Incorporating Alcohol Pharmacotherapies Into Medical Practice

A Treatment Improvement Protocol

TIP 49

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Substance Abuse and Mental Health Services Administration
Center for Substance Abuse Treatment
www.samhsa.gov

AUD PHARMACO-THERAPIES

1 Introduction

In This Chapter . . .

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 healthcare 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 buproprion 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 Laboratories 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 ≤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)*	Inform patients to contact the prescribing professional immediately Monitor patients for onset or worsening of depression Obtain a psychiatric consult and/or prescribe antidepressant medication as necessary Discontinue acamprosate
Severe and/or persistent diarrhea	Treat with Imodium® or Pepto-Bismol® Recommend appropriate dietary changes Reduce acamprosate dosage or discontinue use if diarrhea remains intolerable after treatment

*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, Lehert, 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	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. FDA approves disulfiram to treat alcohol dependence in the United States. Wyeth-Ayerst Laboratories begins manufacturing Antabuse® tablets (now manufactured by PLIVA and distributed in the United States by Odyssey Pharmaceuticals). 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.
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, γ-aminobutyric acid, or glutamate receptors directly. However, it does have some central nervous system effects, inhibiting enzyme dopamine β-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 nonprescription 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 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.

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

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 paresthesias (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.

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

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.