

# Incorporating Alcohol Pharmacotherapies into Medical Practice



# What Is a TIP?

Treatment Improvement Protocols (TIPs), developed by the Center for Substance Abuse Treatment (CSAT), part of the Substance Abuse and Mental Health Services Administration (SAMHSA) within the U.S. Department of Health and Human Services (HHS), are best-practice guidelines for the treatment of substance use disorders. CSAT draws on the experience and knowledge of clinical, research, and administrative experts to produce TIPs, which are distributed to facilities and individuals across the country. As alcohol and drug use disorders are increasingly recognized as a major problem, the audience for TIPs is expanding beyond public and private treatment facilities to include practitioners in mental health, criminal justice, primary care, and other healthcare and social service settings.

## TIP Development Process

TIP topics are based on the current needs of substance abuse treatment professionals and other healthcare practitioners for information and guidance. After selecting a topic, CSAT invites staff from Federal agencies and national organizations to be members of a resource panel that reviews an initial draft prospectus and outline and recommends specific areas of focus as well as resources that should be considered in developing the content for the TIP. These recommendations are communicated to a consensus panel composed of experts on the topic who have been nominated by their peers. In partnership with Knowledge Application Program writers, consensus panel members participate in creating a draft document and then meet to review and discuss the draft. The information and recommendations on which they reach consensus form the foundation of the TIP. A panel chair ensures that the guidelines mirror the results of the group's collaboration.

A diverse group of experts closely reviews the draft document. Once the changes recommended by these field reviewers have been incorporated, the TIP is prepared for publication, in print

and online. TIPs can be accessed via the Internet at <http://www.kap.samhsa.gov>.

Although each TIP strives to include an evidence base for the practices it recommends, CSAT recognizes that the field of substance abuse treatment is evolving, and research frequently lags behind the innovations pioneered in the field. A major goal of each TIP is to convey “front-line” information quickly but responsibly. For this reason, recommendations proffered in the TIP are based on either panelists’ clinical experience or the literature.

## TIP Format

CSAT is embarking on a new approach to and format for TIPs:

- Most of the fundamental research that forms the evidence basis for a particular TIP is not provided in the TIP itself. Rather, those who wish to review the supporting research can access an annotated bibliography and literature review via the Internet at <http://www.kap.samhsa.gov>. These online resources include abstracts along with references; the online bibliography and literature review are updated every 6 months for 5 years after publication of the TIP.
- TIPs focus on how-to information. Coverage of topics is limited to what the audience needs to understand and use to improve treatment outcomes.

- TIPs increasingly use quick-reference tools such as tables and lists in lieu of extensive text discussion, making the information more readily accessible and useful for treatment providers.

## How TIP 49 Is Organized

This TIP, *Incorporating Alcohol Pharmacotherapies Into Medical Practice*, revises and expands on TIP 28, *Naltrexone and Alcoholism Treatment*, and includes discussion of the other medications currently approved for treating alcohol use disorders (AUDs). It provides the basic information, evidence- and consensus-based guidelines, tools, and resources necessary to help health-care practitioners treat patients with AUDs.

Chapter 1 provides an overview of the use of medications to treat AUDs. Chapters 2 through 5 present detailed information about each medication:

- Chapter 2—Acamprosate
- Chapter 3—Disulfiram
- Chapter 4—Oral Naltrexone
- Chapter 5—Extended-Release Injectable Naltrexone.

Finally, Chapter 6 discusses factors to consider when treating patients with medications for AUDs. The appendices in the TIP provide handy resources for practitioners.

# 1 Introduction

## In This Chapter . . .

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## Alcohol Use Disorders in Medical Settings

Many health problems or mental disorders that healthcare practitioners (particularly those in primary care) encounter in their everyday practices derive from or are complicated by alcohol use disorders (AUDs). Consequently, healthcare practitioners are in key positions to manage the care of large numbers of individuals with AUDs. However, only a small percentage of these patients are actually treated for AUDs in these settings.

The U.S. Food and Drug Administration (FDA) has approved four medications to treat AUDs. These medications make treatment in primary care and other general medical settings a viable adjunct or alternative to specialty care, with many potential advantages. The consensus panel for this Treatment Improvement Protocol (TIP) believes that direct intervention by healthcare practitioners to treat AUDs is both possible and practical.

Screening for and providing brief interventions to treat AUDs in general medical settings promote healthy life choices and increase the likelihood of recovery, especially for patients who have not yet progressed to chronic alcohol dependence, those with comorbid medical disorders being treated in these settings, and those who otherwise would not seek or receive treatment for their AUDs. Interventions in primary care provide an opportunity to educate and motivate patients who are alcohol dependent and need long-term care to consider a specialty substance abuse treatment program.

From the patient's viewpoint, initiating treatment in a healthcare practitioner's office may be more acceptable than entering a specialty substance abuse treatment program. Perceived or actual barriers to these programs, such as stigma, cost, employment concerns, lack of family or social support, misunderstandings

about the nature of treatment, and lack of program availability, discourage many patients from seeking specialty treatment for AUDs. In fact, the number of persons with alcohol or substance use disorders who received treatment at a private doctor's office increased from 254,000 in 2005 to 422,000 in 2006 (Office of Applied Studies, 2007).

#### Terms Used in TIP 49

**Abstinence.** The point at which a person has refrained from any use of alcohol or illicit drugs.

**Alcohol use disorders.** As used in the *Diagnostic and Statistical Manual of Mental Disorders IV-TR* (American Psychiatric Association, 2000), encompasses alcohol *abuse and dependence*. This TIP uses the term broadly to encompass the range of alcohol use problems, from intermittent binge drinking to hazardous drinking to chronic alcohol abuse and dependence.

**Brief intervention.** A treatment modality in which treatment approaches ranging from simple suggestions and unstructured counseling and feedback to more formal structured methods (e.g., motivational enhancement) are used, usually in short one-on-one sessions between the practitioner and patient.

**Healthcare practitioners.** Individuals with prescribing privileges, including physicians, physician assistants, and nurse practitioners.

**Medical management.** The components of brief intervention such as patient education, feedback, motivational enhancement, and medication monitoring that facilitate medication adherence.

**Specialty substance abuse treatment or specialty substance abuse care.** The integrated group of counseling and complementary services offered in substance abuse treatment programs. Services focus on achieving and maintaining long-term recovery from AUDs and other substance use disorders.

Initiating treatment in a physician's office offers advantages for these patients:

- Screening, diagnosis, and treatment of AUDs can increase patient motivation and cooperation (versus the effect of delays between screening, diagnosis, and treatment when patients are referred to specialty programs).
- Integration of treatment for AUDs with that for comorbid medical disorders may increase the likelihood of adherence to treatment and overall patient recovery.
- Familiarity with the primary care setting and "mainstream" methods (e.g., medical management) to treat AUDs reduces the stigma surrounding AUDs.
- The ongoing relationship a patient has with a healthcare practitioner may make referral to specialty substance abuse care more acceptable to a patient.

Helping patients with AUDs can be gratifying; few interventions in medicine can lead to such substantial improvement in individual and public health. This TIP provides a resource to assist the healthcare provider in this effort.

## Audience for TIP 49

The intended audience for this TIP includes physicians and other healthcare practitioners who can prescribe and administer medications for AUDs, in either specialty substance abuse treatment programs or healthcare settings such as primary care physicians' offices. Other addiction professionals (e.g., counselors) who want to understand how these medications work and to review the recommended guidelines for medication-assisted treatment of AUDs also will find the book useful.

## Recognition of Alcohol Dependence as a Chronic Illness

Research has clarified the strong similarity between substance dependence and other chronic illnesses (e.g., asthma, diabetes, hypertension) for which primary care physician-administered pharmacotherapy and medical management are routine practices (reviewed by McLellan, Lewis, O'Brien, & Kleber, 2000, p. 1693). Genetics, personal choice, and environmental factors contribute to both substance dependence and other illnesses. Research into the pathophysiologic effects of alcohol and drugs—including enduring and possibly permanent neurophysiologic changes—provides further evidence that substance dependence is a chronic illness. By addressing AUDs in their practices, healthcare practitioners also address the source of substantial risk for many other health problems in their patients (see *Why Use Medications To Treat Alcohol Dependence?* on page 5).

## Purpose of TIP 49

This TIP provides clinical guidelines for the proper use of medications in the treatment of AUDs. The underlying objective is to expand access to information about the effective use of these medications, not only in specialty substance abuse treatment programs but also in physicians' offices and other general medical care settings. Members of the Clinical Research Roundtable of the Institute of Medicine have identified failure to disseminate information about and implement new therapies proven effective in clinical trials as a principal roadblock to healthcare improvement in the United States (Crowley et al., 2004). TIP 49 addresses this problem for the pharmacotherapy of AUDs.

## Costs and Prevalence of AUDs

Annual economic costs of AUDs in the United States have been estimated at approximately \$185 billion (Harwood, 2000) and include the following:

- Direct treatment costs
- Lost earnings
- Costs of other medical consequences, including premature death
- Costs of accidents and emergencies
- Criminal justice costs.

Approximately 7.9 percent of Americans ages 12 and older (about 19.5 million people) met standard diagnostic criteria for alcohol abuse or dependence in 2006 (Office of Applied Studies, 2007). However, only 1.6 million people with an AUD received treatment at a specialty facility (Office of Applied Studies, 2007). Of those who did *not* receive treatment, just 3.0 percent thought they needed treatment and 40.6 percent tried to get treatment but were unable to (Office of Applied Studies, 2007).

## Findings on Medication-Assisted Treatment for AUDs

Researchers continue to evaluate the efficacy of numerous compounds to treat AUDs. To date, FDA has approved four medications for treatment of AUDs:

- Acamprosate (Campral®)
- Disulfiram (Antabuse®)
- Oral naltrexone (ReVia®, Depade®)
- Extended-release injectable naltrexone (Vivitrol®).

This TIP provides recommended guidelines for using the four FDA-approved medications in clinical practice.

Although the mechanisms of action of these medications in treating AUDs are not fully understood, knowledge about them is growing.

Researchers are evaluating the efficacy of combinations of medications and the use of individual medications along with behavioral approaches to treat AUDs (e.g., Mason, 2005b). In 2006, an ambitious clinical trial—the Combining Medications and Behavioral Interventions (COMBINE) study, sponsored by the National Institute on Alcohol Abuse and Alcoholism (NIAAA)—compared the relative efficacy of two medications (acamprosate and naltrexone) administered individually, together, or in combination with specialty substance abuse treatment or medical management to improve treatment for alcohol dependence (Anton et al., 2006). The results of this study are noted in this TIP when applicable for treatment planning and decisionmaking, and a review of the research can be accessed in the online literature review for this TIP (<http://www.kap.samhsa.gov>).

## Access to Medication-Assisted Treatment for AUDs

Although precise numbers are unknown, it seems that a small percentage of Americans being treated for AUDs receive any of the four FDA-approved medications for their disorder. Most specialty substance abuse care is provided outside medical settings by nonmedical personnel (e.g., counselors) and is based on psychosocial approaches, such as cognitive-behavioral therapy and motivational enhancement, reinforced by participation in community 12-Step or mutual-help groups. These programs increase rates of abstinence and prevent serious relapse for many patients. Unfortunately, many people needing treatment for AUDs do not get it (Office of Applied Studies, 2007).

Advances in medication development and behavioral treatment methods are providing the tools needed to improve long-term recovery for patients in specialty treatment settings. These advances increase access to and effective use of AUD treatment services in general medical settings.

The medications discussed in this TIP help people maintain abstinence or decrease drinking and avoid serious setbacks after the initial withdrawal period. None of the four FDA-approved medications is considered a “magic bullet.” Developing new and more effective medications remains a high priority for researchers in this field.

## Information Updates in This TIP

TIP 49 updates the information in TIP 28, *Naltrexone and Alcoholism Treatment* (Center for Substance Abuse Treatment [CSAT], 1998). It also builds on TIP 24, *A Guide to Substance Abuse Services for Primary Care Physicians* (CSAT, 1997). When TIP 28 was published, FDA had approved only two medications for the treatment of AUDs: disulfiram and oral naltrexone. FDA has since approved two more medications: acamprosate and extended-release injectable naltrexone. These four medications have unique pharmacological actions and profiles of effects, and they produce different types of outcomes in individual patients, hence, the need for separate guidelines on their use. As more information about these medications becomes available, it will be added to the online bibliography and literature review that supplement this TIP. (See Format, Approach, and Organization of TIP 49, page 7.)

## What TIP 49 Does Not Cover

This TIP assumes that a patient’s health-care practitioner is acquainted with

screening and diagnostic procedures, the patient has a diagnosed AUD, and the patient has gone through (or has not needed) detoxification. Therefore, the following information about treating AUDs is not covered in this TIP:

- Screening and diagnostic assessment for AUDs. The reader can refer to *Helping Patients Who Drink Too Much: A Clinician's Guide* (NIAAA, 2006), available at <http://www.niaaa.nih.gov>. NIAAA's *A Pocket Guide for Alcohol Screening and Brief Intervention* is in Appendix B of this TIP.
- Detoxification and methods to deal with initial withdrawal symptoms. This information is covered in TIP 45, *Detoxification and Substance Abuse Treatment* (CSAT, 2006a). Excerpts from the Quick Guide based on TIP 45 are in Appendix C of this TIP.
- Medical conditions associated with excessive alcohol use such as cirrhosis. Treatment for these disorders is covered in resources from NIAAA (<http://www.niaaa.nih.gov/Publications/AlcoholResearch>).

## Specialty Treatment Versus Screening and Brief Intervention

Treatment of AUDs can be viewed as continuum-of-care options that include choices of treatment settings, types and levels of treatment services, and medications. Services may range from screening and brief intervention to specialty treatment, with numerous levels of care in between. Primary care practitioners can provide screening, brief interventions, and medical management for many patients who have AUDs or are at risk for alcohol-related disorders but are not receiving care.

Decisions about care level, setting, and type of treatment should be based on patient assessment and commitment to change, as well as treatment availability. For example, the most appropriate patients for brief interventions in a physician's office—and the least appropriate for long-term treatment in a substance abuse treatment program—are those whose drinking exceeds what is recommended, but who are not dependent (NIAAA, 2006).

## Why Use Medications To Treat Alcohol Dependence?

When implemented according to recommended guidelines, medication-assisted treatment combined with brief intervention or more intensive levels of nonpharmacologic treatment can do the following:

- Reduce postacute withdrawal symptoms that can lead to a return to drinking (e.g., acamprosate's hypothesized mechanisms of action)
- Lessen craving and urges to drink or use drugs (e.g., naltrexone)
- Decrease impulsive or situational use of alcohol (e.g., disulfiram).

In addition, maintaining a therapeutic alliance with a healthcare practitioner can achieve the following:

- Improve patients' attitudes toward change
- Enhance motivation
- Facilitate treatment adherence, including participation in specialty substance abuse care and support groups.

The Collaborative Study on the Genetics of Alcoholism indicates a genetic link between how an individual experiences



alcohol and his or her susceptibility to an AUD (reviewed by Edenberg, 2002). Risk of chronic AUDs appears higher for people with certain genetic variants. Further identification of these genes may lead to new medications for treating AUDs that can help repair, alter, or disrupt alcohol's negative effects.

According to a recent review, chronic heavy drinking can cause long-lasting changes in brain cell receptors and other types of neuroadaptations (Oscar-Berman & Marinkovic, 2003). These neuroadaptations are linked with cognitive and behavioral changes, resulting in the need to drink more to ward off craving and symptoms of withdrawal. Studies reviewed by Hoffman and colleagues (2000) found that neuroadaptations related to symptoms of withdrawal and persistent craving may trigger relapse even after prolonged abstinence.

Pharmacotherapy has revolutionized the treatments of brain-based disorders, including mental disorders such as depression, and treatments for these disorders are increasingly provided by healthcare practitioners. Making such treatments available in general medical settings can improve continuity and accessibility of care. Expansion in treatment settings is underway in opioid addiction treatment. Although most opioid addiction treatment is provided in specialty programs (i.e., methadone treatment clinics), the growing use of buprenorphine by physicians in office-based settings is increasing access to treatments. The widespread use of bupropion in primary care settings for smoking cessation is another example of how the boundaries of addiction treatment have expanded.

Medication-assisted treatment of AUDs is consistent with treatment of other chronic disorders such as diabetes or hypertension. Long-term, perhaps indefinite, use of medication for patient stabilization is

reasonable. Medication for AUDs may be employed indefinitely or intermittently along with interventions aimed at changing lifestyle practices to sustain recovery.

Research into alcohol dependence and treatment has shown that integrating brief intervention and counseling and an appropriate medication can have a synergistic or additive effect and improve treatment outcome. Medication can reduce the cravings that disrupt recovery. When cravings are decreased, counseling is more likely to strengthen the individual's coping resources, which are necessary to promote medication adherence and behavioral change. Summaries of research findings have highlighted the following beneficial effects of medication-assisted treatment for AUDs (Garbutt, West, Carey, Lohr, & Crews, 1999; Kranzler & Van Kirk, 2001; O'Malley & Kosten, 2006):

- Lengthens periods of abstinence, which in turn can increase individual coping capacities necessary for long-term recovery
- Prevents a lapse from becoming a full-blown relapse
- Allows brain cells to readapt to a normal nonalcoholic state, helping patients stabilize, think more clearly, have more positive emotional responses, strengthen coping mechanisms, enhance self-esteem, and increase motivational readiness for change
- Relieves symptoms of protracted withdrawal (a hypothesized mechanism of action of acamprosate)
- Supports the effects of psychosocial treatment and sustains the gains of intervention.

The consensus panel for this TIP believes that providing brief interventions (including pharmacotherapy) for AUDs in physicians' offices and general medical

settings is a reasonable, practical, and desirable trend that should be greatly expanded. The panel also recommends that screening and periodic reassessment of *all* patients for AUDs should become regular parts of patient management in primary care and general medical practices because the problem has been shown to be more widespread than many primary care practitioners have realized. At a minimum, patients diagnosed with health problems often associated with AUDs should receive alcohol disorder screening.

## Format, Approach, and Organization of TIP 49

The format and approach used in this TIP differ substantially from those used in other TIPs:

- Most of the evidence base for medication-assisted treatment for AUDs is not included in this TIP. Those who wish to review the research base can access the annotated bibliography and literature review via the Internet at <http://www.kap.samhsa.gov>. The online bibliography and literature review will be updated every 6 months for 5 years after publication of TIP 49.
- TIP 49 focuses on how-to information about medication-assisted treatment for AUDs. Coverage is limited to what the audience needs to understand to use these medications to improve treatment outcomes.
- Increased use of quick-reference tools such as tables and lists in lieu of extensive text discussion makes the information readily accessible and useful for physicians and other practitioners.

Practical information and guidelines for treating patients with acamprosate, disulfiram, oral naltrexone, or extended-release injectable naltrexone are presented in Chapters 2 through

5, respectively. Each chapter follows a template: general description of the medication, rationale for its use, how to use it, which patients are most appropriate for the medication, and clinical advice.

Chapter 6 covers practical information about patient management during pharmacotherapy that applies to all four FDA-approved medications for AUDs, including how to do the following:

- Integrate pharmacotherapy for AUDs into clinical settings
- Assess appropriateness of medications for patients with AUDs
- Choose AUD medications
- Choose psychosocial interventions
- Develop and adjust treatment plans
- Educate patients about pharmacotherapy for AUDs
- Monitor patient progress in medication treatment
- Discontinue AUD medications.

Appendices include the following:

- Bibliography (Appendix A)
- NIAAA's *A Pocket Guide for Alcohol Screening and Brief Intervention* (Appendix B)
- Excerpts from the Quick Guide for Clinicians Based on TIP 45, *Detoxification and Substance Abuse Treatment* (Appendix C)
- Excerpts from the Quick Guide for Clinicians Based on TIP 24, *A Guide to Substance Abuse Services for Primary Care Clinicians* (Appendix D)
- Lists of the TIP's resource panelists and field reviewers (Appendices E and F, respectively).

# 2 Acamprosate

## Acamprosate At a Glance

**Chemical name:** Calcium acetyl homotaurinate.

**Trade name:** Campral® Delayed-Release Tablets.

**U.S. distributor:** Forest Pharmaceuticals (subsidiary of Forest Laboratories, Inc.), St. Louis, MO.

**U.S. Food and Drug Administration approval to treat alcohol dependence:** July 2004.

**Dosage/How taken:** Two 333 mg delayed-release tablets by mouth three times per day, with or without food (a lower dose may be effective with some patients and *must* be used with those with impaired renal function). Pills are swallowed whole, *not* crushed or broken.

**How supplied:** Opaque bottles or Dose Paks of 180 enteric-coated 333 mg tablets.

**Storage:** Keep out of reach of children; keep tightly closed in original container; store at room temperature, away from excess heat and moisture (not in the bathroom or near a sink); discard when outdated or no longer needed.

## What Is Acamprosate?

Acamprosate was the third medication, after disulfiram and naltrexone, to receive U.S. Food and Drug Administration (FDA) approval for postwithdrawal maintenance of alcohol abstinence. Acamprosate's mechanism of action has not been clearly established, but it is thought that acamprosate helps modulate and normalize alcohol-related changes in brain activity, thereby reducing symptoms of postacute (protracted) withdrawal, such as disturbances in sleep and mood, that may trigger a relapse to drinking.

## Brief History of Development

The French pharmaceutical company Laboratoires Meram began clinical development and testing of acamprosate in 1982. From 1982 to 1988, acamprosate was tested for safety and for efficacy as a treatment for alcohol dependence. Based on these studies, in 1989 Laboratoires Meram was granted marketing authorization for acamprosate in France under the trade name

Aotal®. Since then, acamprosate has been extensively used and studied throughout Europe and, subsequently, in the United States.

Although acamprosate has been used in Europe for more than 20 years, it was not approved by FDA until July 2004. Acamprosate became available for use in the United States in January 2005, under the trade name Campral® Delayed-Release Tablets (Merck Santé, a subsidiary of Merck KGaA, Darmstadt, Germany). Campral is currently marketed in the United States by Forest Pharmaceuticals.

## Pharmacology

Acamprosate's action in maintenance of alcohol abstinence is not completely understood, but evidence indicates that acamprosate interacts with the glutamate neurotransmitter system, reducing and normalizing the pathologic glutamatergic hyperactivity that occurs during protracted withdrawal from alcohol. It is hypothesized that this normalization leads to a reduction of common symptoms of protracted, or postacute, withdrawal such as insomnia, anxiety, and restlessness—symptoms that may contribute to a patient's return to alcohol use (reviewed by Litten, Fertig, Mattson, & Egli, 2005; Myrick & Anton, 2004; Thomson Healthcare, Inc., 2006). Chick, Lehert, and Landron (2003) have proposed that patients who returned to drinking while taking acamprosate drank less, and less frequently, than those taking placebo.

The bioavailability of acamprosate after oral administration is approximately 11 percent, and stable plasma concentrations are reached within 5 days of taking the medication. Acamprosate is not metabolized and is excreted primarily by the kidneys as acamprosate.

## Why Use Acamprosate?

### Efficacy

Considerable evidence supports the efficacy of acamprosate in the treatment of alcohol use disorders (AUDs). Numerous European trials have found acamprosate significantly more effective than placebo in reducing drinking days, increasing complete abstinence, and lengthening time to relapse. Evidence from U.S. studies has been mixed. The Combining Medications and Behavioral Interventions (COMBINE) study did not find acamprosate to be more effective than placebo (Anton et al., 2006). However, some analyses and reviews have concluded otherwise (although these analyses did *not* include data from the COMBINE study). A meta-analysis (an analysis of the outcome data of multiple individual studies) of European studies concluded that acamprosate is moderately effective in achieving and maintaining abstinence (Bouza, Magro, Muñoz, & Amate, 2004). This analysis of 12 studies found that acamprosate increased the continuous abstinence rate and doubled continuous abstinence duration compared with placebo. Similarly, a review of clinical trials by Mann (2004) concluded that acamprosate is more effective than placebo in the short and long term. Mason and colleagues (2006) found acamprosate to be superior to placebo only when controlling for patient characteristics associated with treatment efficacy. They also found acamprosate superior to placebo for a subgroup of patients motivated to achieve total abstinence.

Methodological differences between U.S. and European studies may account for differing results. These differences have included the following:

- Duration of pretreatment abstinence required

- Duration of treatment (European studies tended to be longer than U.S. studies)
- Concomitant medications allowed (European studies tended to be more flexible in allowing medications than U.S. studies)
- Nature and intensity of psychosocial treatment (U.S. studies tended to have more standardized and intensive psychosocial treatments)
- Outcome measures used
- Severity of participants' AUDs.

A thorough discussion of acamprosate efficacy studies is in this TIP's online literature review.

## Safety

Acamprosate has a good safety profile:

- Patients maintained on acamprosate have not developed tolerance for or dependence on it, and it appears to have no potential for abuse.
- It carries virtually no overdose risk; even at overdoses up to 56 grams (a normal daily dose is 2 grams), acamprosate was generally well tolerated by patients (Thomson Healthcare, Inc., 2006).
- Most side effects are mild and transient, lessening or disappearing within the first few weeks of treatment (diarrhea tends to persist).
- Although there is a pharmacokinetic interaction by which acamprosate can increase naltrexone blood levels, there are no other clinically significant interactions between acamprosate and other medications (Johnson et al., 2003).

Acamprosate also has advantages over other medications for treating AUDs in some patients:

- Because acamprosate is not metabolized by the liver, it can be used safely even by patients with severe liver disease, unlike oral or injectable naltrexone or disulfiram.
- Because it does not affect endogenous or exogenous opioids, it can be used with patients receiving opioid maintenance therapy (reviewed by Myrick & Anton, 2004) or undergoing treatment with opioids for acute or chronic pain, unlike oral or injectable naltrexone.
- Because acamprosate does not interact with benzodiazepines or other medications used in medical detoxification, it can be continued safely if a patient returns to drinking and subsequently requires detoxification.

## How Is Acamprosate Used?

### Initiating Treatment With Acamprosate

Acamprosate is typically initiated 5 days following drinking cessation. However, acamprosate can be used safely with alcohol (and with benzodiazepines), and it *can* be started during medically supervised withdrawal. Acamprosate therapy should be maintained if a patient relapses to alcohol use. Acamprosate reaches full effectiveness in 5 to 8 days.

