usually are not serious, and they usually subside within a few days. Do not stop your medication until you have called your medical clinician. If you are concerned about any symptoms you are having, call your medical clinician.

Name of medical clinician: _____

During clinic hours (name): _____ Phone: _____

After clinic hours (name): _____ Phone: _____

Nausea

Take your medication with food.

Take Pepto-Bismol® according to package instructions or as prescribed by your medical clinician.

Vomiting

Call your medical clinician.

Diarrhea

Take Pepto-Bismol® according to package instructions or as prescribed by your medical clinician.

If diarrhea persists, drink plenty of nonalcoholic fluids and call your medical clinician.

Significant or persistent abdominal pain

Call your medical clinician.

Headache

Use nonprescription headache medications according to package instructions. It is important to avoid alcohol when taking headache medications.

If headache persists, call your medical clinician.

Dizziness, Nervousness, Anxiety, Insomnia

If dizziness, nervousness, anxiety, or insomnia are significant or persistent, call your medical clinician.

Do not start herbal over-the-counter or prescribed medications without first discussing their use with your medical clinician.

Form C–6

Sample Medical Emergency Card

To Medical Personnel Treating This Person in an Emergency:

This person may be taking an investigational new drug (acamprosate) and/or the oral opioid antagonist naltrexone hydrochloride. If this is a medical emergency and the treating medical staff need to know what medication the person is taking, call the 24-hour emergency number listed on the back of the card.

In an emergency situation for people who are receiving fully blocking doses of naltrexone hydrochloride, a suggested plan of management is regional analgesia, conscious sedation with a benzodiazepine, use of nonopioid analgesics, or general anesthesia.

In a situation requiring opioid analgesia, the amount of opioid required may be greater than usual, and the resulting respiratory depression may be deeper and more prolonged.

A rapidly acting opioid analgesic that minimizes the duration of respiratory depression is preferred. The amount of analgesic administered should be titrated to the needs of this person. Nonreceptor-mediated actions may occur (e.g., facial swelling, itching, generalized erythema, or bronchoconstriction), presumably caused by histamine release.

Irrespective of the drug chosen to reverse naltrexone hydrochloride blockade, this person should be monitored closely by appropriately trained personnel in a setting equipped and staffed for cardiopulmonary resuscitation.

Important information regarding the patient and the practitioner who prescribed medication that may be naltrexone and/or acamprosate:

Patient's name: _____ Phone: _____

Patient's ID #: _____ Treatment ID #: _____

Date treatment began: ___ ___/___ ___/___ ___ ends: ___ ___/___ ___/___ ___

Name of physician: _____

Pharmacy phone: _____

24-hour emergency phone: _____

Form C–7

Name and Location of AA Pamphlet Relevant to Pharmacotherapy

Name: "The AA Member—Medications and Other Drugs"

Location: Available through local AA organization

Form C–8

Listing of Local Mutual-Support Groups

Provide listing of local meeting times and places for relevant mutual-support groups.

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National Institute on Alcohol Abuse and Alcoholism
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