Before initiating treatment, healthcare practitioners should do the following:

- Conduct or refer patients for a thorough medical exam and assessment (as described in Chapter 6—Patient Management).
- Perform renal function tests (a standard panel for urea, electrolytes, and serum creatinine) to rule out severe renal impairment.

## Side Effects, Contraindications, and Cautions

Exhibit 2-1 lists acamprosate’s side effects. The most common side effect of acamprosate is diarrhea. This and other side effects are usually mild and resolve quickly. In some patients, diarrhea is severe and persistent. Patients should be instructed not to discontinue acamprosate if they experience side effects and to inform their prescribing professional.

Exhibit 2-2 lists acamprosate contraindications, and Exhibit 2-3 lists cautions.

## Patient Management

Ways for managing adverse reactions to acamprosate are listed in Exhibit 2-4.

There is no evidence that acamprosate impairs renal function. Followup laboratory work is not necessary unless evidence of renal impairment exists at treatment initiation.

## Patient Education

In addition to giving patients the general patient education guidelines discussed in

Chapter 6, healthcare providers should ensure that patients taking acamprosate know the following:

- The benefits and limitations of acamprosate
- What to expect—
  - Possible side effects
  - Full effectiveness in 5–8 days
- For women of childbearing age, the importance of using an effective birth control method
- To continue taking acamprosate if a slip or relapse occurs and to inform their prescribing professional immediately
- To notify the prescribing professional immediately if they begin to have suicidal thoughts, if they begin to feel depressed, or if an existing depression worsens
- That tablets should not be crushed
- Not to take extra medication if a dose is missed and it is time to take the next dose.

**Exhibit 2-1**  
**Acamprosate Side Effects**

Most Common Side Effect	Less Common Side Effects	
Diarrhea	Suicidal ideation (less common, but serious)	Insomnia
	Intestinal cramps	Anxiety
	Headache	Muscle weakness
	Flatulence	Nausea
	Increased or decreased libido	Itchiness
		Dizziness

**Exhibit 2-2**  
**Acamprosate Contraindications**

Patient Condition or Circumstance	Treatment Recommendation
Previous hypersensitivity to acamprosate or its components	Do not prescribe acamprosate
Severe renal impairment (creatinine clearance $\leq 30$ mL/min)	Do not prescribe acamprosate

**Exhibit 2-3**  
**Acamprosate Cautions**

Patient Condition or Circumstance	Treatment Recommendation
Moderate renal impairment (creatinine clearance 30–50 mL/min)	Reduce dosage to one 333 mg tablet daily
Pregnant or nursing women	Avoid using acamprosate unless potential benefits outweigh risks (Acamprosate is FDA pregnancy category C; it is unknown whether acamprosate is excreted in human milk.)
Age 65 or older	Because of a higher risk of diminished renal function in persons 65 or older, perform baseline and frequent renal function tests; acamprosate has not been evaluated for safety or efficacy in geriatric populations
Children or adolescents	Prescribe with caution; acamprosate has not been evaluated for safety or efficacy in pediatric or adolescent populations

**Exhibit 2-4**  
**Adverse Reactions to Acamprosate and Their Management**

Adverse Reaction	Management
Suicidal ideation, suicide attempts (very uncommon, but serious)*	<p>Inform patients to contact the prescribing professional immediately</p> <p>Monitor patients for onset or worsening of depression</p> <p>Obtain a psychiatric consult and/or prescribe antidepressant medication as necessary</p> <p>Discontinue acamprosate</p>
Severe and/or persistent diarrhea	<p>Treat with Imodium® or Pepto-Bismol®</p> <p>Recommend appropriate dietary changes</p> <p>Reduce acamprosate dosage or discontinue use if diarrhea remains intolerable after treatment</p>

\*Suicidal ideation is closely linked with substance use disorders, with or without acamprosate use. More information about managing the risk can be found at the National Suicide Prevention Center's Web site (<http://www.sprc.org>) and at the Suicide Prevention for Physicians Web site (<http://suicideandmentalhealthassociationinternational.org/preventionphy.html>).

## Who Is Appropriate for Treatment With Acamprosate?

Research on patient-specific characteristics as predictors of acamprosate efficacy has not identified any particular characteristics (e.g., level of physiological dependence on alcohol, age of onset, gender) that predict acamprosate treatment outcomes (Verheul, Leher, Geerlings,

Koeter, & Van Den Brink, 2005). However, evidence exists that acamprosate is most effective for patients who, at treatment onset, are motivated for complete abstinence rather than decreased drinking (Mason et al., 2006).

As noted earlier, acamprosate does not affect endogenous or exogenous opioids, so it may be particularly appropriate for patients who are receiving opioid maintenance therapy (reviewed by Myrick &

Anton, 2004), at risk of relapsing to opioid use, or undergoing treatment with opioids for pain. Because there are no clinically significant drug interactions with acamprosate, it can be a safe medication for patients who are coping with multiple medical issues and are taking many other medications.

Acamprosate must be taken three times per day. Extra support will be needed for patients with cognitive deficits or who otherwise might have trouble remembering and adhering to a schedule. Seven-day dosing pillboxes or blistercard packages that indicate the time of day for each dose may be useful.

## Treatment Duration and Discontinuing Acamprosate

The effectiveness and safety of acamprosate have been evaluated for up to 1 year. The length of time a particular patient takes acamprosate will be determined, ideally, with input from the prescribing professional, the specialty treatment provider, and the patient. Discontinuation of acamprosate may be considered once a patient has achieved stable abstinence from alcohol, reports diminished craving, and has established a sound plan and support for ongoing recovery. Acamprosate therapy also may be discontinued if a patient is not adhering to the medication regimen. Acamprosate should not be discontinued just because a patient returns to alcohol use.

There is no withdrawal syndrome associated with discontinuing acamprosate, and it is not necessary to taper the dose.

## Final Clinical Thoughts

Evidence from European studies and clinical experience suggest acamprosate can be an effective medication for the treatment of AUDs. Acamprosate has several attractive features, including its minimal side effects, lack of negative liver effects, and drug interaction profiles. For many patients, these features make it a worthwhile agent to try despite its small therapeutic effect. Hence, the clinician using medications to treat patients with alcohol dependence should be familiar with acamprosate and its use and may find it a useful medication for certain patients (e.g., those treated with opioid analgesics) or under certain circumstances (e.g., for a patient who is taking several other medications). The healthcare provider may also find it useful when combined with other alcohol treatment medications and with psychosocial support.

Because acamprosate must be taken three times per day, providers must pay particular attention to patient adherence. Providers can help patients adhere to the regimen by helping them develop ways to remember, such as wearing a “reminder” bracelet, setting a watch alarm, implementing a recovery-oriented ritual around taking the medication, or providing them with a special pillbox or blistercard pack.



# 3 Disulfiram

## Disulfiram At a Glance

**Chemical name:** Bis(diethylthiocarbamoyl) disulfide.

**Trade name:** Antabuse®.

**U.S. distributor:** Odyssey Pharmaceuticals, Inc., East Hanover, NJ.

**U.S. Food and Drug Administration approval to treat alcohol dependence:** 1951.

**Dosage/How taken:** Tablet by mouth once daily (also may be crushed and mixed with water, coffee, tea, milk, soft drink, or fruit juice).

**How supplied:** Bottles of 100 or 1,000 250 mg tablets or bottles of 50, 100, or 500 500 mg tablets.

**Storage:** Keep out of reach of children; keep tightly closed in original container; store at room temperature, away from excess heat and moisture (not in the bathroom or near a sink); discard when outdated or no longer needed.

## What Is Disulfiram?

Disulfiram was the first medication approved by the U.S. Food and Drug Administration (FDA) to treat chronic alcohol dependence. In its pure state, disulfiram is a white to off-white, odorless, almost tasteless powder, which is soluble in water and alcohol. Disulfiram, an alcohol-aversive or alcohol-sensitizing agent, causes an acutely toxic physical reaction when mixed with alcohol. Continuing research and clinical findings have clarified disulfiram's mode of action and established its safe and effective use in the treatment of alcohol use disorders (AUDs) in some patient groups.

## Brief History of Development

Exhibit 3-1 summarizes disulfiram's development history.

## Exhibit 3-1 Brief History of Disulfiram Development

Dates	Events
1930s	Disulfiram's alcohol-aversive effects are first observed when workers in the vulcanized rubber industry, exposed to tetraethylthiuram disulfide, become ill after drinking alcohol.
1947	In Copenhagen, researchers studying compounds to treat parasitic stomach infections take a small dose of disulfiram to check its side effects. Later they become ill after an alcoholic drink. They conclude that an interaction of disulfiram and alcohol is responsible and conduct a study to confirm their findings (Hald & Jacobsen, 1948).
Late 1940s, early 1950s	<p>The Danish group performs additional studies of disulfiram treatment for alcohol dependence. Basing its initial paradigm on aversion conditioning, it administers high disulfiram doses (e.g., 1,000 to 3,000 mg daily) to maximize patient reactions.</p> <p>FDA approves disulfiram to treat alcohol dependence in the United States.</p> <p>Wyeth-Ayerst Laboratories begins manufacturing Antabuse® tablets (now manufactured by PLIVA and distributed in the United States by Odyssey Pharmaceuticals).</p> <p>Ruth Fox, M.D., the founding president of the American Society of Addiction Medicine, is the first American to use disulfiram to treat alcohol dependence, starting in 1949. When her patients report serious side effects, Fox reduces the dosage and counsels them on the severe reactions that could result from drinking alcohol. She concludes that disulfiram is effective in deterring drinking in patients with alcohol dependence and treats about 2,500 patients with disulfiram.</p>
Late 1950s to the present	After reports of severe reactions, including some deaths, therapeutic emphasis shifts from using disulfiram for aversion conditioning to using it to support abstinence. This entails using lower dosages to control disulfiram toxicity, excluding patients with myocardial infarction or cirrhosis of the liver, and combining the medication with other types of support.

## Pharmacology

### ***Aversive treatment***

Unlike other medications approved to treat alcohol dependence, disulfiram does not affect brain opiate,  $\gamma$ -aminobutyric acid, or glutamate receptors directly. However, it does have some central nervous system effects, inhibiting enzyme dopamine  $\beta$ -hydroxylase and affecting serotonergic function. Whether disulfiram directly decreases the urge to drink remains uncertain. However, disulfiram definitely disrupts the metabolism of alcohol, causing a severe reaction when patients mix disulfiram and alcohol. Patient knowledge of a possible severe reaction to alcohol consumption

is thought to increase the patient's motivation to remain abstinent. Some experts (e.g., Schuckit, 2006) question disulfiram's effectiveness because the time between alcohol ingestion and the reaction can be as long as 30 minutes and the intensity of the reaction is unpredictable.

### ***Effect on oxidation of alcohol***

Normally, the enzyme alcohol dehydrogenase in the liver and brain transforms alcohol into acetaldehyde. The enzyme aldehyde dehydrogenase (ALDH), also in the liver and brain, oxidizes the acetaldehyde byproduct into acetic acid. Disulfiram blocks this oxidation by inhibiting ALDH, causing a rapid rise

of acetaldehyde in the blood when alcohol is consumed. The result is called a *disulfiram–alcohol reaction*, and it may increase the acetaldehyde concentration in blood to 5 to 10 times that occurring without disulfiram. Disulfiram does not appear to affect the rate of alcohol elimination from the body.

***The disulfiram–alcohol reaction***

The disulfiram–alcohol reaction usually begins about 10 to 30 minutes after

alcohol is ingested. Its adverse effects range from moderate to severe (Exhibit 3-2). Intensity varies with individual patient characteristics. The reaction is generally proportional to the amounts of disulfiram and alcohol ingested. Mild effects may occur at blood alcohol concentrations of 5 to 10 mg/100 mL. At 50 mg/100 mL, effects usually are fully developed. When the concentration reaches 125 to 150 mg/100 mL, unconsciousness may occur. Although

**Exhibit 3-2**  
**Possible Effects of the Disulfiram–Alcohol Reaction**

Body Part Affected	Moderate	Severe
Body skin	Sweating Warmth and flushing, particularly on upper chest and face	None
Respiratory system	Hyperventilation Respiratory difficulty/dyspnea	Respiratory depression
Head, neck, throat	Acetaldehyde breath odor Blurred vision Head and neck throbbing Thirst	None
Stomach, digestive system	Nausea/vomiting	None
Chest, heart, circulatory system	Chest pain/palpitations Hypotension Tachycardia	Cardiovascular collapse Arrhythmia Myocardial infarction (in individuals with preexisting coronary artery disease) Acute congestive heart failure (in individuals with preexisting myocardial dysfunction)
Brain/nervous system	Vertigo Syncope Marked uneasiness Confusion	Seizures
Other	Weakness	Death

disulfiram–alcohol reactions can be life threatening, as indicated in Exhibit 3-2, the reduced dosages and careful patient medical screening now in practice have made this outcome extremely rare.

Early researchers believed that patients needed to experience at least one supervised disulfiram–alcohol reaction to understand its effects. The practice of deliberately inducing a reaction by giving large doses of disulfiram in conjunction with “alcohol challenges” has been abandoned. A clear, convincing description of the reaction is considered sufficient for most patients.

### ***Disulfiram absorption and elimination***

About 80 to 95 percent of ingested disulfiram is absorbed from the gastrointestinal tract and rapidly distributed to tissues and organs. It is then metabolized to various mixed disulfides. The unabsorbed fraction is excreted. Disulfiram is irreversibly bound to ALDH. It can take up to 2 weeks for the body to synthesize sufficient unbound enzyme to metabolize alcohol adequately. This is why alcohol ingestion may produce unpleasant symptoms for up to 2 weeks after a patient has taken the last dose of disulfiram.

## **Why Use Disulfiram?**

Disulfiram may work as an adjunct to psychosocial treatment to eliminate alcohol consumption for patients who can achieve initial abstinence of at least 12 hours, are committed to maintaining abstinence, agree to take the medication, and do not have contraindications to disulfiram.

### **Efficacy**

Findings on the efficacy of disulfiram treatment are mixed. (To review some reports, see the online annotated bibliography and literature review at <http://www.kap.samhsa.gov>.)

### ***Positive findings***

Studies concluding that disulfiram is effective in treating AUDs frequently emphasize the circumstances in which it is administered to patients. In particular, the level and quality of supervision a patient receives while taking disulfiram are believed to be important elements in its success (e.g., Brewer, Meyers, & Johnsen, 2000; Kristenson, 1995). Some studies have found that court-ordered disulfiram therapy promotes efficacy by increasing adherence to the disulfiram regimen (Martin, Clapp, Alfers, & Beresford, 2004; Martin, Mangum, & Beresford, 2005). Use of incentives, contracting with the patient and a significant other to ensure adherence, providing regular reminders to the patient, and patient behavioral training and social support also may enhance disulfiram efficacy by increasing treatment adherence.

Most experts (e.g., Schuckit, 2006) agree that an optimum disulfiram response requires its use in a specialty substance abuse treatment program. One study suggests that disulfiram might be more effective in promoting short-term abstinence and treatment retention after detoxification than in preventing long-term relapse (e.g., Chandrasekaran, Sivaprakash, & Chitraleka, 2001). Nevertheless, the most rigorous study of disulfiram therapy (Fuller et al., 1986) showed unequivocally that disulfiram (250 mg/day), compared with placebo (1 mg/day) or a vitamin, reduced the proportion of days of alcohol consumption for the duration of the study (1 year) in male veterans who reported some drinking. However, there were no differences between treatment groups in the percentage of veterans sustaining abstinence throughout the study period.

### ***Negative findings***

Some experts dismiss disulfiram as a viable treatment option, particularly in primary care settings. This conclusion

is based on mixed results with disulfiram in clinical trials and the severe adverse effects that may result from the disulfiram–alcohol reaction, as well as concerns about other potentially serious side effects and “problems with compliance” (Williams, 2005, pp. 1776–1777). The capacity to arrange ongoing supervision of disulfiram ingestion may be limited in a primary care setting.

### ***Appropriate patients***

The consensus panel concludes that disulfiram is most effective for patients who have undergone detoxification or are in the initiation stage of abstinence, especially when they are committed to abstinence and receive adequate, ongoing supervision. Disulfiram may not reduce the urge to drink alcohol. However, it may assist in motivating the patient not to drink. As with other medications, general efficacy also increases when disulfiram is administered in conjunction with intensive behavioral interventions.

Patients with severely impaired judgment or who are highly impulsive from a severe mental illness or cognitive impairment may be inappropriate candidates for treatment with disulfiram.

### **Safety**

Disulfiram has been used to treat AUDs for almost 60 years. Deaths from the disulfiram–alcohol reaction have become rare because lower dosages are used and patients with severe cardiac disease are excluded from disulfiram treatment (Chick, 1999). Its hepatotoxicity in some patients remains a concern (see Side Effects, Contraindications, and Cautions on page 20).

Side effects of disulfiram are usually minor (see Exhibit 3-4, page 20). Severe adverse reactions are uncommon (see Exhibit 3-8, page 23). However, patients receiving disulfiram should be monitored for hepatotoxicity (see Timing of

Laboratory Work, page 21). Disulfiram may cause hepatitis, but the risk is low. Estimates of disulfiram-induced hepatitis are between 1 in 25,000 (Wright, Vafier, & Lake, 1988) and 1 in 30,000 (Chick, 1999, p. 427) patients treated per year. A disproportionate number of these cases may be associated with use of disulfiram to treat nickel allergy (an unusual but known indication for use of disulfiram).

A black-box warning about treatment with disulfiram is included in the Antabuse package insert. Before administering disulfiram, the clinician should inform patients and their families about the disulfiram–alcohol reaction, including that this reaction may occur for up to 14 days between the last ingested dose of disulfiram and alcohol consumption.

#### **Disulfiram Black-Box Warning**

Disulfiram should never be administered to a patient who is in a state of alcohol intoxication or without the patient’s full knowledge. The physician should instruct relatives accordingly.

## **How Is Disulfiram Used?**

### **Before Initiating Treatment With Disulfiram**

Physicians should not administer disulfiram until the following steps have been taken:

- Educate the patient about disulfiram and obtain informed consent.
- Wait until the patient has abstained from alcohol at least 12 hours and/or breath or blood alcohol level is zero.
- Perform a physical exam, baseline liver and kidney function tests, and a pregnancy test for women. Perform an electrocardiogram if clinically indicated (e.g., history of heart disease).

- Complete a medical and psychiatric history. Determine allergies to disulfiram or other drugs; prescription and non-prescription medications taken, including vitamins; history of cardiovascular disease, diabetes, thyroid disease, seizure disorder, central nervous system impairment, or kidney or liver disease; and for women, reproductive status, including current pregnancy or plans to become pregnant or to breast-feed.

### Supervised Ingestion

There is strong evidence that supervised ingestion is necessary for disulfiram therapy compliance (e.g., Brewer et al., 2000; Kristenson, 1995; reviewed by Fuller & Gordis, 2004). Although not absolutely essential, supervised administration by a pharmacist, healthcare provider, or family member is preferred as a key component of the treatment plan.

### Dosage

Exhibit 3-3 summarizes standard dosage information for disulfiram.

Additional dosage information includes the following:

- Instruct patients who experience sedation with disulfiram to take it at bedtime. If daytime sedation persists, adjust the dosage downward.
- If a patient can drink alcohol without problems when compliant with the

**Exhibit 3-3  
Disulfiram Dosages**

Initial dosage	250 mg/day in 1 morning or evening dose for 1–2 weeks
Average maintenance dosage	250 mg/day
Dosage range	125–500 mg/day
Maximum dosage	500 mg/day

routine starting dose (which is rare), increase the dosage (dosage may be increased up to 500 mg/day with careful monitoring). Never exceed 500 mg/day.

- Instruct patients who miss a dose to take it as soon as they remember. However, if it is almost time for the next dose, they should skip the missed dose.
- Tell patients never to take a double dose of disulfiram.

### Side Effects, Contraindications, and Cautions

Disulfiram can cause minor side effects (Exhibit 3-4). The common side effects typically occur during the first 2 weeks of therapy and wane either spontaneously or after a decrease in the disulfiram dosage.

**Exhibit 3-4  
Disulfiram Side Effects**

Skin/acneiform eruptions*	Headache
Allergic dermatitis*	Impotence
Mild drowsiness	Metallic or garlic-like aftertaste
Fatigue	

\*Dermatologic side effects often can be managed with concomitant antihistamines.

Hepatic toxicity including hepatic failure resulting in transplantation or death has been reported. Severe and sometimes fatal hepatitis associated with disulfiram therapy may develop even after many months of therapy. Hepatic toxicity has occurred in patients with or without a history of abnormal liver function.

Patients should be instructed to call their physician immediately if they develop symptoms of possible hepatic impairment (Exhibit 3-5).

Exhibit 3-6 summarizes contraindications for disulfiram therapy, and Exhibit 3-7 summarizes cautions.

### Exhibit 3-5 Symptoms of Disulfiram-Induced Hepatic Impairment

Excessive tiredness	Vomiting
Weakness	Yellowness of the skin/eyes
Lack of energy	Dark urine
Loss of appetite	Fever
Upset stomach	Light-colored stools

### Patient Management

Exhibit 3-8 lists severe adverse reactions that may occur with disulfiram and ways to manage them. These reactions are uncommon.

### *Drug interactions with disulfiram and their management*

Exhibit 3-9 describes the most common drug interactions with disulfiram and their clinical management.

### *Timing of laboratory work*

Exhibit 3-10 summarizes the recommended laboratory testing regimen for disulfiram therapy. In general, liver function requires ongoing monitoring because of disulfiram's occasional association with hepatic injury. In contrast to liver injury caused by alcohol, which typically shows a high aspartate aminotransferase-to-alanine aminotransferase ratio, disulfiram liver injury usually shows equivalent and very high elevations of both enzymes (Bjornsson, Nordlinder, & Olsson, 2006). Pregnant women should discontinue taking disulfiram immediately. Urine toxicology screening is not an ideal method of detecting alcohol use, although it sometimes can detect use that occurred within a few hours of test administration.

### *Disulfiram overdose and its management*

Severe cases of disulfiram poisoning have been reported, mainly in children who

### Exhibit 3-6 Disulfiram Contraindications

Patient Condition or Circumstance	Treatment Recommendation
Known hypersensitivity to disulfiram or other thiuram derivatives used in pesticides and rubber vulcanization; sulfur or nickel allergy	Do not administer disulfiram.
Psychosis	Disulfiram is relatively contraindicated in patients with decompensated psychoses but can be used with caution in treated, stable patients with schizophrenia or other psychotic disorders.
Severe myocardial disease and/or coronary occlusion	Disulfiram is relatively contraindicated in patients with severe myocardial disease or coronary occlusion, with clinical risk of disulfiram therapy balanced against clinical risk of ongoing alcohol abuse. Perform an electrocardiogram before and during disulfiram therapy and follow closely.
Pregnant or nursing women	Although disulfiram is not absolutely contraindicated, it should be avoided because risk to the fetus is unknown. (Pregnant patients should receive behavioral treatment, on an inpatient basis if necessary.) Do not give disulfiram to nursing mothers. Patients should discontinue nursing before taking disulfiram.

## Exhibit 3-7 Disulfiram Cautions

Patient Condition or Circumstance	Treatment Recommendation
History of cardiac disease, diabetes mellitus, hypothyroidism, epilepsy, cerebral damage, chronic or acute nephritis, hepatic cirrhosis, or hepatic insufficiency	Use with caution. No evidence exists that patients with preexisting liver disease are more likely to suffer severe hepatotoxicity from disulfiram therapy.
Patients with hepatitis C	According to current available evidence, if baseline transaminase levels are normal or only moderately elevated (less than five times the upper limit of normal), use with careful monitoring of liver function.
Children and adolescents	Safety and efficacy for children has not been determined. One study indicates that disulfiram can be safe and effective with adolescents (Niederhofer & Staffen, 2003). Administer with caution.
Patients receiving or who have recently received metronidazole, paraldehyde, alcohol, or alcohol-containing preparations (e.g., cough syrups, tonics); also patients exposed to ethylene dibromide or its vapors (e.g., in paint, paint thinner, varnish, shellac)	Do not use disulfiram until substances are out of the patient's system.
Patients using products that contain alcohol in disguised forms (e.g., vinegars, sauces, aftershave lotions, liniments)	Instruct patients to test any alcohol-containing product before using it by applying some to a small area of the skin for 1 to 2 hours. If there is no redness, itching, or unwanted effects, the product may be used safely.
Age 61 or older	Dosages may need to be decreased.

have ingested large amounts because of patients' negligent handling or storage of their medication. Symptoms of overdose include drowsiness followed by coma or persistent nausea, vomiting, aggressive or psychotic behavior, and ascending flaccid paralysis that can reach the cranial nerves. Treatment consists of administration of oxygen therapy, glucose (5 percent intravenously), and sodium ascorbate (1 gram intravenously). The patient should be kept in bed and as quiet as possible with appropriate symptomatic treatment.

### ***Addressing reported drinking***

Patients seemingly on an adequate maintenance dosage of disulfiram who report that they can drink with impunity could be disposing of their tablets without taking them. Physicians should not

conclude that disulfiram is ineffective until patients are proved to have been taking their daily tablets. Once patient adherence is confirmed, the physician should consider increasing the disulfiram dosage (see Exhibit 3-3, page 20) or changing the patient to another medication.

Genetic factors may influence sensitivity to disulfiram in some patients (reviewed by Kenna, McGeary, & Swift, 2004a, 2004b). Wide individual differences exist in the activity of the target enzyme ALDH. Individuals with low intrinsic ALDH activity are more likely to exhibit high sensitivity to disulfiram, and those with high intrinsic ALDH are more likely to show little or no sensitivity to disulfiram.



### Managing a disulfiram–alcohol reaction

The duration of the disulfiram–alcohol reaction varies from 30 to 60 minutes in mild cases to several hours or until the alcohol is metabolized in more severe cases. When effects are severe, supportive measures may be needed to restore blood pressure and treat shock. Administration of oxygen or carbogen (95 percent oxygen, 5 percent carbon dioxide), large intravenous doses of vitamin C (1 g), ephedrine sulfate, or intravenous antihistamines may be indicated. Potassium levels should be monitored particularly in patients on digitalis because hypokalemia has been reported.

### Patient Education

Patients should receive thorough education about disulfiram. Use of disulfiram should include ongoing monitoring, medical management, and counseling. Used *without* proper patient education,

motivation, and supportive intervention, disulfiram is unlikely to have more than a brief effect on drinking patterns, particularly in patients with poor medication compliance, more severe forms of alcohol dependence, or both.

In addition to giving patients the general patient education discussed in Chapter 6, healthcare providers should educate patients about the following key points regarding disulfiram therapy:

- Benefits and limitations of disulfiram
- What to expect from disulfiram and normal time to full effect
- Complete information about the disulfiram–alcohol reaction
- Strong cautions about surreptitious drinking while on disulfiram
- Warnings about using alcohol in disguised forms, such as in sauces, vinegars, cough mixtures, aftershave lotions, or liniments

### Exhibit 3-8

### Adverse Reactions to Disulfiram and Their Management

Adverse Reaction	Management
Optic neuritis	Usually diagnosed after patient complains of visual disturbance. Discontinue disulfiram and conduct an ophthalmologic examination.
Peripheral neuritis, polyneuritis, peripheral neuropathy	Usually diagnosed after patient complains of paresthasias (numbness or tingling). Discontinue disulfiram and observe patient or arrange for neurological evaluation.
Hepatitis, including cholestatic and fulminant hepatitis, as well as hepatic failure*	When symptoms of hepatic dysfunction are reported or observed (see Exhibit 3-5), perform a medical history and physical examination and obtain followup liver function tests. When clinical or laboratory evidence of hepatic dysfunction is found, discontinue disulfiram immediately. Maintain clinical monitoring of symptoms and liver function. Follow findings to resolution.
Psychosis	Psychotic reactions to disulfiram have been noted, usually attributable to high disulfiram dosage associated with toxicity to other drugs (e.g., metronidazole, isoniazid) or the unmasking of underlying psychoses in patients stressed by alcohol withdrawal. When psychosis is diagnosed and other interacting drugs are present, reduce or discontinue disulfiram and treat underlying psychoses as indicated.

\*Serious disulfiram-induced hepatic injury occurs rarely, and the precise etiology is unknown.

- Importance of continued counseling and 12-Step or mutual-help group participation during disulfiram therapy
- Importance of informing the counselor and prescribing professional if a slip or relapse occurs
- Importance of telling physicians or dentists that the patient is taking disulfiram when he or she is scheduled for surgery, including dental surgery
- Importance of carrying a safety identification card indicating that the patient is taking disulfiram, symptoms of possible disulfiram–alcohol reactions, and the physician or institution to contact in an emergency
- Symptoms of potential neurologic injury to report immediately to the physician
- Symptoms of potential liver injury to report immediately to the physician.

### Exhibit 3-9 Drug Interactions With Disulfiram

Drug	Effect With Disulfiram	Recommended Action
Benzodiazepines Chlordiazepoxide (Librium®) Diazepam (Valium®)	Decreases plasma clearance of chlordiazepoxide or diazepam	Substitute oxazepam (Serax®) or lorazepam (Ativan®)
Isoniazid	May cause unsteady gait, changes in mental state	Discontinue disulfiram if either effect is noted
Rifampin (Rifidin®, Rimactane®)	If used with isoniazid to treat tuberculosis, see isoniazid effects above	Adjust dosages as needed
Metronidazole (Flagyl®)	Leads to a greater likelihood of confusion or psychosis	Do not prescribe disulfiram and metronidazole concomitantly
Oral anticoagulant (e.g., warfarin [Coumadin®])	Inhibits warfarin metabolism	Adjust dosages as needed
Oral hypoglycemic	Produces disulfiram-like reactions with alcohol	Monitor carefully if prescribing oral hypoglycemics and disulfiram concomitantly
Phenytoin (Dilantin®)	Increases serum levels through CYP 450 2C9 inhibition	Obtain baseline phenytoin serum level before disulfiram therapy; reevaluate level during therapy; adjust dosage if phenytoin level increases
Theophylline	Increases serum levels through CYP 450 1A2 inhibition	Obtain baseline theophylline serum level before disulfiram therapy; reevaluate level during therapy; adjust dosage if theophylline serum level increases
Tricyclic antidepressants, amitriptyline (Elavil®)	May cause delirium with concurrent administration	Adjust dosages, discontinue disulfiram, or switch to another class of antidepressant medication
Desipramine (Norpramin®), imipramine (Tofranil®)	Decreases total body clearance and increases elimination half-life and peak plasma levels of desipramine or imipramine	Monitor closely; adjust dosages if needed

## Exhibit 3-10 Laboratory Testing in Disulfiram Therapy

Interval/Period	Type of Test
Before starting disulfiram therapy to confirm abstinence and determine baselines after stabilization	Breath or blood alcohol tests (if clinically indicated to confirm abstinence)  Liver function tests: Alanine aminotransferase, aspartate aminotransferase, gamma glutamyltransferase, alkaline phosphatase, lactate dehydrogenase, bilirubin, total protein, albumin, prothrombin time  Complete blood count, routine chemistries (if clinically indicated)  Kidney function tests: Routine blood urea nitrogen (BUN), creatinine  Pregnancy test (women of childbearing age)
10–14 days after initiation of therapy and then monthly (or more frequently) for first 6 months of therapy; every 3 months thereafter	Liver function tests: Alanine aminotransferase, aspartate aminotransferase, gamma glutamyltransferase, bilirubin
Monthly during therapy	Pregnancy test (women of childbearing age)
As clinically indicated during therapy	Kidney function tests: BUN, creatinine  Urine toxicology screen: Perform only when concern exists about unreported alcohol or drug use

Clinicians are advised to document that a patient has received and understands the information described above and to obtain the patient's informed written consent to treatment before prescribing disulfiram.

- Patients who maintain abstinence during treatment
- Patients who are codependent on or also abuse cocaine.

### Who Is Appropriate for Treatment With Disulfiram?

- Patients motivated for treatment and committed to total abstinence
- Patients capable of understanding the consequences of drinking alcohol while taking disulfiram
- Medically appropriate patients
- Patients who can receive supervised dosing
- Patients who are abstinent from alcohol

### Treatment Duration and Discontinuing Disulfiram

Prolonged disulfiram administration does not produce tolerance. Daily, uninterrupted dosing may be continued until the patient has established stable, long-term alcohol abstinence. Depending on the patient, disulfiram therapy may continue for months or years. A 9-year study of 180 patients with chronic alcohol dependence (Krampe et al., 2006) concluded that the beneficial action of long-term (12- to 20-month) supervised disulfiram therapy was psychological, not pharmacological, because placebo worked as well as disulfiram. Nevertheless, the study found

that the likelihood that a patient would remain continuously abstinent years after termination of medication therapy was directly related to the length of time the patient continued supervised therapy with either disulfiram or placebo.

For some patients who have completed successful treatment with disulfiram and who are facing anticipated high-risk relapse situations such as social events or travel, it may be appropriate to restart disulfiram along with behavioral interventions to help them cope with the high-risk situation and avoid relapse.

No withdrawal syndrome is associated with discontinuing disulfiram, but patients must be warned that disulfiram–alcohol reactions may occur within 2 weeks of discontinuing the medication.

## Final Clinical Thoughts

Disulfiram appears to have modest clinical efficacy in maintaining alcohol abstinence in patients with AUDs, particularly when administered under supervision. Patients who are motivated for treatment, commit to abstinence,

have supervised dose administration, and understand and participate in their treatment appear to derive the greatest benefits from disulfiram therapy. However, disulfiram does not appear to produce overall higher abstinence rates than placebo. Disulfiram therapy also has rare but serious risks of neurologic and hepatic toxicity. Patients require careful clinical and laboratory monitoring during disulfiram therapy. Disulfiram can be considered for any patient who is alcohol dependent, does not display contraindications, has a goal of total abstinence, and can comply with appropriate monitoring.

Clinical visits in which the practitioner and patient discuss the risks and benefits of disulfiram therapy can motivate the patient to commit to alcohol abstinence. In addition to the pharmacologic actions of the medication, the patient's simply deciding to take the medication can enhance motivation for abstinence. The risks associated with disulfiram are well known and serious. However, patients can benefit from disulfiram as long as they receive careful clinical and laboratory monitoring to manage the risks associated with this therapy.

# 4 Oral Naltrexone

## Oral Naltrexone At a Glance

**Chemical name:** Naltrexone hydrochloride (morphinan-6-one, 17-[cyclopropylmethyl]-4,5-epoxy-3,14-dihydroxy-[5 $\alpha$ ]).

**Trade names:** ReVia<sup>®</sup>; Depade<sup>®</sup>.

**U.S. distributor:** Barr Pharmaceuticals, Inc., Pomona, NY; Mallinckrodt, Inc., St. Louis, MO.

**U.S. Food and Drug Administration approval to treat alcohol dependence:** 1994.

**Dosage/How taken:** Tablet by mouth once daily.

**How supplied:** Bottles of 30 or 100 50 mg tablets (ReVia); bottles of 30 or 100 25, 50, and 100 mg tablets (Depade).

**Storage:** Keep out of reach of children; keep tightly closed in original container; store in a cool, dry place, away from excess heat and moisture (not in the bathroom or near a sink); discard when outdated or no longer needed.

## What Is Oral Naltrexone?

Naltrexone hydrochloride is a relatively pure and long-lasting opioid antagonist. Oral naltrexone has been used to treat opioid dependence for many years and has been approved to treat alcohol use disorders (AUDs) since 1994. Naltrexone reduces both the rewarding effects of alcohol and craving for it.

## Brief History of Development

Naltrexone was first synthesized in 1963 by Endo Laboratories, which was acquired by DuPont in 1969. Naltrexone was initially developed to treat addiction to opioids and was approved by the U.S. Food and Drug Administration (FDA) for the treatment of addiction to drugs such as heroin, morphine, and oxycodone in 1984. DuPont branded naltrexone as Trexan<sup>®</sup> and promoted it for the treatment of opioid addiction.

Animal studies conducted in the 1980s established that naltrexone decreased alcohol consumption through its action at the opiate receptors. Human clinical trials followed that confirmed that naltrexone, when used in combination with psychosocial therapy, could reduce cravings for alcohol and decrease relapse rates to alcohol use (O'Malley et al., 1992; Volpicelli, Alterman, Hayashida, & O'Brien, 1992; Volpicelli, Watson, King, Sherman, & O'Brien, 1995).

With FDA approval of naltrexone to treat AUDs in 1994, DuPont renamed the drug ReVia®. ReVia and a generic version of naltrexone are now manufactured by Barr Pharmaceuticals. Mallinckrodt also manufactures naltrexone under the brand name Depade®.

## Pharmacology

Drinking alcohol enhances endogenous opioid activity. Several researchers who conducted animal studies observed that, under certain conditions, administration of small doses of morphine (an opioid agonist) increased consumption of alcohol in rats (Czirr, Hubbell, Milano, Frank, & Reid, 1987; Reid, Czirr, Bensinger, Hubbel, & Volanth, 1987; Reid, Delconte, Nichols, Bilsky, & Hubbell, 1991). Some researchers also reported that administration of opioid antagonists, including naloxone (which is similar to naltrexone), decreased alcohol consumption (Hubbell et al., 1986; Reid et al., 1991). It can be concluded that the rewarding effects of alcohol are mediated at least partly through the opiate system. Two teams of researchers, Woodson and Holman and Benjamin and colleagues (as cited in Spanagel & Zieglansberger, 1997), reported that these rewarding effects are reduced when opioid antagonists block opiate receptor occupancy, thereby decreasing the amount of the neurotransmitter dopamine released from the nucleus accumbens. According

to Spanagel and colleagues (as cited in Spanagel & Zieglansberger, 1997), the mesolimbic dopamine reward system is important in initiating and maintaining the use of many substances of abuse, including alcohol, and may mediate both the positive effects of alcohol and the development of craving.

Oral naltrexone is rapidly and nearly totally absorbed in the gastrointestinal tract and is metabolized almost exclusively by the liver to the primary active metabolite, 6-β-naltrexol. Peak naltrexone plasma concentrations are reached within 1 hour of dosing. The long-acting properties of naltrexone are due primarily to 6-β-naltrexol, which has an elimination half-life of 13 hours. Naltrexone achieves therapeutic effectiveness rapidly following the initiation of oral dosing.

## Why Use Oral Naltrexone?

Naltrexone appears to be effective for attenuating craving in people who are alcohol dependent (Monti et al., 1999, 2001). By blocking craving, naltrexone may enhance the ability of patients to abstain from drinking. By blocking the pleasure from alcohol, naltrexone also may reduce the amount of heavy drinking in those who do drink.

## Efficacy

A meta-analysis (Bouza, Magro, Muñoz, & Amate, 2004) of 19 controlled clinical trials of naltrexone for treatment of AUDs (most of which were randomized and single or double blind) found that, compared with using placebo, short-term treatment (less than or equal to 12 weeks) with naltrexone significantly improved relapse rates during active treatment and a medication-free followup period. Short-term naltrexone treatment was also linked with a lower percentage

of drinking days, fewer drinks per drinking day, longer times to relapse, more days of abstinence, and lower total alcohol consumption during treatment. Naltrexone may afford people with AUDs a measure of control that can prevent a slip from becoming a full-blown relapse. A European meta-analysis (Roozen et al., 2006) corroborated the positive findings of the Bouza and other studies.

A more thorough discussion of oral naltrexone efficacy studies is in the TIP's online literature review (<http://www.kap.samhsa.gov>).

## Safety

Naltrexone has a low incidence of common adverse events. Naltrexone's FDA-approved label includes a black-box warning regarding hepatotoxicity, although these reversible effects tend to be associated with much higher doses than those used in routine clinical practice (e.g., 300 mg/day or more) and tend to occur only after a patient is on these high doses for extended periods.

As an opioid antagonist, naltrexone competitively displaces opioid medications from their binding sites, precipitating

withdrawal. Healthcare providers must ensure that patients have been fully withdrawn from all opioids before considering therapy with naltrexone.

## How Is Oral Naltrexone Used?

### Initiating Treatment With Oral Naltrexone

FDA labeling recommends that treatment with naltrexone not begin until signs and symptoms of acute alcohol withdrawal have subsided. At least 3 days of abstinence are usually recommended, with as many as 7 days if possible. Patients may experience fewer medication side effects (particularly nausea) if they are abstinent from alcohol when they begin treatment with naltrexone. However, it is safe for patients to begin taking naltrexone during medically supervised withdrawal or if they are actively drinking.

Before initiating treatment with naltrexone, healthcare practitioners should do the following:

- Conduct a medical evaluation that includes a physical exam, psychosocial assessment, and laboratory testing, including toxicological screening and liver function testing to establish suitability for medication and to establish a baseline for comparison
- Discuss the risks of naltrexone use during pregnancy and advise women of childbearing age to use birth control while taking naltrexone
- Ensure that patients are not regular users of opioids (illicit drugs, opioid maintenance medications, or opioid pain medications) to avoid precipitating withdrawal
- Strongly caution patients of the unpleasant physical effects of opioid

### Oral Naltrexone Black-Box Warning

Naltrexone has the capacity to cause hepatocellular injury when given in excessive doses.

Naltrexone is contraindicated in acute hepatitis or liver failure, and its use in patients with active liver disease must be carefully considered in light of its hepatotoxic effects.

The margin of separation between the apparently safe dose of naltrexone and the dose causing hepatic injury appears to be only fivefold or less. Naltrexone does not appear to be a hepatotoxin at the recommended doses.

Patients should be warned of the risk of hepatic injury and advised to stop the use of naltrexone and seek medical attention if they experience symptoms of acute hepatitis.

withdrawal that will result if patients are not completely detoxified from opioids.

## Dosage

Exhibit 4-1 summarizes dosage information for oral naltrexone. Naltrexone's duration of action (which is greater than 24 hours) allows a variety of flexible dosing schedules. Although 50 mg of naltrexone is currently the FDA recommended daily dose for treating AUDs, evidence from an open-label, small-scale trial suggested that higher doses (up to 150 mg/day) may be effective in reducing alcohol consumption in patients with complicated conditions (Oslin et al., 1999). Recent results from the large, multisite Combining Medications and Behavioral Interventions (COMBINE) study suggest that 100 mg naltrexone in combination with a brief medical management intervention is efficacious and well tolerated in patients dependent on alcohol (Anton et al., 2006). Mean adherence (the ratio of pills taken from returned blistercard pack counts to those prescribed throughout 16 weeks of treatment) for this higher naltrexone dose was more than 85 percent, and only 12 percent of patients required a dose reduction.

## Side Effects, Contraindications, and Cautions

An attractive feature of naltrexone for treating patients who are alcohol dependent is that, like disulfiram and acamprosate, the medication has virtually no abuse potential and patients do not develop tolerance for its efficacy. Side effects are generally mild and often diminish over time (Exhibit 4-2), although less common reactions and some potentially serious reactions have been reported (Exhibit 4-3). Nausea is one of the most frequently reported side effects. One study (O'Malley, Krishnan-Sarin, Farren, & O'Connor, 2000) suggests that women may be particularly susceptible to this side effect, which the authors argue supports the use of risk-minimizing strategies, such as gradual dosing starting with a lower dose, requiring abstinence for a specific amount of time before starting naltrexone, and providing support and supervision to help patients cope with nausea until it subsides. However, in clinical studies side effects were rarely cited by patients as reasons for discontinuing treatment with naltrexone.

Data on safety and effectiveness with adolescents are limited. The results of a recent small, open-label pilot study

**Exhibit 4-1  
Oral Naltrexone Dosages**

Initial dosage for most patients	50 mg/day in a single tablet
Initial dosage for patients at risk of adverse events (e.g., women, younger patients, those with shorter abstinence)	12.5 mg/day (quarter tablet) or 25 mg/day (half tablet) for 1 week, taken with food (2 weeks, if necessary); gradually increase to 50 mg/day
Average maintenance dosage	50 mg/day

**Exhibit 4-2  
Oral Naltrexone Side Effects**

Most Common	Less Common
Nausea	Diarrhea, constipation, stomach pains, cramps
Vomiting	Chest pain, joint/muscle pain
Headache	Rash
Dizziness	Difficulty sleeping
Fatigue	Excessive thirst, loss of appetite
Nervousness	Sweating
Anxiety	Increased tears
Somnolence	Mild depression
	Delayed ejaculation



suggest that naltrexone is well tolerated in adolescents seeking treatment and may reduce alcohol consumption and craving (Deas, May, Randall, Johnson, & Anton, 2005). However, additional work is needed before widespread naltrexone use in this population can be recommended.

Exhibit 4-4 lists situations in which use of naltrexone may require careful consideration or monitoring. Naltrexone is considered FDA pregnancy category

C, meaning its effects on the fetus are unknown. Women of childbearing age should be informed of this and counseled to use effective birth control when sexually active. Some clinicians may choose to obtain a pregnancy test before starting naltrexone and whenever pregnancy is suspected. If a patient becomes pregnant while using naltrexone, the clinician and patient should decide whether to continue the medication, given the potential risks and benefits.

### Exhibit 4-3 Naltrexone Contraindications

Patient Condition or Circumstance	Treatment Recommendation
Current illicit opioid use (as indicated by self-report or a positive urine screen) or buprenorphine (Suboxone® or Subutex®) or methadone maintenance therapy for the treatment of opioid dependence; currently undergoing opioid withdrawal	Do not prescribe oral naltrexone; consider an alternative medication
Acute hepatitis or liver failure	Do not prescribe oral naltrexone
Anticipated need for opioid analgesics within the next 7 days	Do not prescribe oral naltrexone
History of sensitivity to naltrexone, to structurally similar compounds (e.g., naloxone or nalmefene), or to any inactive ingredients in the tablet	Do not prescribe oral naltrexone

### Exhibit 4-4 Naltrexone Cautions

Patient Condition or Circumstance	Treatment Recommendation
Active liver disease	Monitor liver function frequently
Moderate to severe renal impairment	Use with careful monitoring (naltrexone is eliminated through the kidneys)
Pregnant and nursing women	Do not prescribe during pregnancy and nursing unless potential benefits outweigh risks (oral naltrexone is FDA pregnancy category C; it is unknown whether oral naltrexone is excreted in human milk)
Women of childbearing age	Caution patients that effects on fetus are unknown and encourage use of an effective birth control method
Serum aminotransferase levels greater than 5 times the upper limit of normal	Generally avoid, unless potential benefits outweigh risks
Chronic pain syndromes; acute or recurring need for opioid analgesics	Have patients abstain from naltrexone for at least 3 days (conservatively, 7 days) before initiating opioid analgesics

## Exhibit 4-5

### Adverse Reactions to Naltrexone and Their Management

Adverse Reaction	Management
Nausea	Suggest that the patient take naltrexone with complex carbohydrates (e.g., bread) rather than on an empty stomach Suggest that the patient take naltrexone with a tablespoon of simethicone (e.g., Gas-X® and Mylicon®) or bismuth subsalicylate (e.g., Pepto-Bismol®) Reduce dose or cease for 3 or 4 days and reinstate at lower dose
Liver toxicity	Discontinue naltrexone
Precipitated opioid withdrawal	Discontinue further doses of naltrexone Provide supportive treatments (i.e., hydration and antispasmodic and antidiarrheal medications) until opioid withdrawal symptoms resolve Provide $\alpha$ -2-agonists such as clonidine to mitigate some withdrawal symptoms; watch for enhanced side effects of clonidine, including dizziness, hypotension, fatigue, and headache
Naltrexone overdose	Treat symptomatically under close supervision Contact poison control for most recent information

### Patient Management

Exhibit 4-5 lists adverse reactions and their management. Patients should call their physician if they experience any signs or symptoms of liver disease. Exhibit 4-6 lists symptoms of liver disease.

Exhibit 4-7 lists interactions between naltrexone and other drugs.

The consensus panel recommends that liver function tests (i.e., ALT, AST, gamma glutamyltransferase, bilirubin) be performed before naltrexone treatment begins and at intervals thereafter. In healthy patients without liver disease, typical intervals can be 1, 3, and 6 months, then yearly thereafter. Liver function tests should be performed more frequently if baseline liver function test results are high, there is a history of hepatic disease, a potential hepatotoxic medication is also prescribed, or the patient is taking doses higher than 50 mg/day. Naltrexone should be used cautiously in patients whose serum

aminotransferase results are greater than five times the upper limit of normal.

A careful drug use history and urine toxicological screening should be used to confirm abstinence from opioids, including prescribed pain medications, and a lack of opioid dependence before initiating treatment. A comprehensive urine test should be used to measure methadone and other opioids. However, urine testing can be subject to error because typical urine screening tests may not cover all opioids and samples can be tampered with to affect the results.

### Exhibit 4-6 Signs and Symptoms of Liver Disease

Abdominal pains that last more than a few days	Fatigue
Light-colored bowel movements	Fever
Dark, tea-colored urine	Nausea
Yellowing of the eyes or skin	Weakness

## Exhibit 4-7 Drug Interactions With Oral Naltrexone

Drug	Effect With Oral Naltrexone
Cough/cold medications	May decrease benefit if medication contains an opioid
Antidiarrheal medications	May block benefit if medication contains an opioid
Opioid analgesics	May require greater amount of analgesic than usual and may result in deeper and more prolonged respiratory depression than if the patient were not taking naltrexone
Thioridazine	May result in lethargy and somnolence
Yohimbine	May result in anxiety and increased pulse and blood pressure
Nonsteroidal anti-inflammatory drugs (NSAIDs)	May result in liver enzyme elevations (i.e., aspartate aminotransferase [AST] and alanine aminotransferase [ALT]) in combination with regular use of very high doses of naltrexone (200–250 mg/day) (Kim, Grant, Adson, & Rimmel, 2001); this effect has not been observed in the recommended therapeutic dose range of naltrexone (50–100 mg)

### Patient Education

In addition to the general patient education guidelines discussed in Chapter 6, education about naltrexone should precede its use. Patients should be informed of the following:

- The effects of naltrexone on the fetus are unknown, so women who are pregnant or think they may be pregnant should inform their physician.
- The symptoms of protracted alcohol withdrawal (e.g., sleep disturbance) may overlap with side effects of naltrexone; patients should be reassured that symptoms typically improve with time.
- Naltrexone blocks the effects of opioids in prescription drugs such as pain relievers (e.g., morphine, oxycodone) and antidiarrheal and antitussive medications. Physicians should inform patients about other options for pain relief.
- Administering opioids to overcome naltrexone's blockade of the opiate receptors increases the risk of overdose, respiratory arrest, coma, and death.
- After taking naltrexone for some time and then stopping it, patients may be more sensitive to lower doses of opioids and thus risk overdose if they take opioids.
- Patients should continue to take naltrexone if they slip and return to drinking because it may help limit the severity of relapse.
- Participation in psychosocial interventions (e.g., cognitive-behavioral or other specialized treatment) and 12-Step or other mutual-help groups can increase the effectiveness of therapy with naltrexone.
- Patients should carry a medical alert card that indicates they are taking naltrexone and lists the physician or institution to contact in an emergency.

# Who Is Appropriate for Treatment With Oral Naltrexone?

## Patients Who Are Motivated or Monitored

A study by Volpicelli and colleagues (1997) concluded that patient compliance with naltrexone dosing is associated with treatment retention and positive treatment outcomes. As a result, it is important that either the patient be highly motivated for treatment or a medication monitoring plan be used to encourage naltrexone use if the patient is not highly motivated. To maximize compliance, physicians should observe dosing or encourage a family member or significant other to monitor medication use, especially at the beginning of treatment with naltrexone. Strategies such as incentives and feedback on medication compliance have been incorporated into treatment planning to enhance compliance. After the patient's motivation has increased and he or she feels better and stronger, medication monitoring may no longer be needed.

## Patients Who Are Abstinent From Opioids

Naltrexone is an opioid antagonist; patients who are using opioids, being maintained on opioid replacement therapy, or anticipating surgery or dental work that will require opioid analgesics are not good candidates for treatment with naltrexone. Naltrexone's opioid antagonist properties may make it a particularly good treatment option for individuals with a history of opioid abuse/dependence who are seeking treatment for AUDs because naltrexone will reduce the reinforcing effects of and curb cravings for both opioids and alcohol.

## Pain Management

As an opioid antagonist, naltrexone blocks the effect of opioid analgesics. Typical doses of narcotic analgesics (e.g., codeine, morphine, oxycodone, hydrocodone) may not be effective. Fortunately, many nonopioid analgesic medications (e.g., aspirin, NSAIDs) and procedures (e.g., regional nerve block) can still be used for analgesia.

When opioids must be used, it is possible to reverse the naltrexone blockade using higher than usual doses of opioids. However, because of the potential for opioid-induced respiratory depression, reversal of naltrexone blockade should be done only in medical settings with the provision for respiratory support.

Naltrexone does not block aspirin, acetaminophen, or NSAIDs, including ibuprofen and naproxen sodium. It does not block the effects of local anesthetics such as lidocaine or general (nonopioid) anesthetics. (If patients taking naltrexone require opioid pain medication, a rapidly acting opioid analgesic is recommended to minimize the duration of respiratory depression. Patients should be monitored closely.)

## Patients With Intense Alcohol Craving

Patients with intense alcohol cravings during treatment may experience greater medication benefit than patients with low levels of alcohol craving (Monterosso et al., 2001). Also, patients with more somatic complaints may have better outcomes when treated with naltrexone compared with patients with less physical distress. Both human laboratory studies and clinical trials have suggested that patients with a family history of alcohol dependence may benefit more from naltrexone treatment than patients without a family history of alcohol dependence (Monterosso et al., 2001; Rubio et al., 2005).

## Treatment Duration and Discontinuing Oral Naltrexone

The FDA label states that naltrexone should be taken for up to 3 months to treat AUDs. Healthcare providers should tailor the length of treatment to individual patients. Naltrexone has been administered to patients who are alcohol dependent for 6 months to 1 year with no additional safety concerns (Ballidin et al., 2003; O'Malley et al., 2003).

One controlled study (Hernandez-Avila et al., 2006; Kranzler et al., 2003) addressed targeted use of naltrexone during periods of risk for problem alcohol use. The findings and clinical experience support periodic or targeted dosing. Because of naltrexone's efficacy in reducing the rewarding effects of alcohol consumption (McCaul, Wand, Eissenberg, Rohde, & Cheskin, 2000) and reducing cravings for alcohol (O'Malley et al., 1992), patients who achieve abstinence may benefit from taking naltrexone at times when they are at higher risk of relapse, such as on vacations, on holidays, or during a personal tragedy.

Discontinuation of oral naltrexone is not associated with a withdrawal syndrome, and it is not necessary to taper the dose. Providers should remind patients that they should not take opioid medications for at least 3 days and that they may be more sensitive to the effects of opioid drugs (see Patient Education, page 33).

## Final Clinical Thoughts

Controlled clinical trials have demonstrated that naltrexone can be an effective medication for the treatment of patients who are alcohol dependent. Clinicians indicate that some patients report that naltrexone helps, and some report no difference with its use. These

anecdotal reports provide intriguing suggestions that particular patient types or subgroups may be more likely than other groups to respond to naltrexone. A recent finding has suggested that a variant in a gene encoding for the  $\mu$  opiate receptor (OPRM1) in the opiate neurotransmitter system may predict response to naltrexone treatment in people dependent on alcohol (Anton et al., 2008). When treated with naltrexone and a medical management intervention, 87.1 percent of persons carrying the less prevalent Asp40 variant had a good clinical outcome, compared with only 54.8 percent of individuals with the more common Asn40/Asn40 genotype (odds ratio, 5.75; confidence interval, 1.88–17.54); no difference between groups was observed in placebo treatment outcomes. This finding suggests that OPRM1 genotyping may be a useful procedure for improving identification of those patients most likely to benefit from naltrexone treatment for alcohol dependence. It also suggests that clinicians should not become discouraged if the first patients they prescribe naltrexone for do not find it beneficial. Naltrexone's efficacy is modest, but it is significantly better than placebo in most studies, and some patients benefit from naltrexone therapy.

Although attention is frequently drawn to the risks of hepatotoxicity with naltrexone, this rarely occurs, is typically reversible, and is more likely with very high doses used over a sustained period. It is unfortunate that such effects have become so closely associated with naltrexone, but the clinician would be prudent to monitor liver function.

Naltrexone—and all the medications described in this TIP—does not “cure” AUDs the way an antibiotic cures bacterial pneumonia. However, as a part of comprehensive treatment, it may increase the likelihood of sustained remission from problem alcohol use.

# 5 Extended-Release Injectable Naltrexone

## Extended-Release Injectable Naltrexone At a Glance

**Chemical name:** Naltrexone for extended-release injectable suspension.

**Trade name:** Vivitrol®.

**U.S. distributor:** Alkermes, Inc., Cambridge, MA (manufacturer); Cephalon, Inc., Frazer, PA (distributor).

**U.S. Food and Drug Administration approval to treat alcohol dependence:** 2006.

**Dosage/How taken:** 380 mg intramuscular injection once every 4 weeks.

**How supplied:** Single-use cartons, containing one 380 mg vial of Vivitrol microspheres, one vial containing 4 mL (to deliver 3.4 mL) diluent for the suspension of Vivitrol, one 5 mL prepackaged syringe, one 20-gauge ½-inch needle, and two 20-gauge 1½-inch needles.

**Storage:** Store entire dose pack in refrigerator (2–8° C, 36–46° F); store unrefrigerated Vivitrol at temperatures not exceeding 25° C (77° F) for no more than 7 days before administration; do not freeze.

## What Is Extended-Release Injectable Naltrexone?

Extended-release injectable naltrexone is a microsphere formulation of the opioid antagonist (blocker) medication naltrexone. It is administered by intramuscular (IM) gluteal injection once a month. The extended-release injectable form helps address patient noncompliance, which can limit the effectiveness of oral naltrexone (Volpicelli et al., 1997).

## Brief History of Development

Interest existed in developing an injectable, long-acting naltrexone formulation for many years. Various long-acting naltrexone formulations were studied, but there was particular interest in the polylactide (Nuwaysner, DeRoo, Balskovich, & Tsuk, 1990) and polylactide glycolide (PLG) polymer (Sharon & Wise, 1981). These polymers are prepared from naturally occurring sugar

acids (lactic acid and glycolic acid), are known to be safe, and are used widely in human and veterinary medicine (e.g., in absorbable sutures and biodegradable orthopedic screws). The U.S. Food and Drug Administration (FDA) approved Alkermes' PLG polymer formulation of extended-release injectable naltrexone for treating alcohol dependence in April 2006.

## Pharmacology

Some behavioral effects of alcohol are caused by alcohol acting to release endogenous opioid neurotransmitters (e.g., endorphins, enkephalins, dynorphins) that bind to opiate receptors in the brain. Opioid antagonists, such as naltrexone, bind to opiate receptors and block the action of both opioid medications and opiate neurotransmitters.

The injectable naltrexone plasma concentration peaks approximately 2 hours after IM injection followed by a second peak approximately 2 to 3 days later. Beginning approximately 7 days after dosing, plasma concentrations slowly decline, maintaining a therapeutic naltrexone blood level over 4 weeks and avoiding daily peaks and troughs that occur with oral naltrexone. Steady state is reached at the end of the dosing interval following the first injection.

Unlike oral naltrexone, injectable naltrexone does not undergo first-pass metabolism in the liver. As a consequence, the total monthly dose of naltrexone administered is considerably less for extended-released (380 mg) compared with oral naltrexone (1,500 mg). Therefore, the peak concentration of the drug to which the liver is exposed is substantially less for injectable naltrexone than for oral naltrexone. Because naltrexone-induced hepatotoxicity is dose dependent, injectable naltrexone would be expected to show less hepatotoxicity than the oral form; however, a direct comparison of relative hepatotoxicity of

the two medications has not yet been performed.

## Why Use Extended-Release Injectable Naltrexone?

### Efficacy

Findings on the efficacy of naltrexone in general to treat alcohol use disorders (AUDs) are briefly discussed in Chapter 4, page 28. More detailed information is included in the TIP's online annotated bibliography and literature review at <http://www.kap.samhsa.gov>. Garbutt and colleagues (2005) conducted a 6-month, randomized clinical trial of injectable naltrexone to assess its tolerability and efficacy. A group of patients receiving IM injection of 380 mg of injectable naltrexone (along with psychosocial support) had a 25-percent decrease in the event rate of heavy drinking days compared with those receiving placebo. Patients receiving a lower dose (190 mg) of injectable naltrexone also had a significant decrease (17 percent) in the event rate of heavy drinking days compared with those receiving placebo.

The FDA Center for Drug Evaluation and Research (CDER) analysis of the study data concluded that injectable naltrexone is effective only in those who were abstinent at baseline. CDER's analysis emphasized the proportion of patients who did not relapse to heavy drinking (FDA CDER, personal communication, 2008). O'Malley and colleagues (2007) conducted a secondary analysis of outcomes from the Garbutt study to determine whether patients with lead-in abstinence of 4 or more days also experienced particularly good treatment outcomes—a practical issue in U.S. detoxification settings, where detoxification commonly takes 4 days. They found that injectable naltrexone prolongs abstinence

### Enhanced Medication Compliance

A major benefit of using an extended-release formulation in the treatment of AUDs is decreased concern about compliance with daily administration, thus ensuring efficacy of naltrexone delivery and therapeutic effect. In a randomized, double-blind, clinical trial, there were no differences in drinking outcomes in 175 patients with alcohol dependence assigned to minimal psychosocial treatment and treated with either oral naltrexone or placebo (Chick et al., 2000). However, when only those subjects demonstrating greater than 80-percent medication compliance were included in the analysis, oral naltrexone was found to be effective.

The importance of medication compliance is further supported by a clinical trial that compared oral naltrexone with placebo in 97 individuals with alcohol dependence receiving weekly one-on-one counseling. Among individuals who were treatment compliant, those receiving oral naltrexone reported fewer episodes of heavy drinking (14 percent vs. 52 percent) and had fewer drinking days (2.8 percent vs. 11 percent) than those receiving placebo, whereas the drinking outcomes in the noncompliant individuals did not differ from individuals who received placebo (Volpicelli et al., 1997).

and reduces both the number of drinking days and the number of heavy drinking days in patients who are abstinent for as few as 4 days before starting treatment.

The online literature review provides more detailed information on these and other efficacy studies.

### Safety

Injectable naltrexone appears to be well tolerated, with a side effects profile similar to that of oral naltrexone (with the exception of injection-site reactions). Like oral naltrexone, the injectable formulation carries a black-box warning regarding liver toxicity (see Chapter 4, page 29). However, because of its lack of first-pass metabolism, injectable naltrexone significantly reduces liver

exposure to the drug, reducing the risk of potential liver toxicity.

## How Is Extended-Release Injectable Naltrexone Used?

Treatment with injectable naltrexone should be part of a management program that provides patient education, addresses the psychological and social problems of patients, and encourages attendance at 12-Step or mutual-help meetings or other community support.

Before initiating treatment with injectable naltrexone, healthcare practitioners should do the following:

- Conduct a physical examination
- Determine liver function (alanine aminotransferase [ALT], aspartate aminotransferase [AST], gamma glutamyltransferase [GGT], and bilirubin)
- Obtain toxicological screening tests.

Naltrexone is an opioid antagonist, so individuals who are opioid dependent may experience opioid withdrawal. Treatment with injectable naltrexone should not be initiated unless the patient is opioid free for 7 to 10 days (or at least 14 days for patients who have been taking methadone for more than 3 to 4 weeks), as determined by medical history or toxicological screening.

Patients being maintained on buprenorphine (Suboxone<sup>®</sup> or Subutex<sup>®</sup>) or methadone for the treatment of opioid dependence cannot undergo treatment with naltrexone. Before administering injectable naltrexone, physicians should advise patients of the unpleasant physical effects of opioid withdrawal that will result if patients are not completely detoxified from opioids. Injectable naltrexone is available through specialty pharmacies.



## How To Administer

Injectable naltrexone should be administered only by a medical professional (e.g., physician, nurse, physician assistant) who can administer IM (gluteal) injections. Injectable naltrexone comes in a kit that contains a vial of naltrexone as a dry powder that must be reconstituted with a liquid diluent immediately before use. The kits must be refrigerated during storage but should be brought to room temperature 30 to 60 minutes before the injection. The reconstituted microspheres in solution must be mixed vigorously to prevent clumping, which can clog a needle during injection. A syringe and two needles are provided—one for mixing the microspheres with the diluent and one for injecting the suspension into the upper outer quadrant of the gluteal muscle. The medication is administered every 4 weeks. If a dose is delayed or missed, the next injection should be administered as soon as possible. However, it is not recommended that medication be readministered earlier than 4 weeks or at a higher dose than 380 mg.

Proper IM injection technique is essential. Serious injection site reactions, sometimes requiring extensive surgical debridement, have been observed with Vivitrol. CDER reports that these severe reactions may be more common if the product is inadvertently administered subcutaneously, rather than intramuscularly (FDA CDER, personal communication, 2008).

## Side Effects, Contraindications, and Cautions

Exhibit 5-1 lists the most common side effects experienced by patients treated with injectable naltrexone. As when using oral naltrexone, patients should contact their physician if they experience signs or symptoms of liver disease (see Exhibit 4-6 on page 32).

### Exhibit 5-1 Extended-Release Injectable Naltrexone Side Effects

Injection site reactions (sometimes severe)	Fatigue
Nausea	Back pain
Vomiting	Upper abdominal pain
Headache	Decreased appetite
Dizziness	

Injectable naltrexone carries the same contraindications as oral naltrexone (see Exhibit 4-3 on page 31) plus those listed in Exhibit 5-2. There are no data on use of naltrexone in children or adolescents; treatment of these populations with naltrexone is not recommended.

Injectable naltrexone should be used with many of the cautions applicable to oral

### Exhibit 5-2 Extended-Release Injectable Naltrexone Contraindications

Patient Condition or Circumstance	Treatment Recommendation
History of sensitivity to PLG, carboxymethylcellulose, or any components of the diluent	Do not administer injectable naltrexone
Anticipated need for opioid analgesics within the next 30 days	Do not administer injectable naltrexone
Patient obesity	Do not administer injectable naltrexone if patient's body mass precludes IM injection with the provided 1.5-inch needle  Inadvertent subcutaneous injection may cause a severe injection-site reaction

naltrexone (see Exhibit 4-4 on page 31) plus the cautions listed in Exhibit 5-3. Injectable naltrexone should be used cautiously with individuals with current or recent opioid dependence for two reasons. First, these individuals are at risk for overdose of opioids if they use large amounts of opioids to overcome naltrexone's opioid blockade (to feel the effects of the drugs). Second, naltrexone blockade can decrease tolerance for opioids, making a person more sensitive to their effects. If a person stops taking naltrexone, then takes what used to be a "normal" dose of opioids, overdose with respiratory depression can result.

### Patient Management

Possible adverse reactions are the same as those for oral naltrexone (see Exhibit 4-5 on page 32). In addition, injection-site reactions are common adverse reactions to administration of injectable naltrexone. Some pain and tenderness at the injection site are common and are similar to those occurring after any IM injection. Usually, this pain resolves within several days. A

small lump at the injection site frequently occurs and resolves over 2 to 4 weeks. However, patients should be instructed to seek immediate medical attention if skin at the injection site becomes painful, red, and swollen and does not improve within 1 week after the injection. As noted above, severe injection-site reactions are possible.

Patients taking injectable naltrexone also should be monitored for depression. The package label states:

In controlled clinical trials of Vivitrol, adverse events of a suicidal nature (suicidal ideation, suicide attempts, completed suicides) were infrequent overall, but were more common in patients treated with Vivitrol than in patients treated with placebo (1% vs. 0). In some cases, the suicidal thoughts or behavior occurred after study discontinuation, but were in the context of an episode of depression which began while the patient was on study drug. In the 24-week, placebo-controlled pivotal trial, adverse events involving depressed mood were reported by 10% of patients treated with Vivitrol 380 mg, as compared to 5% of patients treated with placebo injections.

Patients who take injectable naltrexone should undergo the same tests as those required for patients taking oral naltrexone (see page 32).

Overdose should not be a concern for patients receiving injectable naltrexone because it is unlikely that patients will receive more than one IM injection per month.

### Patient Education

In addition to the general patient education guidelines discussed in Chapter 6, patient education specific to injectable naltrexone should precede use.

**Exhibit 5-3  
Extended-Release Injectable  
Naltrexone Cautions**

Patient Condition or Circumstance	Treatment Recommendation
Thrombocytopenia or coagulation disorders	Monitor carefully for 24 hours after injection
Recent opioid dependence	Explain to the patient the risk of precipitated withdrawal if the patient has used opioids recently  Explain to the patient that the opioid-blocking effects last for at least 30 days and that the risks associated with a return to opioid use are significant

Healthcare providers should ensure that patients understand the following:

- Once naltrexone is injected, it is impossible to remove it from the body; if problems occur, the effects can last up to 30 days.
- The onset of naltrexone's effects will probably occur within several hours although full effectiveness may not occur for 2 to 3 days following first injection. The duration of the effects appears to be 30 days.
- Injectable naltrexone blocks the effects of opioids and opioidlike drugs (e.g., heroin, opioid analgesics, opioid-based antidiarrheals, and antitussives) for up to 30 days, which may complicate the treatment of pain if it occurs during this period. Patients should be assured that other options for analgesia exist.
- Injectable naltrexone blocks low to moderate doses of opioids, but large doses of heroin or other opioids may lead to serious injury, coma, or death. For patients with a history of opioid use, the use of injectable naltrexone may lower tolerance for opioids, resulting in a greater

sensitivity to lower doses of opioids after injectable naltrexone treatment is discontinued; this increased sensitivity could result in overdose and respiratory depression.

- Injectable naltrexone is more likely to reduce drinking if it is used in conjunction with psychosocial interventions, such as specialized substance abuse treatment and community supports (e.g., counseling, 12-Step, or other mutual-help groups).
- Patients should carry a safety ID card that indicates they are taking injectable naltrexone.

## Who Is Appropriate for Treatment With Extended-Release Injectable Naltrexone?

This medication should be considered for individuals with alcohol dependence who have not responded to other pharmacological and behavioral treatments, in particular those who have problems with treatment adherence. The medication

### Pain Management

As an opioid antagonist, injectable naltrexone blocks the effects of opioid analgesics. Pain management for patients taking naltrexone is discussed in Chapter 4, page 34. Pain management for patients using injectable naltrexone can be even more complicated because the medication is long acting. The package insert offers the following advice:

In an emergency situation in patients receiving Vivitrol, a suggested plan for pain management is regional analgesia, conscious sedation with a benzodiazepine, and use of non-opioid 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 which minimizes the duration of respiratory depression is preferred. The amount of analgesic administered should be titrated to the needs of the patient. Non-receptor mediated actions may occur and should be expected (e.g., facial swelling, itching, generalized erythema, or bronchoconstriction), presumably due to histamine release.

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

could be considered a first-line therapy for any patient who is alcohol dependent, interested in treatment, and not subject to the contraindications listed in Exhibit 4-3 and Exhibit 5-2. However, the monthly cost of injectable naltrexone is significantly higher than that of oral naltrexone and may not be a viable choice for many patients.

For *optimal* results with injectable naltrexone, candidates for treatment should meet several criteria:

- They must be medically appropriate to receive naltrexone.
- They should not be using opioids currently or have evidence of recent use.
- They should not be anticipating surgery or have a condition, such as chronic pain, for which opioid analgesics may be required in the future.
- They should not have severe liver or kidney disease, although naltrexone can be used cautiously in persons with mild to moderate hepatic impairment or mild renal insufficiency.
- They should not have a condition, such as a bleeding disorder or obesity, that prevents them from receiving a deep IM injection.
- They should have been abstinent for at least 4 days.
- They should be motivated to maintain abstinence or to reduce their drinking.
- They should be willing to participate in psychosocial substance abuse treatment such as counseling and support groups.

The consensus panel believes that the opioid antagonist properties of injectable naltrexone may make it a good treatment option for individuals who are seeking treatment for alcohol dependence and who are in recovery from co-occurring opioid use. However, no evidence for efficacy

in this population is available, and injectable naltrexone has not been approved for the treatment of opioid dependence.

## Treatment Duration and Discontinuing Extended-Release Injectable Naltrexone

Research has not yet clearly defined the optimal duration of treatment with injectable naltrexone. Healthcare providers may consider discontinuing injectable naltrexone once a patient has achieved stable abstinence from alcohol and has established a sound plan and support for ongoing recovery or if a patient is not compliant with the medication regimen. Like oral naltrexone, injectable naltrexone may be useful for short periods when a patient in stable recovery is at particular risk for relapse to problem alcohol use.

Patients discontinuing injectable naltrexone should be reminded that they should not take any opioid medications for *at least* 30 days from the date of their last injection. Patients also should be warned that after discontinuing treatment they may be more sensitive to the effects of opioid drugs (see Patient Education on page 41).

## Final Clinical Thoughts

Physicians may be concerned that the decreased frequency of required medical visits that comes with monthly medication will result in decreased use of medical and psychosocial services, making patients less likely to attend counseling, 12-Step, or mutual-help group meetings. Treatment with injectable naltrexone is new, but the experience of the consensus panel suggests that patients who return monthly for their injectable

naltrexone continue to participate in treatment and to attend these groups.

Possible target patients include those who are unable to maintain medication adherence for some reason (e.g., poor memory) and those who would prefer not to have the burden of remembering to take medication daily.

Because injectable naltrexone is the newest form of a medication for

the treatment of AUDs, the optimal situations for its use remain to be defined. However, it combines two attractive features: a medication for which there is substantial evidence for efficacy and a delivery system that eliminates daily medication compliance. As such, it represents an important addition to the list of medications for the treatment of alcohol dependence.

# 6 Patient Management

## In This Chapter . . .

Integrating Medication for Alcohol Dependence Into Clinical Practice Settings

Initial Assessment

Choosing a Medication

Combination Therapy

Choosing a Psychosocial Intervention

Developing a Treatment Plan

Patient Awareness

Monitoring Patient Progress

Modifying the Treatment Strategy

Discontinuing Pharmacotherapy

Final Clinical Thoughts

## Integrating Medication for Alcohol Dependence Into Clinical Practice Settings

Pharmacotherapy for alcohol use disorders (AUDs) is underused both in specialized substance abuse treatment programs and in office-based medical practice. The consensus panel acknowledges that much resistance to pharmacotherapy exists—from third-party payers, some clinicians, some individuals participating in self-help groups who view medications as substituting a pill for self-empowerment and self-responsibility, and some patients and their families. The diagnoses of alcohol dependence and abuse, as well as hazardous alcohol use, continue to carry significant social stigma that affects both the person who is alcohol dependent and healthcare providers. This stigma continues to exist, in part, because of a lack of understanding of alcohol dependence as a treatable medical disorder. In addition, providers often worry that persons who are alcohol dependent have complicated conditions that take too much time to treat.

Healthcare providers are, however, in ideal practice settings to identify and treat AUDs among users of healthcare services. AUDs are associated with many medical (e.g., hypertension, gastritis) and behavioral (e.g., major depressive disorder, psychoses) health conditions. Screening, identifying, and treating patients with AUDs have the potential to improve the health of many primary care patients, decrease healthcare costs, and prevent the serious sequelae of alcohol misuse. A full discussion of reimbursement issues is outside the scope of TIP 49; however, healthcare practitioners can find useful information in *SBI Reimbursement Guide: How to Use Existing Codes to Bill for Alcohol Screening and Brief Intervention/Counseling*, prepared by Ensuring Solutions for Alcohol Problems at the George Washington University Medical Center. The guide is available at [http://www.ensuringsolutions.org/resources/resources\\_show.htm?doc\\_id=385233](http://www.ensuringsolutions.org/resources/resources_show.htm?doc_id=385233).

Patients with AUDs may be more likely to see a healthcare provider than to seek treatment at a specialty addiction treatment program; these patients represent an untapped reservoir of individuals who are not receiving needed treatment. Medications can be a potent means of enhancing treatment for many persons who are alcohol dependent; medications present healthcare providers a unique way to contribute to treatment. Some aspects of using maintenance medications (e.g., the need for concurrent psychosocial treatment and for monitoring drinking behavior) may seem different from usual medical practice. However, integrating maintenance medications into practice should not present any more difficulty than, for example, beginning to prescribe antidepressant or antihypertensive medications. Monitoring a patient's maintenance medication regimen is typically less complicated than medication regimens for other chronic conditions, such as diabetes or coronary disease.

Healthcare providers may find that using maintenance medication provides them with an opportunity to have a significant effect on patients' overall health status, social functioning, and family relationships. This chapter describes information needed for choosing maintenance medications for patients, making effective referrals, and monitoring patients' progress.

## Initial Assessment

Persons with AUDs often have physical and social sequelae from excessive alcohol consumption. AUDs influence the incidence, course, and treatment of many medical and behavioral health conditions. Identifying, assessing, and treating AUDs can occur concurrently with assessment and treatment of other medical problems. As noted in Chapter 1, a thorough discussion of screening and assessment for AUDs is outside the scope of this TIP.

The reader can refer to *Helping Patients Who Drink Too Much: A Clinician's Guide* (National Institute on Alcohol Abuse and Alcoholism [NIAAA], 2006), available at <http://www.niaaa.nih.gov>. An online course (worth one continuing medical education unit) based on the guide is also available at <http://www.niaaa.nih.gov/Publications/EducationTrainingMaterials/VideoCases.htm>. NIAAA's *A Pocket Guide for Alcohol Screening and Brief Intervention* is in Appendix B of this TIP.

Once an AUD diagnosis has been made, thorough assessments for substance use and social, medical, and psychiatric histories are essential in evaluating the consequences of dependence and identifying problems that can be addressed concurrently with treatment. Evaluation can identify or rule out contraindications to therapy with specific medications. At the very least, a clinician considering a patient's pharmacologic treatment for alcohol dependence should perform a physical exam; order laboratory tests; assess psychiatric status; obtain substance use, treatment, and social histories; and assess motivation for change.

## Physical Exam and Laboratory Testing

Because alcohol dependence can harm many organ systems and certain conditions may preclude pharmacotherapy with a particular maintenance medication, a physical exam and laboratory testing should be performed before any treatment is initiated.

Medical complications of excessive alcohol consumption are common and numerous, and TIP 49 cannot discuss them all. However, common medical conditions such as hypertension and gastritis and common psychiatric conditions such as depression can be incited or exacerbated by AUDs. Various patient complaints can be related to alcohol consumption,

including dyspepsia, sleep problems, sexual difficulties, depressed mood, and irritability. AUDs also contribute to progression of morbidity for many diseases. For instance, according to a recent review of the literature (Conigliaro, Justice, Gordon, & Bryant, 2006), excessive alcohol consumption increases the morbidity associated with HIV and viral hepatitis and can complicate medical treatment for these conditions. In addition, existing conditions, such as hepatic or renal disease or pain syndromes, either acute or chronic, may contraindicate treatment with particular maintenance medications.

### **Physical exam**

Although physical exam findings may not be specific to alcohol consumption or alcohol disorders, a thorough physical exam can often corroborate clinician suspicions of an AUD and may help with disease monitoring. Patients with AUDs may have no specific abnormal exam findings. However, when present, abnormal exam findings provide evidence of the severity of a patient's AUD. Longstanding alcohol consumption may present with many "classic" physical exam features, including physical manifestations of cirrhosis, encephalopathy, and vitamin deficiencies. Alcohol consumption can incur tachycardia (including supraventricular tachycardias), tremor (hand or tongue), elevated blood pressure, hepatosplenomegaly, a tender liver edge, peripheral neuropathy, spider angiomas, conjunctival injection, and unexplained trauma (Conigliaro, Delos Reyes, Parran, & Schulz, 2003).

Because AUDs often co-occur with drug use, the physical exam may help the clinician identify comorbid substance use problems. For example, smoking cigarettes frequently co-occurs with excessive alcohol use; smoking, along with alcohol use, may increase heart rate and promote tachyarrhythmias. Needle marks, hard

blackened veins, and abscesses in the arms, hips, buttocks, thighs, or calves may indicate concomitant injection drug use. Inhaled drugs, such as crack cocaine, often cause a brown tongue, nasal septum abnormalities, or diffuse wheezes.

### **Laboratory testing**

In addition to helping healthcare practitioners assess a patient's overall health status, initial laboratory testing can identify the presence of AUDs, alcohol-related damage, and contraindications for use of particular medications. Initial and followup laboratory testing may motivate patients and reinforce their progress in treatment. Exhibit 6-1 provides a list of useful laboratory tests that can identify patients with significant alcohol consumption.

#### **Exhibit 6-1 Useful Laboratory Tests**

- Breath or blood alcohol tests
- Urine toxicology
- Gamma glutamyltransferase (GGT)
- Liver function tests, including serum aspartate aminotransferase (AST)
- Complete blood count
- Testing for vitamin deficiencies
- Renal function tests: Standard panel for urea (blood urea nitrogen), electrolytes, and serum creatinine
- Pregnancy test (women of childbearing age)

**Identifying AUDs and illicit drug use.** Laboratory tests are more specific than sensitive for detecting alcohol problems, and there is no single laboratory test that is sensitive or specific for AUD diagnoses. Detection of AUDs is improved when laboratory tests are combined with other screening strategies (Escobar, Espi, & Canteras, 1995; Gordon et al., 2001). However, certain tests *help* healthcare



providers identify AUDs and possible alcohol-related abnormalities.

*Blood/breath/urine alcohol and toxicological screening.* Blood alcohol levels and urine/breath tests for alcohol are useful measures of recent alcohol consumption. They determine acute physical or legal incapacity to do specific tasks. Initial laboratory work also should include a urine toxicology screen to assess for other substances.

*Biomarkers for AUDs.* Alcohol biomarkers are physiological indicators of alcohol exposure or ingestion and may reflect the presence of an AUD. Although tests such as serum carbohydrate-deficient transferrin (CDT) levels are not often used in primary care practice, some evidence suggests that they might be used to screen for chronic alcohol consumption and to monitor consumption during treatment under certain conditions (Bell, Tallaksen, Try, & Haug, 1994). For example, an increase in CDT over time may suggest an increase in alcohol consumption (Sorvajarvi, Blake, Israel, & Niemela, 1996).

In addition to assessing impairment in liver functioning, AST and GGT can be used as biomarkers because they are often elevated in persons who recently consumed significant amounts of alcohol (Aithal, Thornes, Dwarakanath, & Tanner, 1998; Bell et al., 1994; Yersin et al., 1995). Some studies suggest that biomarkers such as AST, GGT, and CDT are most useful for screening when used in combination (Aithal et al., 1998; Sillanaukee, Aalto, & Seppa, 1998).

Testing for another biomarker, ethyl glucuronide (EtG), is becoming widely available in the United States and is increasingly being used for screening. This marker is highly sensitive for alcohol. This sensitivity is a potential drawback as well as a strength, as exposure to even small amounts (such as

those found in some foods and cosmetic items) can trigger a positive test result.

More detailed information about the use (and misuse) of biomarkers for identifying AUDs and other substance use disorders can be found in the *Substance Abuse Treatment Advisory, The Role of Biomarkers in the Treatment of Alcohol Use Disorders* (Center for Substance Abuse Treatment [CSAT], 2006b).

### **Identifying alcohol-related damage and medication contraindications.**

Several laboratory tests help healthcare practitioners establish a patient's overall health status as well as identify alcohol-related damage and contraindications for using certain medications.

*Complete blood count.* Alcohol overuse causes anemia and has direct toxic effects on bone marrow. An assessment of hematologic laboratory indices is essential when considering pharmacologic treatment of AUDs. Many persons who are alcohol dependent have macrocytosis, and the mean corpuscular volume is often elevated.

*Testing for vitamin deficiencies.* People with AUDs may not eat well, and several vitamin deficiencies can occur that lead to abnormal cellular functions. Thiamine, folic acid, and pyridoxine deficits are common in people with chronic AUDs, and these deficiencies contribute to abnormal cell growth. Vitamin deficiencies may lead to Wernicke-Korsakoff's/amnestic syndrome in patients with severely excessive alcohol consumption.

*Hepatic and renal testing.* Consideration of treatment of AUDs with pharmacotherapy requires the clinician to consider evaluating organ systems that are involved in the metabolism and excretion of these medications. For example, naltrexone and disulfiram should be used with caution in patients with liver disease, and naltrexone and acamprosate

should be used with caution in patients with renal impairment. Therefore, hepatic and renal system testing should be done before initiating use of these medications. Finally, all four medications used to treat AUDs are U.S. Food and Drug Administration (FDA) pregnancy category C; women of childbearing age should receive a pregnancy test before pharmacotherapy is initiated.

**Motivating patients for treatment and reinforcing progress.** Providing feedback about patients' initial test results, compared with norms, and the health risks associated with these results can be a powerful way to increase patients' motivation and adherence to treatment. Laboratory tests help healthcare providers objectively monitor patients' progress in treatment and provide patients with objective reinforcement by demonstrating biologic evidence of their improving health status.

## Psychiatric Assessment

Psychiatric conditions (such as major depression, generalized anxiety disorder, posttraumatic stress disorder, schizophrenia, and personality disorders) frequently co-occur with excessive alcohol consumption (Kranzler & Rosenthal, 2003). Some psychiatric symptoms resolve with abstinence, and others lessen. Nonetheless, the prescribing professional should assess the patient for these disorders and for suicidal ideation or intent (or refer the patient for assessment). Untreated psychiatric conditions can seriously interfere with a patient's ability to comply with pharmacotherapy and psychosocial treatment for alcohol dependence and can cause the patient preventable suffering. More information on co-occurring psychiatric disorders can be found in TIP 42, *Substance Abuse Treatment for Persons With Co-Occurring Disorders* (CSAT, 2005).

## Substance Use Assessment

After healthcare providers have ascertained that a patient has an AUD, they should obtain an adequate history of the patient's substance use and of prior treatments for AUDs. Providers should determine whether the patient has experienced alcohol withdrawal syndrome because this syndrome can indicate a need for more specialized care than primary care providers can typically provide. More information about alcohol withdrawal and detoxification is in TIP 45, *Detoxification and Substance Abuse Treatment* (CSAT, 2006a). Excerpts of the Quick Guide for Clinicians based on TIP 45 are in Appendix C.

During the assessment, providers should assess the quantity and frequency of alcohol consumption, patterns of alcohol consumption (e.g., persistent, occasional, binge use), episodes of use, duration of use, and consequences of alcohol consumption. The NIAAA clinician's guide suggests a stepwise approach that consists of assessment of any use, quantity/frequency of use, and harm associated with alcohol consumption (NIAAA, 2006). NIAAA's *A Pocket Guide for Alcohol Screening and Brief Intervention*, a condensed version of the clinician's guide, is in Appendix B. Exhibit 6-2 lists key questions to quickly assess quantity and frequency of alcohol use, based on a "standard drink" in the United States that contains 14 grams of pure alcohol (about 0.6 fluid ounces or 1.2 tablespoons). More detailed information about what constitutes a standard drink is in Appendix B.

The history also should include use of substances other than alcohol, especially opioids, as well as the patient's history of use, misuse, or abuse of prescription medications. Misuse of opioid medications may complicate or contraindicate

## Exhibit 6-2 Questions To Assess Quantity and Frequency of Consumption

How often do you have a drink containing alcohol?

How many drinks containing alcohol do you have on a typical day when you are drinking?

How often do you have five or more drinks on one occasion?

SOURCE: Babor, Higgins-Biddle, Saunders, & Monteiro, 2001.

treatment with naltrexone. Abuse of sedatives and tranquilizers may complicate detoxification and treatment.

A complete assessment includes a patient's current involvement in or history of professional treatment or mutual-help group involvement, including the following:

- Detoxification episodes
- Pharmacotherapy interventions
- Specialty substance abuse treatment episodes (including when, where, modality, duration, and outcome)
- Individual therapy
- 12-Step (e.g., Alcoholics Anonymous) or other mutual- or self-help program involvement.

This information can assist the provider in treatment planning and advocating for psychosocial treatment as an adjunct to pharmacologic treatment for alcohol dependence.

### Social History

Understanding a patient's social situation identifies problems that may interfere with treatment and that necessitate referral for ancillary services. Asking a patient basic questions about his or her

work, legal, living, and family situations can yield information that is critical to treatment planning:

- What is the patient's family situation? Who should be included in treatment planning? Who can monitor a patient's medication compliance?
- Is the patient on probation at work? Could this be a means of motivating medication compliance?
- What is the patient's living situation? Are extra measures required to ensure medication compliance? Are psychosocial treatment modalities (residential vs. outpatient) recommended?

### Assessing Motivation for Change

Before offering treatment for alcohol dependence, providers should assess patients' readiness to change drinking behavior. Through this assessment, patients and providers develop mutually agreeable intervention and treatment plans. Exhibit 6-3 provides questions that determine patients' readiness for change.

Regardless of patients' readiness to change, they should, at a minimum, be willing to be in a supportive relationship with their healthcare provider. If the relationship is strained by dishonesty or mistrust, initial willingness to take medication and ongoing compliance with a medication regimen may suffer. In addition, patients should be willing to consider adjunctive options including specialty treatment, other independent psychosocial treatment providers, or forms of community support. A review of the literature suggests that although psychosocial interventions increase rates of abstinence and decrease alcohol consumption, a significant proportion of patients relapse to drinking within 1 year (Mason, 2005a). Healthcare providers, however, can play a significant role in motivational enhancement and relapse prevention. More information about

### Exhibit 6-3 Questions To Assess Patients' Readiness for Change

In what ways are you concerned about your drinking?  
How much does this concern you?  
What are the reasons you see for making a change?  
How do you feel about changing your drinking?  
How ready are you to change your drinking?  
What do you think will happen if you don't make a change?  
What do you think you want to do about your drinking?  
What do you think would work for you, if you needed to change?

stages of change and motivational enhancement is in TIP 35, *Enhancing Motivation for Change in Substance Abuse Treatment* (CSAT, 1999b).

## Choosing a Medication

Scant research exists to guide clinicians in choosing the best medication for a particular patient. This lack of guidance results in part from the inconsistent findings of pharmacotherapy efficacy trials among subsets of patient populations. These inconsistent results may be related to the multiple factors associated with the effectiveness of these medications. Further research with larger patient samples is necessary before the proposed relationships can have a definitive influence in the individual decisionmaking process.

Each chapter in this TIP that discusses a particular medication for treating AUDs summarizes the evidence that is available regarding the type of patient most appropriate for the medication; a more detailed discussion of patient–medication

matching is found in the TIP's online literature review (<http://www.kap.samhsa.gov>). In addition to considering the characteristics that research has indicated *may* be relevant to choosing a medication, providers need to consider the patient's:

- Past experience with particular maintenance medications
- Opinion about which medication may be most helpful
- Level of motivation for abstinence
- Medical status and contraindications for each medication
- History of medication compliance.

Exhibit 6-4 provides a decision grid to help providers make decisions about pharmacotherapy. This grid is based on existing evidence regarding patient–medication matching, medication contraindications, and the clinical experiences of consensus panelists. Exhibit 6-5 provides a quick-reference guide for comparing maintenance medications.

## Combination Therapy

A number of studies have found that treatment outcomes improve when naltrexone is combined with acamprosate or disulfiram, particularly for patients who responded poorly to therapy with any of these medications alone (reviewed by Kiefer et al., 2003; Kiefer & Wiedemann, 2004). Besson and colleagues (1998) reported that co-administration of disulfiram improved the action of acamprosate. One study reports that combining acamprosate with naltrexone boosted plasma levels of acamprosate, which may have clinical benefits not achieved by monotherapy with either drug (Mason, 2005a). The Combining Medications and Behavioral Interventions (COMBINE) study (Anton et al., 2006) did not support the efficacy of combination therapy with acamprosate and naltrexone, although

this combination has been used in Europe and Australia with some reported success (Feeney, Connor, Young, Tucker, & McPherson, 2006; Kiefer et al., 2003; Kiefer & Wiedemann, 2004). More information is needed about the efficacy of this strategy, although it may be worth trying with patients who have not benefited from single-drug therapy.

One placebo-controlled but not randomized trial of acamprosate also prescribed disulfiram to patients who requested it (Besson et al., 1998). Patients who received the disulfiram–acamprosate combination had significantly more abstinent days than those who received acamprosate only. However, those who requested disulfiram may have been

more motivated. Because patients were not assigned randomly to the disulfiram–acamprosate regimen, it is unclear whether the combination of disulfiram and acamprosate or motivation was responsible for the results. Another study (Petrakis et al., 2005) found no advantage for the combination of naltrexone and disulfiram in a randomized, placebo-controlled study of patients with a co-occurring Axis I mental disorder and alcohol dependence, but it did find that active medication with either drug produced greater benefit than placebo in this population.

Although no absolute contraindications exist for using disulfiram with either naltrexone or acamprosate, no clear

**Exhibit 6-4**  
**AUD Medication Decision Grid**

Pretreatment Indicators	Acamprosate (Campral®)	Disulfiram (Antabuse®)	Oral Naltrexone (ReVia®, Depade®)	Injectable Naltrexone (Vivitrol®)
Renal failure	X	A	A	A
Significant liver disease	A	C	C	C
Coronary artery disease	A	C	A	A
Chronic pain	A	A	C	C
Current opioid use	A	A	X	X
Psychosis	A	C	A	A
Unwilling or unable to sustain total abstinence	A	X	A	A
Risk factors for poor medication adherence	C	C	C	A
Diabetes	A	C	A	A
Obesity that precludes IM injection	A	A	A	X
Family history of AUDs	A	A	+	+
Bleeding/other coagulation disorders	A	A	A	C
High level of craving	A	A	+	+
Opioid dependence in remission	A	A	+	+
History of postacute withdrawal syndrome	+	A	A	A
Cognitive impairment	A	X	A	A

A = Appropriate to use  
X = Contraindicated

C = Use with caution  
+ = Particularly appropriate

**Exhibit 6-5**  
**Comparison of Approved Medications**  
**for Maintenance of Abstinence From Alcohol\***

	<b>Acamprosate</b>	<b>Disulfiram</b>	<b>Oral Naltrexone</b>	<b>Extended-Release Injectable Naltrexone</b>
Mechanism of action	Not clearly understood; appears to restore to normal the altered balance of neuronal excitation and inhibition induced by chronic alcohol exposure, possibly through interaction with the glutamate neurotransmitter system	Inhibits aldehyde dehydrogenase, causing a reaction of flushing, sweating, nausea, and tachycardia when alcohol is ingested	Not clearly understood; opioid antagonist; blocks the effects of endogenous opioid peptides; appears to attenuate euphoria associated with alcohol use; may make alcohol use less rewarding; may reduce craving	Same as oral naltrexone
Examples of drug interactions	No clinically relevant interactions	Metronidazole; medications containing alcohol; anticoagulants such as warfarin; amytripyline; isoniazid; diazepam	Opioid medications; cough/cold medications; antidiarrheal medications; thioridazine; yohimbine	Presumed same as oral naltrexone; clinical drug interaction studies have not been performed
Common side effects	Diarrhea and somnolence	Transient mild drowsiness; metallic taste; dermatitis; headache; impotence	Nausea; vomiting; anxiety; headache; dizziness; fatigue; somnolence	Same as oral naltrexone, plus injection site reactions; joint pain; muscle aches or cramps
Contra-indications	Severe renal impairment (creatinine clearance $\leq 30$ mL/min)	Hypersensitivity to rubber derivatives; significant liver disease; alcohol still in system; coronary artery disease	Currently using opioids or in acute opioid withdrawal; anticipated need for opioid analgesics; acute hepatitis or liver failure	Same as oral naltrexone, plus inadequate muscle mass for deep intramuscular injection; body mass that precludes deep intramuscular injection; rash or infection at injection site
Cautions	Dosage may be modified for moderate renal impairment (creatinine clearance 30–50 mL/min); pregnancy category C <sup>†</sup>	Hepatic cirrhosis or insufficiency; cerebrovascular disease; psychoses; diabetes mellitus; epilepsy; renal impairment; pregnancy category C <sup>†</sup>	Renal impairment; chronic pain; pregnancy category C <sup>†</sup>	Same as oral naltrexone, plus hemophilia or other bleeding problems
Serious adverse reactions	Rare events include suicidal ideation; severe persistent diarrhea	Disulfiram–alcohol reaction; hepatotoxicity; peripheral neuropathy; psychotic reactions; optic neuritis	Precipitates opioid withdrawal if the patient is dependent on opioids; hepatotoxicity (although it does not appear to be a hepatotoxin at recommended doses)	Same as oral naltrexone plus inadvertent subcutaneous injection may cause a severe injection-site reaction; depression; rare events including allergic pneumonia and suicidal ideation and behavior

\*Based on information in the FDA-approved product labeling or published medical literature.

<sup>†</sup>FDA pregnancy category C: Animal studies have indicated potential fetal risk OR have not been conducted and no or insufficient human studies have been done. The drug should be used with pregnant or lactating women only when potential benefits justify potential risk to the fetus or infant.

current evidence indicates that one combination is more efficacious than any of the three agents alone. There is some concern about concurrent use of naltrexone with disulfiram because of the possibility of additive liver toxicity. In addition, disulfiram should not be used unless the patient's goal is complete abstinence, a goal not necessary when treating with naltrexone or acamprosate. Finally, the literature is not clear that combining disulfiram with either naltrexone or acamprosate improves patient outcomes. Therefore, at this time the consensus panel does not recommend using disulfiram in combination with either naltrexone or acamprosate.

## Choosing a Psychosocial Intervention

Any pharmacologic treatment for alcohol dependence should be used as an adjunct to, not a replacement for, psychosocial treatment. The literature suggests that the medication–psychosocial therapy combination is more effective than either alone. For example, Anton and colleagues (2005, 2006) reported the benefits of combining naltrexone and behavioral interventions for alcohol dependence, including longer time to relapse and increased time between relapse episodes.

Psychosocial treatments are likely to enhance compliance with pharmacotherapy; likewise, pharmacotherapies, to the extent that they reduce craving and help maintain abstinence, may make the patient more open to psychosocial interventions.

## Types of Psychosocial Therapies

As with pharmacotherapy, there is no psychosocial “magic bullet.” However, a number of modalities of psychosocial therapy have been studied and validated for treatment of alcohol use disorders

(reviewed by McCaul & Petry, 2003). Medical management (MM) is often practiced by primary care physicians in patients with diabetes and hypertension treatment. NIAAA developed an MM treatment as part of its COMBINE study (NIAAA, 2004). MM was designed specifically to accompany pharmacotherapy for AUDs and be delivered by medically trained clinicians in a medical setting. MM provides the structure and materials to enable clinicians to do the following:

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

An MM manual is available through NIAAA at <http://www.niaaa.nih.gov>.

Providers in psychiatric practice may provide psychosocial therapies on site. In the context of the primary care setting, however, delivering particular psychosocial therapies (e.g., group therapy) may be difficult because of time constraints, patient population, and lack of training. Brief interventions, motivational enhancement therapy, and MM treatment are more conducive to primary care settings (Anton et al., 2005, 2006). Sources of information about these interventions are listed in Exhibit 6-6. If these types of in-office interventions are not effective with a patient, or if the provider does not have the resources to offer them, providers may need to refer the patient for more intensive or specialized services.

## Exhibit 6-6 Resources for Office-Based Psychosocial Approaches

TIP 34, *Brief Interventions and Brief Therapies for Substance Abuse* (CSAT, 1999a)

KAP Keys for Clinicians Based on TIP 34 (CSAT, 2001a)

Quick Guide for Clinicians Based on TIP 34 (CSAT, 2001c)

TIP 35, *Enhancing Motivation for Change in Substance Abuse Treatment* (CSAT, 1999b)

KAP Keys for Clinicians Based on TIP 35 (CSAT, 2001b)

Quick Guide for Clinicians Based on TIP 35 (CSAT, 2001d)

*Helping Patients Who Drink Too Much: A Clinician's Guide* (NIAAA, 2006)

*NIAAA's A Pocket Guide for Alcohol Screening and Brief Intervention* (see Appendix B)

*Medical Management Treatment Manual: A Clinical Research Guide for Medically Trained Clinicians Providing Pharmacotherapy as Part of the Treatment for Alcohol Dependence* (NIAAA, 2004)

### Referring Patients for Specialty Treatment

Primary care practitioners may need to refer patients for psychosocial therapies, including to specialty substance abuse treatment programs. Many specialty substance abuse treatment programs provide comprehensive treatment services, either directly or through referrals, that address multiple factors affecting recovery. Such programs address not only immediate withdrawal and craving but management of long-term abstinence through the following:

- Pharmacotherapy
- Case monitoring
- Individual, group, and family/couples counseling and therapy
- Other psychosocial services (e.g., vocational counseling)

- Referral to mutual-help groups.

The underlying basis for a specialty program is that optimal outcomes are achieved through a range of complementary services and that, as abstinence lengthens, other issues related to alcohol use become clearer and more amenable to treatment.

A practitioner who is planning to treat patients with alcohol dependence should become familiar with a range of local treatment resources. Developing relationships with treatment staff will facilitate smooth referrals and followup. In addition, understanding something about a program's treatment duration, modality, philosophy, and continuing-care options helps the practitioner better match a patient to appropriate treatment; practitioners can prepare the patient for what to expect, enhancing compliance with the referral. Practitioners can find programs in their areas or throughout the United States by using the interactive Substance Abuse Treatment Facility Locator on the Substance Abuse and Mental Health Services Administration (SAMHSA) Web site at <http://dasis3.samhsa.gov>.

### Mutual- or Self-Help Programs

Mutual- or self-help group support can be critical to long-term recovery. The oldest, best-known, and most accessible mutual-help program is Alcoholics Anonymous (AA) (<http://www.aa.org>). Patients may resist attending AA meetings and may fear that disclosure of medication use may be unwelcome. Although some AA members may have negative attitudes toward medications, the organization itself supports appropriate medication use (AA, 1984). Providers should encourage patients to try different group meetings if they meet with negativity. Lists of local meetings can be obtained from <http://www.aa.org> and given to patients. Dual Recovery Anonymous (<http://www.draonline.org>)



is a 12-Step program for patients with co-occurring psychiatric disorders. Other mutual- or self-help groups include Self Management and Recovery Training (<http://www.smartrecovery.org>) and Women for Sobriety, Inc. (<http://www.womenforsobriety.org>). Although groups other than AA are not available in every community, they do offer a number of online resources. For patients' family members, there are Al-Anon and Alateen meetings (<http://www.al-anon.alateen.org>).

Providers should have a working knowledge of the most common groups so that they can suggest these groups to their patients and discuss patients' participation.

## Developing a Treatment Plan

### Setting Goals: Abstinence or Reduction?

Each patient–provider interaction should assess and clarify outcome goals for the patient. A patient initially may seek to reduce alcohol consumption. Another patient may be motivated for total abstinence. Investigations into prescribing of pharmacotherapy employ both alcohol use reduction outcomes and abstinence outcomes to assess the efficacy of medications to treat alcohol dependence. Clinical outcomes to assess progress include the length of time to first drink, time to heavy drinking, cumulative abstinence days, and drinks per drinking episode. Each provider and patient should set an initial goal and be willing to refine that goal as treatment progresses.

If a patient with an AUD is unwilling to be completely abstinent, he or she may be willing to cut down on alcohol use. Practitioners can work with this while noting that abstinence is the safer strat-

egy and has a greater chance of long-term success.

Certain conditions warrant advising a patient to abstain from rather than reduce drinking. As noted in the NIAAA (2006) clinician's guide, these conditions include when drinkers:

- Are or may become pregnant
- Are taking a contraindicated medication
- Have a medical or psychiatric disorder caused or exacerbated by drinking
- Have an AUD.

For those who drink heavily and who do not have an AUD, the practitioner should use professional judgment to determine whether cutting down or abstaining is more appropriate, based on factors such as (NIAAA, 2006):

- A family history of alcohol problems
- Advanced age
- Injuries related to drinking.

### Elements of a Treatment Plan

A comprehensive pharmacotherapy treatment plan for a patient with an AUD should include the following:

- The medication to be used and a rationale for its use
- Initial and maintenance dosages
- A schedule for followup office visits and laboratory testing for monitoring health status and progress
- Criteria for discontinuing the medication
- A referral and followup plan for concurrent specialty substance abuse treatment, psychiatric treatment, and/or family therapy

- A plan for mutual- or self-help group attendance
- Clarification of family or significant other involvement in treatment
- A plan for treating alcohol-related or other concurrent conditions.

Special attention must be paid to developing a medication compliance plan with the patient. This plan may include the following:

- Specific strategies for remembering to take medications
- Using blistercard packs or pill boxes
- Monitoring medication compliance on an appropriate schedule given the patient's history of compliance with maintenance and other medication regimens
- Involving the patient's family members in monitoring compliance.

## Patient Awareness

Patient awareness is critical to successful pharmacotherapy. When starting any new medication, the patient should understand how the medication works and what to expect while taking it. Particularly when prescribing maintenance medications, treatment providers need to offer that information and guidance to patients. Patients also need to understand that alcohol dependence is a chronic medical disorder. They need to know that they may experience protracted effects from their alcohol use, including postacute withdrawal symptoms (e.g., sleep difficulties). When patients do not feel good, it is a challenge to keep them in treatment. Providers should educate patients to manage their concerns and anxieties. Exhibit 6-7 contains elements of effective patient education, and Exhibit 6-8 is a brief list of information resources providers can give patients.

### Exhibit 6-7 Elements of Patient Education

Information about alcohol dependence as a chronic medical disorder

Description of what to expect in recovery, including symptoms of postacute withdrawal

List of the possible benefits of a particular medication

Information about the medication itself:

- How and when to take it and the importance of complying with the regimen
- When the medication will become fully effective
- Possible common side effects and their expected duration
- Under what conditions the patient should immediately call the provider
- Any cautions regarding daily activities
- Medication interactions

Explanation of the importance for women of childbearing age to use an effective birth control method

Information about what to do if the patient starts drinking after a period of abstinence

Description of the importance of concurrent psychosocial treatment and mutual- or self-help programs

Followup plans

Specific patient education unique to each medication is in the medication chapters.

## Monitoring Patient Progress

As it is with any chronic illness, monitoring of AUDs and pharmacologic treatment is important. Providers should monitor patients' ongoing treatment compliance, abstinence or reduced drinking,

## Exhibit 6-8 Information Resources for Patients

### **Al-Anon/Alateen**

<http://www.al-anon.alateen.org>

1 (888) 425-2666

General information about how to find local meetings

### **Alcoholics Anonymous**

<http://www.aa.org>

(212) 870-3400 (U.S. General Service Office)

General information, publications, and how to find local meetings

### **Dual Recovery Anonymous**

<http://www.draonline.org>

General information, publications, and how to find local meetings

### **National Council on Alcoholism and Drug Dependence**

<http://www.ncadd.org>

(212) 269-7797

Publications about AUDs and information about advocacy

### **NIAAA**

<http://www.niaaa.nih.gov>

Information about AUDs, information for families, and publications

### **SMART Recovery**

<http://www.smartrecovery.org>

1 (866) 951-5357

Information about recovery, online recovery tools, online meetings/chat groups/message boards, how to find face-to-face meetings, and publications

### **SAMHSA**

<http://www.samhsa.gov>

1 (800) 662-HELP (Substance Abuse Treatment Facility Locator)

1 (800) 273-TALK (8255); 1 (800) 799-4889 (TTY) (National Suicide Prevention Lifeline)

Information about substance abuse and self-tests

### **FDA**

<http://www.fda.gov>

1 (888) INFO-FDA

Patient information about medications to treat AUDs

### **Women for Sobriety, Inc.**

<http://www.womenforsobriety.org>

(215) 536-8026

Online recovery tools, online chat groups, how to find face-to-face meetings, and publications

levels of craving, health status, social functioning, and use of other substances so that necessary adjustments in treatment plans can be made.

## Monitoring Adherence

Several means exist for a provider to monitor patients' compliance with treatment plans, including the following:

- Tracking patients' record of keeping (or not keeping) appointments for medication monitoring
- Monitoring prescription refills
- Noting whether patients are keeping agreements about payment for treatment

- Requesting periodic status reports from specialty substance abuse treatment programs, psychiatric referrals, and other psychosocial therapy or support.

## Monitoring Abstinence or Reduction in Alcohol Consumption

The ways in which providers can monitor patients' drinking behavior include the following:

- *Patient self-reports* can be useful indicators of treatment success. The provider should discuss with the patient the quantity and frequency of drinking, especially during stressful periods (e.g., holidays, celebrations, major life changes).

- *Laboratory tests* may include AST, GGT, CDT, EtG, and urine drug screening.

In addition, providers can use periodic Breathalyzer™ tests (although these detect only for a short period following ingestion) to monitor alcohol intake and provide positive feedback to patients who are successful in maintaining abstinence.

## Monitoring Craving

Greatly diminished craving to drink alcohol is an optimum outcome of treatment. To assess craving, a physician can rely largely on the patient's subjective reports, although measures such as the Alcohol Urge Questionnaire (Bohn, Krahn, & Staehler, 1995) may prove useful.

More important than the method of monitoring is consistency in how the patient is asked about craving patterns and trends. Patients should be asked about current craving as well as how they felt over the past week (e.g., as a rating between 1 and 10, with 1 being no craving and 10 the most intense craving the patient has ever experienced). Patients may be asked whether any episodes have caused particular problems for them.

The patterns of craving over time can be useful. Both the provider and the patient can see that the patient's patterns of craving may fluctuate throughout the day and over longer periods; these patterns can assess the appropriateness to continue, adjust, supplement, enhance, or terminate pharmacologic treatment.

Providers should educate the patient about the role of craving in relapse. Learning from and responding optimistically to relapse may increase the patient's motivation to reduce or eliminate alcohol consumption.

## Monitoring Health Status and Social Functioning

Ultimately, the goal of treatment is improved quality of life. It is important to monitor patients' progress over time in the following areas:

- Health
  - Normalization of previously elevated blood pressure
  - Improvement of liver function
  - Stabilization of related medical problems that the patient was experiencing before treatment (e.g., control of blood glucose, stabilization of asthma, cardiomyopathy, encephalopathy, gastritis, ascites and edema)
  - Signs of increased concern about health care, such as seeing a physician for the first time in years and/or increased compliance with prescribed medication regimens not related to AUD treatment (e.g., asthma or blood pressure medications)
- Family/social activities
  - Spending more positive time with children and/or spouse
  - Greater involvement/participation with family members
  - Improved intimate relationships
  - Reduced family conflict
  - Engagement in nondrinking leisure and recreational activities
- Work/vocational status
  - Obtaining employment if previously unemployed
  - Improved attendance at work
  - Fewer job-related and financial problems
  - Improved job performance

- Legal status
  - No parole or probation violations (in a patient with legal problems)
  - No new driving-under-the-influence charges
- Mental status
  - Decreased irritability and anxiety
  - Improved mood
  - Improved sleep
  - Getting appropriate treatment for anxiety disorders, suicidal ideation, depression, or schizophrenia rather than self-medicating with alcohol.

## Monitoring Other Substances of Abuse

It is important to address other substances of abuse that pose the same level of concern and possible adverse consequences. The abuse of other substances can be evaluated by random urinalysis collection and testing and self-reports from the patient. Use of illicit substances, tobacco use, and abuse of prescription and nonprescription medications should be addressed. The patient's agreement or resistance to continuing treatment may indicate his or her willingness to consider other substance use a problem.

## Modifying the Treatment Strategy

An AUD is a chronic illness that, despite treatment, may wax and wane in intensity over time. Some patients may respond to psychosocial interventions, others to pharmacotherapy. Because a patient may respond to one medication and not to another, the provider should be flexible in modifying the medical regimen based on the patient's needs. Furthermore, a patient may choose to be treated for AUDs to reduce, eliminate, or discour-

age further escalation of consumption. A patient's goals may change over time, and providers should adapt to these new objectives.

As with patients who receive treatment for other chronic diseases, patients receiving treatment for AUDs may relapse. If this occurs, the provider should consider several options:

- Increase monitoring of medication adherence
- Increase the dose of the medication
- Change the medication
- Increase or change the intensity of psychosocial treatment to include referring the patient to specialty care
- Examine social, medical, or behavioral factors that contribute to alcohol consumption.

Even after patients and providers have examined the reasons for relapse and have intensified or modified psychosocial treatment or pharmacotherapy, some patients may continue to resist reducing alcohol consumption. A small proportion of patients with AUDs may simply be resistant to treatment. For example, chronic relapsing patients are generally defined as patients who persistently consume alcohol despite regular and intensive social and medical interventions. These patients frequently use emergency services (Thornquist, Biros, Olander, & Sterner, 2002). They may resist or cannot effectively use pharmacological and psychosocial interventions because of poor social or environmental situations or other personal factors. These patients, often labeled as "difficult," contribute to the perception of providers that treating AUDs is unlikely to be successful. Dealing with any chronic condition and changing harmful behavior are difficult. Understanding and accepting these difficulties can help providers keep patients moving forward, even if the pace

is slow. Because treatment of chronic relapsing patients *is* difficult, it should be undertaken by addiction professionals in specialty treatment settings that use a multifaceted approach incorporating social, environmental, medical, behavioral, and motivational interventions.

## Discontinuing Pharmacotherapy

Because an AUD is a chronic disorder, patients may need long-term use of medication or more than one episode of pharmacotherapy. In addition, some patients may benefit from using a medication over short periods to help them through a particularly stressful period or a situation that has typically elicited cravings for alcohol (e.g., a patient may want to take disulfiram or naltrexone while visiting family members who drink excessively).

Ideally, the patient and provider will decide together to discontinue pharmacotherapy. A patient may simply stop taking the medication. A patient also may express a desire to discontinue a medication because of side effects or for other reasons, or a patient will need to discontinue medication because of significant negative changes in laboratory findings or physical health status. Otherwise, the patient and provider may consider discontinuing medication under the following conditions:

- The patient reports substantially diminished craving.
- The patient has maintained stable abstinence over a sustained period.
- The patient feels ready to discontinue the medication.
- The patient is engaged in ongoing recovery, including community supports

(such as attendance at mutual-help group meetings).

None of the medications discussed in this TIP are associated with a withdrawal syndrome, and they do not need to be tapered.

## Final Clinical Thoughts

Management of the patient with an AUD may be seen as a series of stages:

- Assessing the patient's suitability for treatment with a medication
- Determining *which* medication should be used
- Providing and/or referring the patient for psychosocial services
- Assessing the patient's response to medication, including both efficacy (Is it working?) and side effects (Are there problems?).

This process is similar to becoming familiar with any new treatment regimen. AUDs may differ from other common chronic disorders mainly in that health-care providers may perceive that they have few patients with AUDs. However, the pervasiveness of alcohol use and the substantial rates of AUDs in the United States make it extremely unlikely that the clinician is *not* seeing patients with AUDs. The provider simply may not recognize patients with problem alcohol use.

The availability of effective medications that can decrease rates of problem alcohol use or help patients maintain abstinence is an extremely important step forward in the treatment of AUDs. Physicians should become familiar with these medications, with the features of this patient population, and with the services that, combined with medication, can improve treatment outcome. AUDs are treatable medical conditions, and treatment can improve the patient's health and quality of life.

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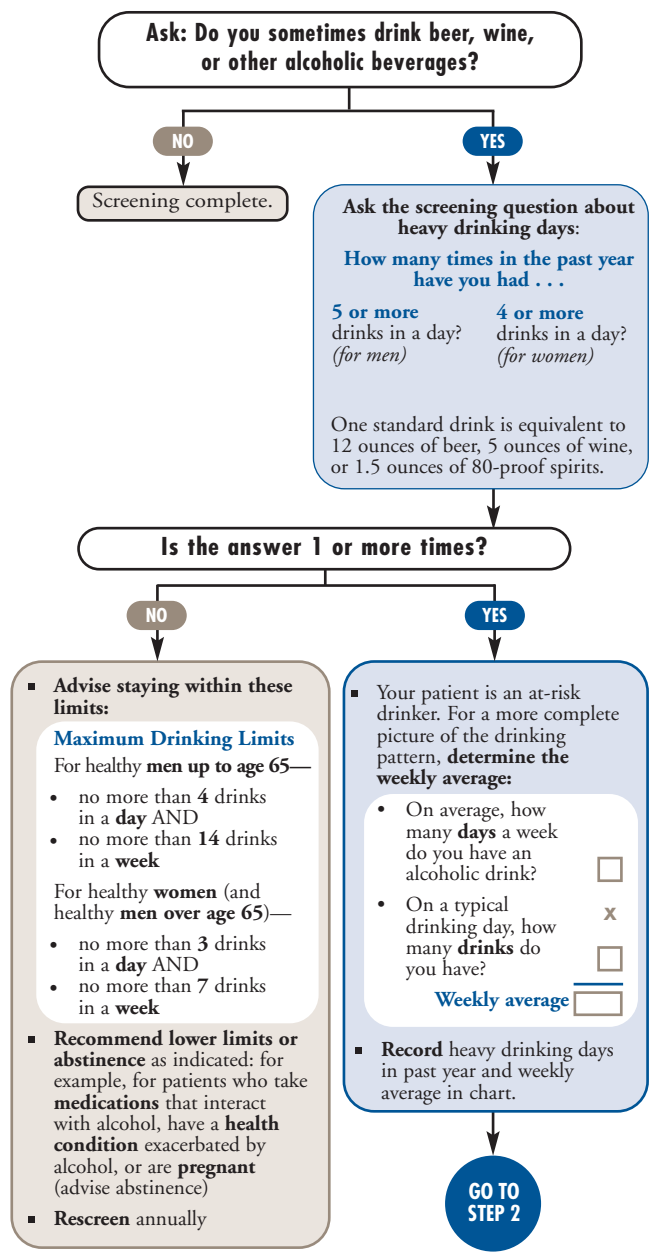
**Appendix B—  
NIAAA's *A Pocket Guide  
for Alcohol Screening  
and Brief Intervention***

Updated

# A POCKET GUIDE FOR Alcohol Screening and Brief Intervention

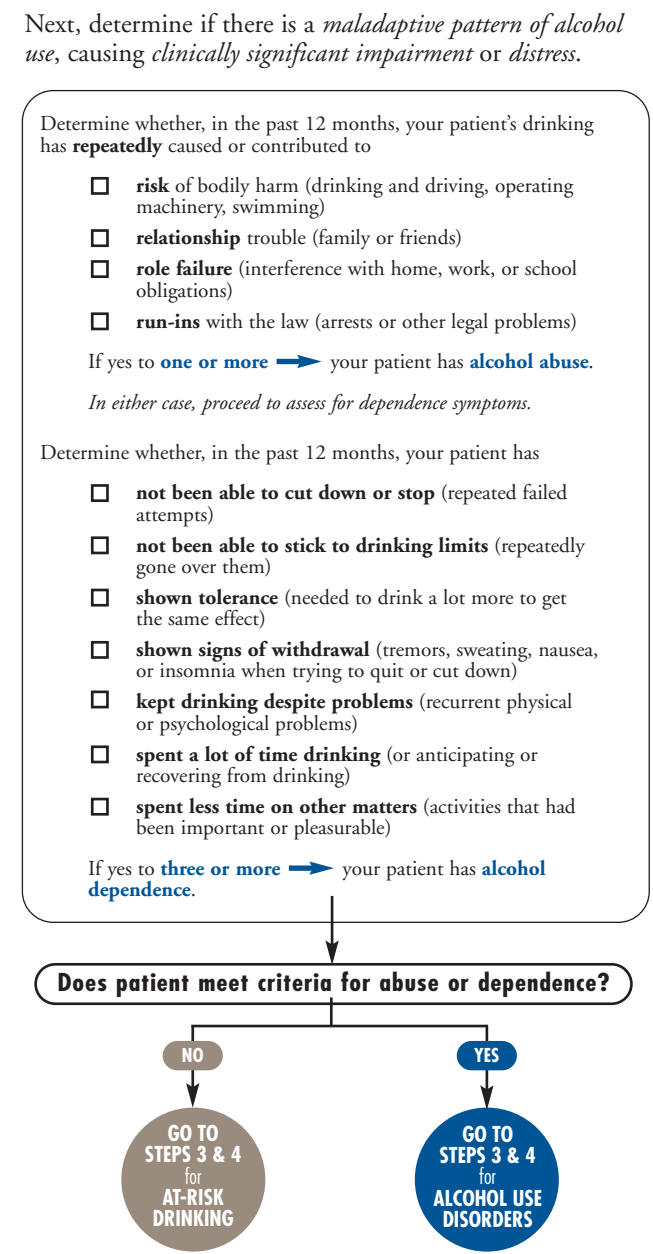
## HOW TO SCREEN FOR HEAVY DRINKING

### STEP 1 Ask About Alcohol Use



## HOW TO ASSESS FOR ALCOHOL USE DISORDERS

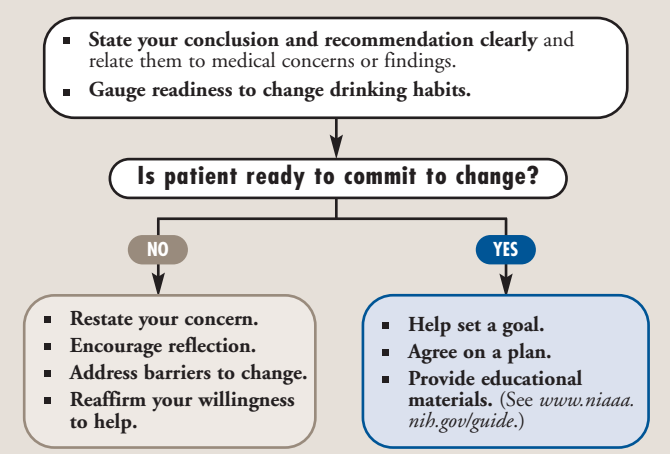
### STEP 2 Assess For Alcohol Use Disorders



## HOW TO CONDUCT A BRIEF INTERVENTION

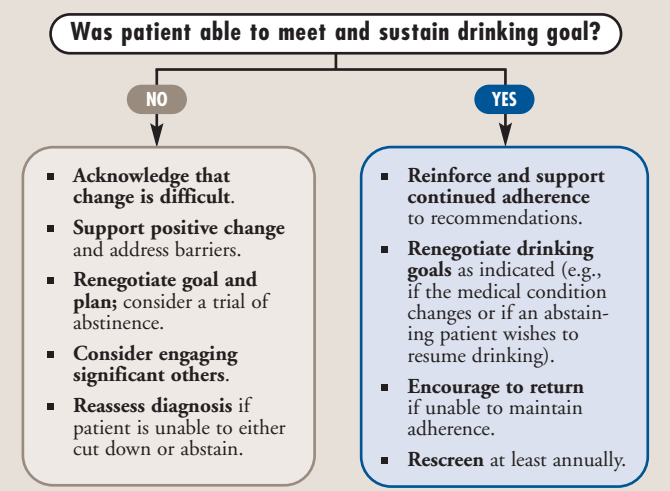
### FOR AT-RISK DRINKING (no abuse or dependence)

#### STEP 3 Advise and Assist



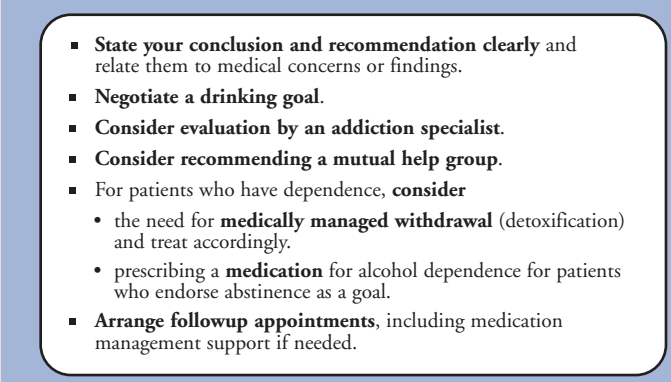
#### STEP 4 At Followup: Continue Support

REMINDER: Document alcohol use and review goals at each visit.



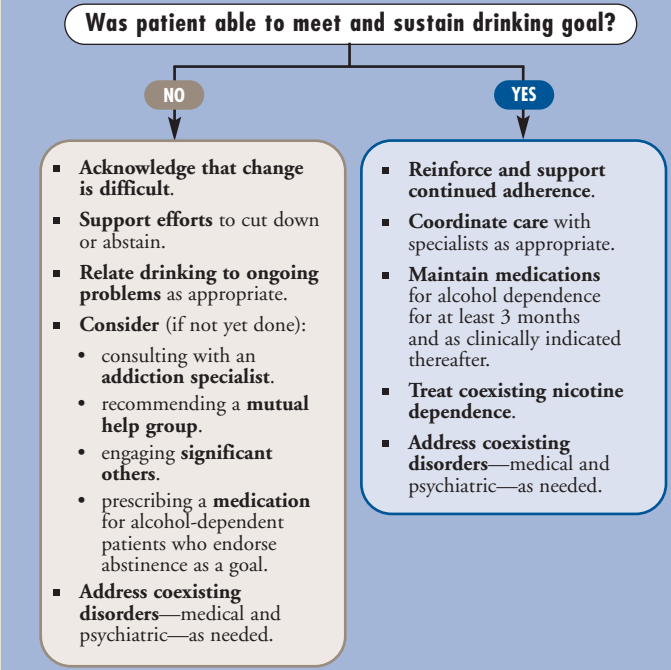
### FOR ALCOHOL USE DISORDERS (abuse or dependence)

#### STEP 3 Advise and Assist







#### STEP 4 At Followup: Continue Support

REMINDER: Document alcohol use and review goals at each visit.






# WHAT'S A STANDARD DRINK?

A standard drink in the United States is any drink that contains about 14 grams of pure alcohol (about 0.6 fluid ounces or 1.2 tablespoons). Below are U.S. standard drink equivalents as well as the number of standard drinks in different container sizes for each beverage. These are approximate, since different brands and types of beverages vary in their actual alcohol content.

STANDARD DRINK EQUIVALENTS	APPROXIMATE NUMBER OF STANDARD DRINKS IN:
<b>BEER or COOLER</b>	
 <p>12 oz. 5% alcohol</p>	<ul style="list-style-type: none"> <li>12 oz. = 1</li> <li>16 oz. = 1.3</li> <li>22 oz. = 2</li> <li>40 oz. = 3.3</li> </ul>
<b>MALT LIQUOR</b>	
 <p>8–9 oz. 7% alcohol</p>	<ul style="list-style-type: none"> <li>12 oz. = 1.5</li> <li>16 oz. = 2</li> <li>22 oz. = 2.5</li> <li>40 oz. = 4.5</li> </ul>
<b>TABLE WINE</b>	
 <p>5 oz. 12% alcohol</p>	<ul style="list-style-type: none"> <li>a 750-mL (25-oz.) bottle = 5</li> </ul>
<b>80-proof SPIRITS (hard liquor)</b>	
 <p>1.5 oz. 40% alcohol</p>	<ul style="list-style-type: none"> <li>a mixed drink = 1 or more*</li> <li>a pint (16 oz.) = 11</li> <li>a fifth (25 oz.) = 17</li> <li>1.75 L (59 oz.) = 39</li> </ul>

\*Note: Depending on factors such as the type of spirits and the recipe, one mixed drink can contain from one to three or more standard drinks.

# DRINKING PATTERNS

WHAT'S YOUR DRINKING PATTERN?	HOW COMMON IS THIS PATTERN?	HOW COMMON ARE ALCOHOL DISORDERS IN DRINKERS WITH THIS PATTERN?
<p><b>Based on the following limits—number of drinks:</b></p> <p>On any <b>DAY</b>—Never more than <b>4</b> (men) or <b>3</b> (women)</p> <p>– and –</p> <p>In a typical <b>WEEK</b>—No more than <b>14</b> (men) or <b>7</b> (women)</p>	<p>Percentage of U.S. adults aged 18 or older*</p>	<p>Combined prevalence of alcohol abuse and dependence</p>
<p><b>Never exceed the daily or weekly limits</b></p> <p>(2 out of 3 people in this group abstain or drink fewer than 12 drinks a year)</p>	 <p>72%</p>	<p>fewer than <b>1 in 100</b></p>
<p><b>Exceed only the daily limit</b></p> <p>(More than 8 out of 10 in this group exceed the daily limit <i>less than once a week</i>)</p>	 <p>16%</p>	<p><b>1 in 5</b></p>
<p><b>Exceed both daily and weekly limits</b></p> <p>(8 out of 10 in this group exceed the daily limit <i>once a week or more</i>)</p>	 <p>10%</p>	<p>almost <b>1 in 2</b></p>

\*Not included in the chart, for simplicity, are the 2 percent of U.S. adults who exceed *only* the weekly limits. The combined prevalence of alcohol use disorders in this group is 8 percent.

**Source:** 2001–2002 National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), a nationwide NIAAA survey of 43,093 U.S. adults aged 18 or older.

# PRESCRIBING MEDICATIONS

The chart below contains excerpts from page 16 of NIAAA's *Helping Patients Who Drink Too Much: A Clinician's Guide*. It does *not* provide complete information and is not meant to be a substitute for the patient package inserts or other drug references used by clinicians. For patient information, visit <http://medlineplus.gov>.

	Naltrexone (Depade <sup>®</sup> , ReVia <sup>®</sup> )	Extended-Release Injectable Naltrexone (Vivitrol <sup>®</sup> )	Acamprosate (Campral <sup>®</sup> )	Disulfiram (Antabuse <sup>®</sup> )
<b>Action</b>	Blocks opioid receptors, resulting in reduced craving and reduced reward in response to drinking.	Same as oral naltrexone; 30-day duration.	Affects glutamate and GABA neurotransmitter systems, but its alcohol-related action is unclear.	Inhibits intermediate metabolism of alcohol, causing a buildup of acetaldehyde and a reaction of flushing, sweating, nausea, and tachycardia if a patient drinks alcohol.
<b>Contraindications</b>	Currently using opioids or in acute opioid withdrawal; anticipated need for opioid analgesics; acute hepatitis or liver failure.	Same as oral naltrexone, plus inadequate muscle mass for deep intramuscular injection; rash or infection at the injection site.	Severe renal impairment (CrCl ≤ 30 mL/min).	Concomitant use of alcohol or alcohol-containing preparations or metronidazole; coronary artery disease; severe myocardial disease; hypersensitivity to rubber (thiuram) derivatives.
<b>Precautions</b>	Other hepatic disease; renal impairment; history of suicide attempts or depression. If opioid analgesia is needed, larger doses may be required, and respiratory depression may be deeper and more prolonged. Pregnancy Category C. Advise patients to carry a wallet card to alert medical personnel in the event of an emergency. For wallet card information, see <a href="http://www.niaaa.nih.gov/guide">www.niaaa.nih.gov/guide</a> .	Same as oral naltrexone, plus hemophilia or other bleeding problems.	Moderate renal impairment (dose adjustment for CrCl between 30 and 50 mL/min); depression or suicidal ideation and behavior. Pregnancy Category C.	Hepatic cirrhosis or insufficiency; cerebrovascular disease or cerebral damage; psychoses (current or history); diabetes mellitus; epilepsy; hypothyroidism; renal impairment. Pregnancy Category C. Advise patients to carry a wallet card to alert medical personnel in the event of an emergency. For wallet card information, see <a href="http://www.niaaa.nih.gov/guide">www.niaaa.nih.gov/guide</a> .
<b>Serious adverse reactions</b>	Will precipitate severe withdrawal if the patient is dependent on opioids; hepatotoxicity (although does not appear to be a hepatotoxin at the recommended doses).	Same as oral naltrexone, plus infection at the injection site; depression; and rare events including allergic pneumonia and suicidal ideation and behavior.	Rare events include suicidal ideation and behavior.	Disulfiram-alcohol reaction, hepatotoxicity, optic neuritis, peripheral neuropathy, psychotic reactions.
<b>Common side effects</b>	Nausea; vomiting; decreased appetite; headache; dizziness; fatigue; somnolence; anxiety.	Same as oral naltrexone, plus a reaction at the injection site; joint pain; muscle aches or cramps.	Diarrhea; somnolence.	Metallic after-taste; dermatitis; transient mild drowsiness.
<b>Examples of drug interactions</b>	Opioid medications (blocks action).	Same as oral naltrexone.	No clinically relevant interactions known.	Anticoagulants such as warfarin; isoniazid; metronidazole; phenytoin; any nonprescription drug containing alcohol.
<b>Usual adult dosage</b>	<p><i>Oral dose:</i> 50 mg daily.</p> <p><i>Before prescribing:</i> Patients must be opioid-free for a minimum of 7 to 10 days before starting. If you feel that there's a risk of precipitating an opioid withdrawal reaction, a naloxone challenge test should be employed. Evaluate liver function.</p> <p><i>Laboratory followup:</i> Monitor liver function.</p>	<p><i>IM dose:</i> 380 mg given as a deep intramuscular gluteal injection, once monthly.</p> <p><i>Before prescribing:</i> Same as oral naltrexone, plus examine the injection site for adequate muscle mass and skin condition.</p> <p><i>Laboratory followup:</i> Monitor liver function.</p>	<p><i>Oral dose:</i> 666 mg (two 333-mg tablets) three times daily; or for patients with moderate renal impairment (CrCl 30 to 50 mL/min), reduce to 333 mg (one tablet) three times daily.</p> <p><i>Before prescribing:</i> Evaluate renal function. Establish abstinence.</p>	<p><i>Oral dose:</i> 250 mg daily (range 125 mg to 500 mg).</p> <p><i>Before prescribing:</i> Evaluate liver function. Warn the patient (1) not to take disulfiram for at least 12 hours after drinking and that a disulfiram-alcohol reaction can occur up to 2 weeks after the last dose and (2) to avoid alcohol in the diet (e.g., sauces and vinegars), over-the-counter medications (e.g., cough syrups), and toiletries (e.g., cologne, mouthwash).</p> <p><i>Laboratory followup:</i> Monitor liver function.</p>

**Note:** Whether or not a medication should be prescribed and in what amount is a matter between individuals and their health care providers. The prescribing information provided here is not a substitute for a provider's judgment in an individual circumstance and the NIH accepts no liability or responsibility for use of the information with regard to particular patients.

# Appendix C— Excerpts From Quick Guide for Clinicians Based on TIP 45\*

## Introduction

The “medical model” of detoxification is characterized by the use of physicians and nursing staff and the administration of medication to assist people through withdrawal safely. The “social model” relies more on a supportive non-hospital environment than on medication to ease the passage through withdrawal.

## Definitions

*Detoxification* is a series of interventions aimed at managing acute intoxication and withdrawal. It denotes a clearing of toxins from the body of the patient who is acutely intoxicated and/or dependent on substances of abuse. Detoxification seeks to minimize the physical harm caused by the abuse of substances.

*Evaluation* entails testing for the presence of substances of abuse in the bloodstream, measuring their concentration, and screening for co-occurring mental and physical conditions. Evaluation also includes a comprehensive assessment of the patient’s medical, psychological, and social situation.

*Stabilization* includes the medical and psychosocial process of assisting the patient through acute intoxication and withdrawal to the attainment of a medically stable, fully supported, substance-free state.

*Fostering the patient’s entry into treatment* involves preparing a patient for entry into treatment by stressing the importance of following through with a complete continuum of care.

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\*TIP 45, *Detoxification and Substance Abuse Treatment*.

## Guiding Principles/Assumptions

The panel of experts who created TIP 45 agreed to the following assumptions, which served as a basis for their work:

1. Detoxification alone is not sufficient treatment for substance dependence but is one part of a continuum of care for substance-related disorders.
2. The detoxification process consists of the following three components:
  - Evaluation
  - Stabilization
  - Fostering patient readiness for and entry into treatment

A detoxification process that does not incorporate all three critical components is considered incomplete and inadequate by the consensus panel.

3. Detoxification can take place in a wide variety of settings and at a number of levels of intensity. Placement should be appropriate to a patient's needs.
4. Persons seeking detoxification should have access to the components of the detoxification process described above, no matter what the setting or the level of treatment intensity.
5. All persons requiring treatment for substance use disorders should receive treatment of the same quality and appropriate thoroughness and should be put into contact with a treatment program for substance use disorders after detoxification.
6. Ultimately, insurance coverage for the full range of detoxification services and followup treatment services is cost-effective. If reimbursement systems do not provide payment for the complete detoxification process, patients may be released prematurely, leading to medically or socially unattended withdrawal.

7. Patients seeking detoxification services have diverse cultural and ethnic backgrounds as well as unique health needs and life situations. Organizations that provide detoxification services need to ensure that they have standard practices in place to address cultural diversity.
8. A successful detoxification process can be measured, in part, by whether an individual who is substance dependent enters, remains in, and is compliant with the treatment protocol of a substance abuse treatment/rehabilitation program after detoxification.

## Overarching Principles for Care During Detoxification Services

- Detoxification services do not offer a “cure” for substance use disorders; they are often a first step toward recovery and a “first door” through which patients pass to treatment.
- Substance use disorders are treatable and there is hope for recovery.
- Substance use disorders are brain disorders and not evidence of moral weakness.
- Patients should be treated with respect and dignity at all times.
- Patients should be treated in a nonjudgmental and supportive manner.
- Services planning should be completed in partnership with the patient and his or her social support network, including family, significant others, or employers.
- All health professionals involved in the care of the patient will maximize opportunities to promote rehabilitation and maintenance activities and to link the patient to appropriate substance abuse treatment immediately after the detoxification phase.



- Active involvement of the family and other support systems, while respecting the patient’s right to privacy and confidentiality, is to be encouraged.
- Patients are treated with due consideration for individual background, culture, preferences, sexual orientation, disability, vulnerabilities, and strengths.

## Levels of Care and Patient Placement

In addition to the general placement criteria for the treatment of substance-related disorders, the *Patient Placement Criteria, Second Edition, Revised* (PPC-2R) of the American Society of Addiction Medicine (ASAM) also indicates a second set of placement criteria, which are more important for the purposes of TIP 45 and this Quick Guide—the five “Adult Detoxification” placement levels of care within Dimension 1 (ASAM, 2001). These “Adult Detoxification” levels of care are:

1. *Level I-D: Ambulatory Detoxification Without Extended Onsite Monitoring* (e.g., physician’s office, home health care agency). This level of care is an organized outpatient service monitored at predetermined intervals.
2. *Level II-D: Ambulatory Detoxification With Extended Onsite Monitoring* (e.g., day hospital service). This level of care is monitored by appropriately credentialed and licensed nurses.
3. *Level III.2-D: Clinically Managed Residential Detoxification* (e.g., non-21medical or social detoxification setting). This level emphasizes peer and social support and is intended for patients whose intoxication and/or withdrawal is sufficient to warrant 24-hour support.
4. *Level III.7-D: Medically Monitored Inpatient Detoxification* (e.g., free-standing detoxification center). Unlike Level III.2-D, this level provides 24-hour medically supervised detoxification services.
5. *Level IV-D: Medically Managed Intensive Inpatient Detoxification* (e.g., psychiatric hospital inpatient center). This level provides 24-hour care in an acute care inpatient setting.

It is important to note that ASAM PPC-2R criteria are only guidelines and that there are no uniform protocols for determining which patients are placed in which level of care. For further information on patient placement, readers are advised to consult TIP 13, *The Role and Current Status of Patient Placement Criteria in the Treatment of Substance Use Disorders* (CSAT 1995).

## Biomedical and Psychosocial Issues

Detoxification presents an opportunity to intervene during a period of crisis and to encourage a client to make changes in the direction of health and recovery. Hence, a primary goal of the detoxification staff should be to build a therapeutic alliance and motivate patients to enter treatment. This process should begin as the patient is being medically stabilized.

## Symptoms and Signs of Conditions That Require Immediate Medical Attention

- Change in mental status
- Increasing anxiety
- Hallucinations
- Temperature greater than 100.4°F (these patients should be considered potentially infectious)

- Significant increases and/or decreases in blood pressure and heart rate
- Insomnia
- Abdominal pain
- Upper and lower gastrointestinal bleeding
- Changes in responsiveness of pupils
- Heightened deep tendon reflexes and ankle clonus, a reflex beating of the foot when pressed rostrally, indicating profound central nervous system irritability and the potential for seizures

## Immediate Mental Health Needs

The following are mental health issues that require immediate attention:

### **Suicidality**

- Patients receiving detoxification services should be evaluated for suicide risk.
- During acute intoxication and withdrawal, it is important to provide an environment that minimizes opportunities for suicide attempts.
- Frequent safety checks should be implemented.
- Patients at risk for suicide should be placed in areas monitored by staff.

### **Anger and aggression**

- All patients who are intoxicated should be considered potentially violent.
- Symptoms associated with increased risk for violence include hallucinations, paranoia, anxiety, and depression.
- Physical restraint should be used as a last resort.

## Initial Biomedical and Psychosocial Evaluation Domains

An initial evaluation will help detoxification staff foresee any variables that might complicate withdrawal. The following is a list of biomedical and psychosocial domains that can affect the stabilization of the patient.

### **Biomedical domains**

- *General health history:* What is the patient's medical and surgical history? Are there any psychiatric or medical conditions? Any known medication allergies? A history of seizures?
- *Mental status:* Is the patient oriented, alert, cooperative? Are thoughts coherent? Are there signs of psychosis or destructive thoughts?
- *General physical assessment with neurological exam:* This will ascertain the patient's general health and identify medical or psychiatric disorders of immediate concern.
- *Temperature, pulse, blood pressure (should be monitored throughout detoxification).*
- *Patterns of substance abuse:* When did the patient last use? What were the substances of abuse? How much of these substances was used and how frequently?
- *Urine and toxicology screen for commonly abused substances.*
- *Past substance abuse treatments or detoxification.*

### **Psychosocial domains**

- *Demographic features:* Gather information on gender, age, ethnicity, culture, language, and education level.
- *Living conditions:* Is the patient homeless or living in a shelter? Are

significant others in the home (and, if so, can they safely supervise)?

- *Violence, suicide risk:* Is the patient aggressive, depressed, or hopeless? Is there a history of violence?
- *Transportation:* Does the patient have adequate means to get to appointments? Do other arrangements need to be made?
- *Financial situation:* Is the patient able to purchase medication and food? Does the patient have adequate employment and income?
- *Dependent children:* Is the patient able to care for children, provide adequate child care, and ensure the safety of children?
- *Legal status:* Is the patient a legal resident? Are there pending legal matters? Is treatment court ordered?
- *Physical, sensory, or cognitive disabilities:* Does the client have disabilities that require consideration?

## Considerations for Specific Populations

### Adolescents

- Adolescents are more likely to drink large quantities of alcohol in a short period of time, making it important that staff be alert to escalating blood alcohol levels.
- Adolescents are more likely to use drugs they cannot identify, to combine multiple substances with alcohol, to ingest unidentified substances, and to be unwilling to disclose drug use.
- Asking open-ended questions and using street terminology for drugs can be helpful in both establishing rapport and obtaining an accurate substance use history.

### Parents with dependent children

- It is of vital importance to ensure that the children of someone receiving detoxification services have a safe place to stay.
- Working with patients to identify supportive family or friends may uncover temporary childcare resources.
- A consult or referral to the treatment facility's social services while the patient is being detoxified is indicated when the care of children is uncertain.

## Alcohol Intoxication and Withdrawal

The following symptoms of alcohol intoxication can vary greatly with the patient's level of tolerance.

*Blood alcohol level is 20–100 mg percent*

- Mood and behavioral changes
- Reduced coordination
- Impairment of ability to drive a car or operate machinery

*Blood alcohol level is 101–200 mg percent*

- Reduced coordination of most activities
- Speech impairment
- Trouble walking
- General impairment of thinking and judgment

- Somnolence, combative or “psychotic” behavior

- “Normal” mental status

*Blood alcohol level is 201–300 mg percent*

- Marked impairment of thinking, memory, and coordination
- Marked reduction in level of alertness

- Memory blackouts
- Nausea and vomiting/aspiration

*Blood alcohol level is 301–400 mg percent*

- Worsening of above symptoms with reduction of body temperature and blood pressure
- Excessive sleepiness/comatose
- Amnesia
- Nausea and vomiting/aspiration
- Death

*Blood alcohol level is 401–800 mg percent*

- Difficulty waking the patient (coma)
- Serious decreases in pulse, temperature, blood pressure, and rate of breathing
- Urinary and bowel incontinence
- Death

The signs and symptoms of acute alcohol withdrawal generally start 6 to 24 hours after the patient takes his last drink. Acute withdrawal may begin when the patient still has significant blood alcohol concentrations. The signs and symptoms may include the following and are highly variable:

- Restlessness, irritability, anxiety, agitation
- Anorexia, nausea, vomiting
- Tremor, elevated heart rate, increased blood pressure
- Insomnia, intense dreaming, nightmares
- Poor concentration, impaired memory and judgment
- Increased sensitivity to sound, light, and tactile sensations
- Hallucinations (auditory, visual, or tactile)

- Delusions, usually of paranoid or persecutory varieties
- Grand mal seizures
- Hyperthermia
- Delirium/disorientation with regard to time, place, person, and situation; fluctuation in level of consciousness

## Management of Alcohol Withdrawal Without Medication

- Indications for the management of alcohol withdrawal without medication have not been established through scientific studies or evidence-based methods.
- The course of alcohol withdrawal is unpredictable; it is impossible to tell who will or will not experience life-threatening complications.
- Positive aspects of the nonmedication approach are that it is highly cost-effective and provides inexpensive access to detoxification for individuals seeking aid.

## Social Detoxification

Social detoxification programs are short-term, nonmedical treatment service for individuals with substance use disorders. A social detoxification program offers room, board, and interpersonal support to intoxicated individuals and individuals in substance use withdrawal. Social detoxification programs vary widely in services offered, but there should always be medical surveillance, including monitoring of vital signs.

TIP 45 provides several guidelines for social detoxification programs:

- Such programs should follow local governmental regulations regarding licensing and inspection.
- It is highly desirable that individuals entering social detoxification be assessed

by primary care practitioners with some substance abuse treatment experience.

- An assessment should determine whether the patient is currently intoxicated and the degree of intoxication, the type of withdrawal syndrome, severity of the withdrawal, information regarding past withdrawals, and the presence of co-occurring psychiatric, medical, and surgical conditions that might require specialized care.
- Particular attention should be paid to individuals who have undergone multiple withdrawals in the past and for whom each withdrawal appears to be worse than previous ones (the so-called kindling effect). Patients with a history of severe withdrawals are not good candidates for social detoxification.
- All social detoxification programs should have personnel who are familiar with the features of substance use withdrawal, have training in basic life support, and have access to an emergency medical system that can provide transportation to emergency departments.

## Management of Alcohol Withdrawal With Medications

It is believed that only a minority of patients with alcoholism will go into significant alcohol withdrawal requiring medication. Identifying that small minority is sometimes problematic, but there are signs and symptoms of impending problems that can alert the caretaker to seek medical attention.

Deciding whether or not to use medical management for alcohol withdrawal requires that patients be separated into three groups:

1. Clients who have a history of the most extreme forms of withdrawal, that of seizures and/or delirium. The medica-

tion treatment of this group should proceed as quickly as possible.

2. Patients who are already in withdrawal and demonstrating moderate symptoms of withdrawal also require immediate medication.
3. The third group includes patients who may still be intoxicated, or who have, at the time of admission, been abstinent for only a few hours and have not developed signs or symptoms of withdrawal. A decision regarding medication treatment for this group should be based on advancing age, number of years with alcohol dependence, and the number of previously treated or untreated severe withdrawals. If there is an opportunity to observe the patient over the next 6 to 8 hours, then it is possible to delay a decision regarding treatment and periodically reevaluate a client of this category.

## Benzodiazepine Treatment for Alcohol Withdrawal

These drugs remain the medication of choice in treating withdrawal from alcohol. The early recognition of alcohol withdrawal and prompt administration of a suitable benzodiazepine will prevent further withdrawal reaction from proceeding to serious consequences.

- *Loading dose of a benzodiazepine.* Administration of a metabolized benzodiazepine may be carried out every 1 to 2 hours until significant clinical improvement occurs or the patient becomes sedated. In general, patients with severe withdrawal may receive 20 mg of diazepam or 100 mg of chlorthalidone every 2 to 3 hours until improvement or sedation prevails. The treatment staff should closely monitor blood pressure, pulse, and respiratory features.

- *Symptom-triggered therapy.* Using the CIWA-Ar or similar alcohol withdrawal rating scales, medical personnel can be trained to recognize symptoms of alcohol withdrawal, make a rating, and based on the rating administer benzodiazepines to their patient only when signs and symptoms reach a particular threshold. A typical routine of administration is as follows: Administer 50 mg of chlordiazepoxide for CIWA-Ar >9 and reassess in 1 hour. Continue administering 50 mg chlordiazepoxide every hour until CIWA-Ar is <10.
- *Gradual, tapering doses.* Once the patient has been stabilized, oral benzodiazepines can be administered on a predetermined dosing schedule for several days and gradually tapered over time. One example of this regimen is that patients might receive 50 mg of chlordiazepoxide or 10 mg of diazepam every 6 hours during the first day of treatment and 25 mg of chlordiazepoxide or 5 mg of diazepam every 6 hours on the second and third days.
- *Single daily dosing protocol.* According to studies, this regimen may be attractive in community or social detoxification settings, particularly if patients could be monitored between doses.

## Limitations of Benzodiazepines in Outpatient Treatment

The interaction of benzodiazepines with alcohol can lead to coma and respiratory suppression, motor incoordination, and abuse. Abuse is usually in the context of the concurrent use of alcohol, opioids, or stimulants. There are two other limitations as well:

- Although benzodiazepines have been studied for 30 years and are effective for suppressing alcohol withdrawal symptoms, their ability to halt the

progressive worsening of each successive alcohol withdrawal is in question.

- Benzodiazepine use to treat outpatients in alcohol withdrawal may “prime” or reinstate alcohol use during their administration.

## Other Medications

The following is a list of other medications sometimes used in detoxification from alcohol:

- Barbiturates
- Anticonvulsants
- Beta blockers/alpha adrenergic agonists
- Antipsychotics
- Relapse prevention agents

## Management of Delirium and Seizures

The major goal of medical detoxification is to avoid seizures and a special state of delirium called delirium tremens (DTs) with aggressive use of the primary detoxification drug. Death and disability may result from DTs or seizures without medical care.

For patients with a history of DTs or seizures, early benzodiazepine treatment is indicated at the first clinical setting. Patients with severe withdrawal symptoms, multiple past detoxifications (more than three), and co-occurring unstable medical and psychiatric conditions should be managed similarly.

### DTs

- Giving the patient a benzodiazepine should not be delayed by waiting for the return of laboratory studies, transportation problems, or the availability of a hospital bed.

- Once full DTs have developed, they tend to run their course despite medication management.
- Patients presenting in severe DTs should have emergency medical transport to a qualified emergency department and generally will require hospitalization.
- Benzodiazepine and/or barbiturate intoxication needs to be treated and assessed differently, given the potentially life-threatening implications of withdrawal from either substance in combination with each other and/or alcohol.

### **Seizures**

- Seizures usually occur within the first 48 hours after cessation or reduction of alcohol, with peak incidence around 24 hours.
  - Someone experiencing a seizure is at greater risk for progressing to DTs, whereas it is extremely unlikely that a patient already in DTs will also then experience a seizure.
  - The occurrence of an alcohol withdrawal seizure happens quickly, usually without warning to the individual experiencing the seizure or anyone around him.
  - Predicting who will have a seizure during alcohol withdrawal cannot be accomplished with any great certainty.
  - Patients having a seizure can be treated with intravenous (IV) diazepam or lorazepam and advanced cardiac life support protocol procedures.
  - Patients who have had a single witnessed or suspected alcohol withdrawal seizure should be immediately given a benzodiazepine, preferably with IV administration.
- ### **Wernicke-Korsakoff's Syndrome**
- Wernicke-Korsakoff's Syndrome is composed of Wernicke's encephalopathy and Korsakoff's psychosis.
  - Wernicke's encephalopathy is an acute neurological disorder featuring oculomotor dysfunction (bilateral abducens nerve palsy-eye muscle paralysis), ataxia (loss of muscle coordination), confusion, and weakness.
  - Korsakoff's psychosis is a chronic neurological condition that includes retrograde and anterograde amnesia (profound deficit in new learning and remote memory) with confabulation (patients make up stories to cover memory gaps).
  - Both syndromes are related to thiamine deficiency.
  - Thiamine initially is given parenterally (in a manner other than through the digestive tract, as by intravenous or intramuscular injection). Afterward, oral administration is the treatment of choice.
  - *Always* give thiamine prior to glucose administration.

# Appendix D— Excerpts From Quick Guide for Clinicians Based on TIP 24\*

## Introduction

Alcohol-related disorders occur in up to 26 percent of general medicine clinic patients, a prevalence rate similar to those for such other chronic diseases as hypertension and diabetes.

Since substance abuse disorders are often chronic conditions that progress slowly, primary care clinicians are in an ideal position to screen for alcohol and drug problems. Studies have shown that primary care clinicians can help patients decrease alcohol consumption through office-based interventions that take only 10 or 15 minutes.

## General Recommendations for Primary Care Clinicians

### Screening

1. Periodically and routinely screen all patients for substance use disorders
2. Ask questions about substance abuse in the context of other lifestyle questions
3. Use the Alcohol Use Disorder Identification Test (AUDIT) to screen for alcohol problems among English-speaking, literate patients, or use the first three quantity/frequency questions from AUDIT, supplemented by the CAGE questionnaire

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\*TIP 24, *A Guide to Substance Abuse Services for Primary Care Clinicians*.



4. Use the CAGE-AID (CAGE Adapted to Include Drugs) to screen for drugs use among patients
5. Ask “Have you used street drugs more than five times in your life?” A positive answer suggests further screening and possibly assessment are needed
6. Ask high-risk patients about alcohol and drug use in combination
7. Ask pregnant women “Do you use street drugs?” If the answer is yes, advise abstinence
8. Use the CAGE, the AUDIT, or the Michigan Alcoholism Screening Test–Geriatric Version (MAST-G) to screen patients over 60
9. Screen adolescents for substance abuse every time they seek medical services

### **Brief Intervention**

1. Perform a brief intervention with patients whose substance abuse problems are less severe
2. Include in the brief intervention feedback about screening results and risk of use, information about safe consumption limits and advice about change, assessment of patient’s readiness to change, negotiated goals and strategies for change, and arrangements for followup visits

### **Assessment and Treatment**

Refer high-risk patients to a specialist, if possible, for in-depth assessment

## **Warning Signs and Risk Factors for Alcohol and Illicit Drug Use**

It is important for primary care clinicians to know patients’ drinking levels to gauge their potential risk for developing problems.

### **Physical Signs: General**

- Dental caries
- Swollen hands or feet
- Swollen parotid glands
- Leukoplakia in mouth
- Gingivitis
- Perforated septum
- Needle track marks
- Skin abscesses, burns on inside of lips
- Disrupted menstrual cycle

### **Physical Signs: Neurological**

- Dilated or constricted pupils
- Slurred, incoherent, or too rapid speech
- Inability to focus (both visually and mentally)
- Unsteady gait
- “Nodding off”
- Blackouts or other periods of memory loss
- Insomnia or other sleep disturbances
- Withdrawal symptoms
- Agitation

## Psychiatric

- Depression
- Anxiety
- Low self-esteem
- Low tolerance for stress
- Other mental health disorders
- Feelings of desperation
- Feelings of loss of control over one's life
- Feelings of resentment

## Behavioral

- Use of other substances
- Aggressive behavior in childhood
- Conduct disorders; antisocial personality
- Impulsiveness and risk taking
- Alienation and rebelliousness
- School-based academic or behavioral problems
- Involvement with criminal justice system
- Poor interpersonal relationships

## Social and Sexual History

- Legal status (minor, in custody)
- Alcohol or drug use by friends
- Level of education
- Occupation/work history
- Sexual preference
- Number of sexual relationships
- Types of sexual activity engaged in
- Whether the patient practices safe sex

## Family

- Use of drugs and alcohol by parents, siblings
- Inherited predisposition to alcohol or drug dependence
- Family dysfunction
- Family trauma
- Marital/cohabitation status
- Domestic violence and other abuse history

## Demographic

- Male gender
- Inner city or rural residence combined with low-socioeconomic status
- Lack of employment opportunities

## Low-Risk and At-Risk

Low-risk drinkers consume less than an average of one to two drinks per day, do not drink more than three or four drinks per occasion, and do not drink in high-risk situations (while pregnant, driving a car, etc.).

At-risk drinkers occasionally exceed recommended guidelines for use. While they are at risk for alcohol-related problems, they may never experience negative consequences as a result of their drinking and represent a prime target for preventive, educational efforts by primary care clinicians.

## Screening Instruments

Asking potentially sensitive questions about substance abuse in the context of other behavioral lifestyle questions appears to be less threatening to patients.

## CAGE-AID

Asking the following questions of every adult routinely and periodically is a cost-effective way of screening for substance abuse and detecting possible problems at an early stage in their development:

- Have you ever felt you ought to **cut down** on your drinking or drug use?
- Have people **annoyed** you by criticizing your drinking or drug use?
- Have you felt bad or **guilty** about your drinking or drug use?
- Have you ever had a drink or used drugs first thing in the morning to steady your nerves or to get rid of a hangover (**eye-opener**)?

**Scoring:** Item responses on the CAGE are scored 0 for “no” and 1 for “yes” answers. Consider conducting a brief intervention (see below) with any patient who scores a one or higher.

## The AUDIT Questionnaire

The AUDIT is designed to be used as a brief structured interview or self-report survey that can easily be incorporated into a general health interview, life-style questionnaire, or medical history. Patients tend to answer it most accurately when:

- The interviewer is friendly and nonthreatening
- The purpose of the questions is clearly related to a diagnosis of their health status
- The patient is alcohol- and drug-free at the time of the screening
- The information is considered confidential

- The questions are easy to understand

Health workers should try to establish these conditions before the AUDIT is given. Answers should be recorded carefully.

In addition to these general considerations, the following interviewing techniques should be used:

- Try to interview patients under the best possible circumstances
- Look for signs of alcohol or drug intoxication—patients who have alcohol on their breath or appear intoxicated may be unreliable respondents
- It is important to read the questions as written and in the order indicated

Circle the number that comes closest to the patient’s answer.

1. How often do you have a drink containing alcohol?
  - (0) Never
  - (1) Monthly or less
  - (2) Two to four times a month
  - (3) Two to three times a week
  - (4) Four or more times a week
2. How many drinks containing alcohol do you have on a typical day when you are drinking?

[Code number of standard drinks.\*]

  - (0) 1 or 2
  - (1) 3 or 4
  - (2) 5 or 6
  - (3) 7 to 9
  - (4) 10 or more

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\*In determining the response categories it has been assumed that one drink contains 10 g of alcohol. In countries where the alcohol content of a standard drink differs by more than 25 percent from 10 g, the response category should be modified accordingly.

3. How often do you have six or more drinks on one occasion?
  - (0) Never
  - (1) Less than monthly
  - (2) Monthly
  - (3) Weekly
  - (4) Daily or almost daily
4. How often during the last year have you found that you were not able to stop drinking once you had started?
  - (0) Never
  - (1) Less than monthly
  - (2) Monthly
  - (3) Weekly
  - (4) Daily or almost daily
5. How often during the last year have you failed to do what was normally expected from you because of drinking?
  - (0) Never
  - (1) Less than monthly
  - (2) Monthly
  - (3) Weekly
  - (4) Daily or almost daily
6. How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session?
  - (0) Never
  - (1) Less than monthly
  - (2) Monthly
  - (3) Weekly
  - (4) Daily or almost daily
7. How often during the last year have you had a feeling of guilt or remorse after drinking?
  - (0) Never
  - (1) Less than monthly
  - (2) Monthly
  - (3) Weekly
  - (4) Daily or almost daily
8. How often during the last year have you been unable to remember what happened the night before because you had been drinking?
  - (0) Never
  - (1) Less than monthly
  - (2) Monthly
  - (3) Weekly
  - (4) Daily or almost daily
9. Have you or has someone else been injured as a result of your drinking?
  - (0) No
  - (2) Yes, but not in the last year
  - (4) Yes, during the last year
10. Has a relative or friend or a doctor or other health worker been concerned about your drinking or suggested you cut down?
  - (0) No
  - (2) Yes, but not in the last year
  - (4) Yes, during the last year

Procedures for scoring AUDIT

**Question 1:**

Never = 0

Monthly or less = 1

Two to four times per month = 2

Two to three times per week = 3

Four or more times per week = 4

**Question 2:**

- 1 or 2 = 0
- 3 or 4 = 1
- 5 or 6 = 2
- 7 to 9 = 3
- 10 or more = 4

**Questions 3–8:**

- Never = 0
- Less than monthly = 1
- Monthly = 2
- Weekly = 3
- Daily or almost daily = 4

**Questions 9–10:**

- No = 0
- Yes, but not in the last year = 2
- Yes, during the last year = 4

The minimum score (for non-drinkers) is 0 and the maximum possible score is 40. A score of 8 or more indicates a strong likelihood of hazardous or harmful alcohol consumption.

**TWEAK Test**

Use the TWEAK test to screen pregnant women.

- T Tolerance:** How many drinks can you hold?
- W** Have close friends or relatives **worried** or complained about your drinking in the past year?
- E Eye-opener:** Do you sometimes take a drink in the morning when you first get up?
- A Amnesia:** Has a friend or family member ever told you about things you said or did while you were drinking that you could not remember?
- K** Do you sometimes feel the need to **cut down** on your drinking?

**Scoring:** A 7-point scale is used to score the test. The “tolerance” question scores 2 points if a woman reports she can hold

more than five drinks without falling asleep or passing out. A positive response to the “worry” question scores 2 points, and a positive response to the last three questions scores 1 point each. A total score of 2 or more indicates a woman is likely to be a risky drinker.

Screen all adults age 60 or older for alcohol and prescription drug abuse as part of their regular physical.

**Michigan Alcoholism Screening Test–Geriatric Version (MAST-G)**

The following are yes or no questions:

1. After drinking have you ever noticed an increase in your heart rate or beating in your chest?
2. When talking with others, do you ever underestimate how much you actually drink?
3. Does alcohol make you so sleepy that you often fall asleep in your chair?
4. After a few drinks, have you sometimes not eaten or been able to skip a meal because you didn’t feel hungry?
5. Does having a few drinks help decrease your shakiness or tremors?
6. Does alcohol sometimes make it hard for you to remember parts of the day or night?
7. Do you have rules for yourself that you won’t drink before a certain time of the day?
8. Have you lost interest in hobbies or activities you used to enjoy?
9. When you wake up in the morning, do you ever have trouble remembering part of the night before?
10. Does having a drink help you sleep?

11. Do you hide your alcohol bottles from family members?
12. After a social gathering, have you ever felt embarrassed because you drank too much?
13. Have you ever been concerned that drinking might be harmful to your health?
14. Do you like to end an evening with a nightcap?
15. Did you find your drinking increased after someone close to you died?
16. In general, would you prefer to have a few drinks at home rather than go out to a social event?
17. Are you drinking more now than in the past?
18. Do you usually take a drink to relax or calm your nerves?
19. Do you drink to take your mind off your problems?
20. Have you ever increased your drinking after experiencing a loss in your life?
21. Do you sometimes drive when you have had too much to drink?
22. Has a doctor or nurse ever said they were worried or concerned about your drinking?
23. Have you ever made rules to manage your drinking?
24. When you feel lonely does having a drink help?

**Scoring:** 5 or more “yes” responses are indicative of an alcohol problem.

## Suggestions for Screening

### *Risk factors for adolescent drug use*

- Physical or sexual abuse
- Parental substance abuse
- Parental incarceration
- Dysfunctional family relationships
- Peer involvement with drugs or alcohol
- Smoking tobacco

### *Red flags*

- Marked change in physical health
- Deteriorating performance in school or job
- Dramatic change in personality, dress, or friends
- Involvement in serious delinquency or crimes
- HIV high-risk activities
- Serious psychological problems

Pregnant women and women older than 60, as well as women who have experienced a major life transition, should be queried about their psychoactive prescription drug use and use of over-the-counter sleep aids.

Clinicians will want to use the screening instrument that best meets the needs of their patient population.

When treating patient populations at high risk for drug abuse, ask questions regarding alcohol and drug use at the same time.

## Following Up on Screening

- All patients who undergo screening for alcohol or drug use should be told the results of the screen.
- Patients with positive results to a screen will need some type of followup. Assessment questions should cover severity of the suspected alcohol or drug involvement, the types and frequency of problems connected with the patient's use, and other special medical and psychiatric considerations.
- If a patient's response to a brief assessment suggests a diagnosis of substance abuse or dependence, the clinician should initiate a referral for an in-depth assessment.
- The clinician can initiate a brief, office-based therapeutic intervention in these situations:
  - Screening reveals only mild to moderate substance abuse problems
  - The patient appears to be at risk for experiencing negative consequences as a result of current patterns
  - Coexisting illness or conditions may be worsened by continued drinking or other medications
  - Patient refuses referral for further assessment or treatment.

## Brief Intervention

Brief interventions as secondary prevention tools have the potential to help an estimated 15 to 20 million heavy drinkers in the U.S. by minimizing serious adverse consequences such as costly emergency room visits, domestic violence, or road accidents.

## Selecting Appropriate Patients for Brief Intervention

In response to screening questionnaires patients can be categorized into one of three groups:

1. Patients who do not appear to have any alcohol- or drug-related problems. These patients require no further intervention.
2. Patients with positive but low scores on any screening tests or who occasionally use marijuana. These patients may be appropriate candidates for brief intervention.
3. Patients with several positive responses to screening questionnaires and suspicious drinking or drug use histories, symptoms of substance dependence, or current use of illicit drugs. These patients need further assessment.

## Conducting Brief Interventions

1. **Give feedback about screening results, impairment, and risks while clarifying the findings**
  - Give prompt feedback to the screening.
  - Present results in a straightforward, nonjudgmental manner and in terms a patient can readily understand.
  - Concerns about potential or actual health effects should be stressed. For example, "At this level of consumption, you are at increased risk for some health problems as well as accidents."
  - Avoid being adversarial and pay attention to semantics. For example, the phrase "people for whom substance abuse is creating a problem" is less off-putting than the labels "alcoholic" or "addict."

- Remain tolerant of the range of patient reactions, including astonishment, embarrassment, hostility, and denial.
  - Try to avoid arguments or discussions about how much others can drink without adverse consequences.
  - Be reassuring that alcohol and drug problems are not anyone’s “fault” and can certainly be addressed during visits.
- 2. Inform the patient about safe consumption limits and offer advice about change**
- Explain what acceptable and safe use levels are for the relevant substance. Low-risk drinking is no more than two drinks per day for men and one drink per day for women.
  - Patients should understand concepts of tolerance and metabolism.
  - Clearly state recommendations about consumption goals, keeping these in the context of lifestyle issues and living habits. For example, “In reviewing your response to our screening questionnaire, I notice that you are drinking a lot of beer on weekends. You don’t seem to have any direct problems as a result, but I’m concerned that driving while intoxicated is not safe and you have a young family to consider.”
  - Clinician authority in offering advice can be strongly motivating.
- 3. Assess the patient’s readiness to change**
- A patient’s reaction to initial feedback about screening results offers strong clues about readiness to change.
  - People with substance abuse disorders generally fall into one of five stages along a continuum that provides a useful framework for monitoring progress:
    - Precontemplation: Not seeing the behavior as a problem or not wanting to change the behavior.
    - Contemplation: Beginning to understand that the behavior is causing difficulties in living or taking a toll on their health and happiness.
    - Preparation/Determination: Considering various options for change.
    - Action: Taking concrete steps to change the behavior in a specific way.
    - Maintenance: Avoiding relapse into problem behavior.
- Be prepared for resistance and setbacks.
  - Avoid the temptation to regard resistance as a challenge to authority or to react in an authoritarian way.
  - Have an emphatic and supportive attitude and create an atmosphere that the patient will be comfortable returning to even if goals are not successfully achieved.
- 4. Negotiate goals and strategies for change**
- With alcohol, suggest that the client reduce consumption to below unsafe or potentially hazardous levels. For example, “Can we set a specific date to reduce your alcohol use? Could you cut back, beginning this week?”
  - If a patient who is using illegal drugs does not feel ready to discontinued use, suggest a tapering schedule.



- The clinician can only remind the patient that reducing or stopping alcohol use or abstaining from other drug use will eliminate the health or social problems substance use is causing: **Ultimately the patient must choose the goal.**
- Suggest that patients keep track of consumption in a daily diary to make them more aware of how much they consume. Even patients who are not ready to change their behavior may be willing to keep a diary.
- Patients will be more motivated to change if they are helping to set goals and develop strategies for change. Some studies have found that self-help manuals can be a helpful adjunct for planning change.
- A written contract is a good idea since sometimes patients forget what they agreed to do.

#### 5. Arrange for followup treatment

- Monitor any health problems or abnormal physical markers.
- Express trust in the patient.
- Confront the patient if he or she is not honest about reporting substance use.

- The use of any form of objective monitoring beyond self-reports of substance abuse must be negotiated between the clinician and the patient.
- Tell patients exactly who will see their medical charts and what information about screening and intervention will be recorded.
- One researcher found that reduction of alcohol consumption correlated with the number of practitioner intervention sessions that were delivered.

### Deciding To Refer for Further Assessment or Treatment

Clinicians should be prepared for the brief intervention to fail: The patient may not be able to achieve or maintain the mutually established goal of reducing or stopping use after one try, or even several tries. Clinicians cannot force a patient to undergo further assessment. However, if problem use persists after a brief intervention, those discussions should serve as a springboard for a more in-depth assessment or specialized treatment.

## CSAT TIPs and Publications Based on TIPs

### What Is a TIP?

Treatment Improvement Protocols (TIPs) are the products of a systematic and innovative process that brings together clinicians, researchers, program managers, policymakers, and other Federal and non-Federal experts to reach consensus on state-of-the-art treatment practices. TIPs are developed under CSAT's Knowledge Application Program to improve the treatment capabilities of the Nation's alcohol and drug abuse treatment service system.

### What Is a Quick Guide?

A Quick Guide clearly and concisely presents the primary information from a TIP in a pocket-sized booklet. Each Quick Guide is divided into sections to help readers quickly locate relevant material. Some contain glossaries of terms or lists of resources. Page numbers from the original TIP are referenced so providers can refer back to the source document for more information.

### What Are KAP Keys?

Also based on TIPs, KAP Keys are handy, durable tools. Keys may include assessment or screening instruments, checklists, and summaries of treatment phases. Printed on coated paper, each KAP Keys set is fastened together with a key ring and can be kept within a treatment provider's reach and consulted frequently. The Keys allow you—the busy clinician or program administrator—to locate information easily and to use this information to enhance treatment services.

- TIP 1** State Methadone Treatment Guidelines—  
*Replaced by TIP 43*
- TIP 2\*** Pregnant, Substance-Using Women—*BKD107*  
Quick Guide for Clinicians *QGCT02*  
KAP Keys for Clinicians *KAPT02*
- TIP 3** Screening and Assessment of Alcohol- and  
Other Drug-Abusing Adolescents—*Replaced*  
*by TIP 31*
- TIP 4** Guidelines for the Treatment of Alcohol-  
and Other Drug-Abusing Adolescents—  
*Replaced by TIP 32*
- TIP 5** Improving Treatment for Drug-Exposed  
Infants—*BKD110*
- TIP 6\*** Screening for Infectious Diseases Among  
Substance Abusers—*BKD131*  
Quick Guide for Clinicians *QGCT06*  
KAP Keys for Clinicians *KAPT06*
- TIP 7** Screening and Assessment for Alcohol and  
Other Drug Abuse Among Adults in the  
Criminal Justice System—*Replaced by TIP 44*
- TIP 8** Intensive Outpatient Treatment for Alcohol  
and Other Drug Abuse—*Replaced by TIPs 46*  
*and 47*
- TIP 9** Assessment and Treatment of Patients With  
Coexisting Mental Illness and Alcohol and  
Other Drug Abuse—*Replaced by TIP 42*
- TIP 10** Assessment and Treatment of Cocaine-  
Abusing Methadone-Maintained Patients—  
*Replaced by TIP 43*
- TIP 11\*** Simple Screening Instruments for Outreach  
for Alcohol and Other Drug Abuse and  
Infectious Diseases—*BKD143*  
Quick Guide for Clinicians *QGCT11*  
KAP Keys for Clinicians *KAPT11*
- TIP 12** Combining Substance Abuse Treatment  
With Intermediate Sanctions for Adults in  
the Criminal Justice System—*Replaced by*  
*TIP 44*
- TIP 13** Role and Current Status of Patient  
Placement Criteria in the Treatment of  
Substance Use Disorders—*BKD161*  
Quick Guide for Clinicians *QGCT13*  
Quick Guide for Administrators *QGAT13*  
KAP Keys for Clinicians *KAPT13*
- TIP 14** Developing State Outcomes Monitoring  
Systems for Alcohol and Other Drug Abuse  
Treatment—*BKD162*
- TIP 15** Treatment for HIV-Infected Alcohol and  
Other Drug Abusers—*Replaced by TIP 37*
- TIP 16** Alcohol and Other Drug Screening of  
Hospitalized Trauma Patients—*BKD164*  
Quick Guide for Clinicians *QGCT16*  
KAP Keys for Clinicians *KAPT16*
- TIP 17** Planning for Alcohol and Other Drug  
Abuse Treatment for Adults in the Criminal  
Justice System—*Replaced by TIP 44*
- TIP 18** The Tuberculosis Epidemic: Legal and  
Ethical Issues for Alcohol and Other Drug  
Abuse Treatment Providers—*BKD173*  
Quick Guide for Clinicians *QGCT18*  
KAP Keys for Clinicians *KAPT18*
- TIP 19** Detoxification From Alcohol and Other  
Drugs—*Replaced by TIP 45*
- TIP 20** Matching Treatment to Patient Needs in  
Opioid Substitution Therapy—*Replaced by*  
*TIP 43*
- TIP 21** Combining Alcohol and Other Drug Abuse  
Treatment With Diversion for Juveniles in  
the Justice System—*(SMA) 08-4073*  
Quick Guide for Clinicians and  
Administrators *QGCA21*
- TIP 22** LAAM in the Treatment of Opiate  
Addiction—*Replaced by TIP 43*
- TIP 23** Treatment Drug Courts: Integrating  
Substance Abuse Treatment With Legal  
Case Processing—*(SMA) 08-3917*  
Quick Guide for Administrators *QGAT23*
- TIP 24** A Guide to Substance Abuse Services for  
Primary Care Clinicians—*(SMA) 08-4075*  
Concise Desk Reference Guide *(SMA)*  
*08-3740*  
Quick Guide for Clinicians *QGCT24*  
KAP Keys for Clinicians *KAPT24*
- TIP 25** Substance Abuse Treatment and Domestic  
Violence—*(SMA) 08-4076*  
A Guide for Treatment Providers *MS668*  
A Guide for Administrators *MS667*  
Quick Guide for Clinicians *QGCT25*  
KAP Keys for Clinicians *KAPT25*
- TIP 26** Substance Abuse Among Older Adults—  
*(SMA) 08-3918*  
A Guide for Treatment Providers *MS669*  
A Guide for Social Service Providers *MS670*  
Physician's Guide *MS671*

\*Under revision

- TIP 26 Substance Abuse Among Older Adults—**  
(SMA) 08-3918  
**Good Mental Health is Ageless PHD881**  
(English), (SMA) 08-3897 (Spanish)  
**Aging, Medicines and Alcohol (SMA) 08-3169**  
(English), (SMA) 08-3898 (Spanish)  
**Quick Guide for Clinicians QGCT26**  
**KAP Keys for Clinicians KAPT26**
- TIP 27 Comprehensive Case Management for Substance Abuse Treatment—**(SMA) 08-4215  
**A Guide for Treatment Providers MS673**  
**Quick Guide for Clinicians QGCT27**  
**Quick Guide for Administrators QGAT27**
- TIP 28 Naltrexone and Alcoholism Treatment—**  
*Replaced by TIP 49*
- TIP 29 Substance Use Disorder Treatment for People With Physical and Cognitive Disabilities—**(SMA) 08-4078  
**Quick Guide for Clinicians QGCT29**  
**Quick Guide for Administrators (SMA) 08-3592**  
**KAP Keys for Clinicians KAPT29**
- TIP 30 Continuity of Offender Treatment for Substance Use Disorders From Institution to Community—**(SMA) 08-3920  
**Quick Guide for Clinicians QGCT30**  
**KAP Keys for Clinicians KAPT30**
- TIP 31 Screening and Assessing Adolescents for Substance Use Disorders—**(SMA) 08-4079  
See companion products for TIP 32.
- TIP 32 Treatment of Adolescents With Substance Use Disorders—**(SMA) 08-4080  
**Quick Guide for Clinicians QGC312**  
**KAP Keys for Clinicians KAPT312**
- TIP 33 Treatment for Stimulant Use Disorders—**  
*BKD289*  
**Quick Guide for Clinicians QGCT33**  
**KAP Keys for Clinicians KAPT33**
- TIP 34 Brief Interventions and Brief Therapies for Substance Abuse—**(SMA) 07-3952  
**Quick Guide for Clinicians QGCT34**  
**KAP Keys for Clinicians KAPT34**
- TIP 35 Enhancing Motivation for Change in Substance Abuse Treatment—**(SMA) 08-4212  
**Faces of Change (SMA) 08-4174**  
**Inservice Training (SMA) 08-4190**  
**Quick Guide for Clinicians QGCT35**  
**KAP Keys for Clinicians KAPT35**
- TIP 36 Substance Abuse Treatment for Persons With Child Abuse and Neglect Issues—**  
(SMA) 08-3923  
**Helping Women Heal—**(SMA) 08-4132  
(English), *PHD981S (Spanish)*  
**Helping Men Heal—**(SMA) 07-4134 (English),  
*PHD1059S (Spanish)*  
**Quick Guide for Clinicians QGCT36**  
**KAP Keys for Clinicians KAPT36**
- TIP 37 Substance Abuse Treatment for Persons With HIV/AIDS—**(SMA) 08-4137  
**HIV/AIDS: Is Your Client at Risk? MS965**  
**Drugs, Alcohol and HIV/AIDS (SMA) 08-4127**  
(English), (SMA) 08-4181 (Spanish)  
**Drugs, Alcohol and HIV/AIDS for African Americans (SMA) 07-4248**  
**Quick Guide for Clinicians QGCT37**  
**KAP Keys for Clinicians KAPT37**
- TIP 38 Integrating Substance Abuse Treatment and Vocational Services—***BKD381*  
**Quick Guide for Clinicians QGCT38**  
**Quick Guide for Administrators QGAT38**  
**KAP Keys for Clinicians KAPT38**
- TIP 39 Substance Abuse Treatment and Family Therapy—**(SMA) 08-4219  
**Quick Guide for Clinicians QGCT39**  
**Quick Guide for Administrators QGAT39**
- TIP 40 Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction—**(SMA) 07-3939  
**Quick Guide for Physicians QGPT40**  
**KAP Keys for Physicians KAPT40**
- TIP 41 Substance Abuse Treatment: Group Therapy—***BKD507*  
**Quick Guide for Clinicians QGCT41**
- TIP 42 Substance Abuse Treatment for Persons With Co-Occurring Disorders—**(SMA) 08-3992  
**Inservice Training (SMA) 08-4262**  
**Quick Guide for Clinicians (SMA) 07-4034**  
**Quick Guide for Administrators QGAT42**  
**KAP Keys for Clinicians (SMA) 08-4036**
- TIP 43 Medication-Assisted Treatment for Opioid Addiction in Opioid Treatment Programs—**  
(SMA) 08-4214  
**Inservice Training (SMA) 08-4341**  
**Quick Guide for Clinicians QGCT43**  
**KAP Keys for Clinicians (SMA) 07-4108**
- TIP 44 Substance Abuse Treatment for Adults in the Criminal Justice System—***BKD526*  
**Alcohol & Drug Treatment (SMA) 07-4292**  
(English), (SMA) 08-4320 (Spanish)  
**Quick Guide for Clinicians QGCT44**  
**KAP Keys for Clinicians (SMA) 07-4150**
- TIP 45 Detoxification and Substance Abuse Treatment—**(SMA) 08-4131  
**Inservice Training (SMA) 08-4331**  
**Quick Guide for Clinicians (SMA) 06-4225**  
**Quick Guide for Administrators (SMA) 06-4226**  
**KAP Keys for Clinicians (SMA) 06-4224**
- TIP 46 Substance Abuse: Administrative Issues in Outpatient Treatment—***BKD545*  
**Quick Guide for Administrators (SMA) 07-4232**
- TIP 47 Substance Abuse: Clinical Issues in Intensive Outpatient Treatment—***BKD551*  
**Quick Guide for Clinicians (SMA) 07-4233**  
**KAP Keys for Clinicians (SMA) 07-4251**
- TIP 48 Managing Depressive Symptoms in Substance Abuse Clients During Early Recovery—**(SMA) 08-4353
- TIP 49 Incorporating Alcohol Pharmacotherapies Into Medical Practice—**(SMA) 09-4380
- TIP 50 Addressing Suicidal Thoughts and Behaviors With Clients in Substance Abuse Treatment—**(SMA) 09-4381



"This course was developed from the public domain document: Incorporating Alcohol Pharmacotherapies Into Medical Practice A Treatment Improvement Protocol TIP 49 and Helping Patients Who Drink Too Much: A Clinician's Guide– National Institute on Alcohol Abuse and Alcoholism (NIAAA), U.S. Department of Health and Human Services, Center for Substance Abuse Treatment, Substance Abuse and Mental Health Services Administration (SAMSA)."