Drug use disorders (DUDs) frequently co-occur with alcohol use disorders, affecting approximately 1.1 percent of the U.S. population. Compared with alcohol use disorders or DUDs alone, co-occurring disorders are associated with a greater severity of substance dependence; co-occurring psychiatric disorders also are common in this patient population. Many effective medications and behavioral treatments are available to treat alcohol dependence and drug dependence when these occur independent of one another. There is a paucity of research, however, specifically focused on the treatment of persons with co-occurring alcohol and other DUDs (AODUDs). The evidence to date on treating this patient population suggests that combining some of the behavioral and pharmacologic treatments that are effective in treating either drug or alcohol use disorders alone may be useful in the AODUD population as well.

KEY WORDS: Alcohol and other drug use disorder (AODUD); dual addiction; comorbid AOD dependence; treatment methods; psychosocial treatment method; behavior therapy; pharmacotherapy; combined treatment; literature review

After a brief discussion of assessment, placement, and treatment matching, this article reviews the literature on evidence-based pharmacologic and behavioral treatment strategies for AOD dependence. It also presents evidence for using specific treatments for AODUDs and provides recommendations on how to implement these treatments.

**Assessment, Placement, and Treatment Matching**

In general, patients with AODUDs have a greater severity of substance dependence than patients with only an alcohol use disorder or a DUD. People with AODUDs are at least as likely to have co-occurring psychiatric disorders as those who have only DUDs and are more likely to have such disorders than those with only alcohol use disorders (Stinson et al. 2005). In addition, people with AODUDs are more likely than those with either drug or alcohol use disorders alone to seek treatment (Stinson et al. 2005). Thus, patients with AODUDs are perhaps best evaluated for treatment planning by a practitioner with specialized expertise in addictive disorders. Although many factors dictate the initial placement and treatment of the AODUD patient (e.g., co-occurring pregnancy or the need for medical detoxification), general guidelines are available. The American Society of Addiction

**Vol. 31, No. 2, 2008**
Evidence-Based Treatments for Individual SUDs

Although a complete review of the behavioral and pharmacologic treatment literature for specific addictive disorders is beyond the scope of this article, this section provides a brief summary of the major treatment modalities that currently are in use. In general, an approach that combines behavioral and pharmacologic treatments is optimal for most patients. However, recent findings from studies of the pharmacotherapy of alcohol dependence have shown that some patients may do well when medication is combined with a minimal behavioral approach focusing on medication adherence (Anton et al. 2006b; Johnson et al. 2003, 2007). In addition, among alcohol-dependent patients, those with a goal of abstinence from alcohol likely have better treatment outcomes. However, because some patients do not subscribe to such a goal, it often is necessary to negotiate a “harm reduction” approach with them, with the option of modifying the goal if their efforts to reduce their drinking substantially are not successful (Mason et al. 2006). In drug dependence treatment, behavioral therapies often are considered primary and medications secondary, except in the case of patients receiving opioid agonist1 maintenance therapy.

Behavioral Therapies

Table 1 lists the research-based behavioral therapies for different SUDs, with a general description of the level of research evidence supporting each of the treatments (McCaull and Petry 2003). Because people with substance dependence often are ambivalent about changing their behavior, some experts consider motivational enhancement therapy (MET) to be an essential element of addictions treatment, although the evidence supporting its use may be strongest in the treatment of alcohol use disorders (Carroll and Onken 2005; McCaul and Petry 2003). MET aims to engage in treatment patients who are resistant to behavioral change and may be the most acceptable therapeutic approach when patients are new to treatment for AODUDs. MET can help to build a working alliance between the patient and practitioner and provide a foundation on which other useful therapies, including medications, may be added. Cognitive-behavioral therapy (CBT) and MET are effective in the treatment of cannabis dependence (Nordstrom and Levin 2007). Contingency management2 interventions also have proven to be effective in treating SUDs (Peirce et al. 2006; Petry and Martin 2002; Prendergast et al. 2006), including reducing both drug use and drinking in alcohol-dependent patients (Petry et al. 2000). In addition to the therapies shown in table 1, an intensive outreach counseling program may be helpful in reducing illicit drug use and returning to treatment patients who drop out from methadone maintenance (Zanis et al. 1996).

A variety of behavioral approaches have shown efficacy in the treatment of alcohol use disorders (see table 1).

---

Table 1 Summary of Research on Behavioral Therapies for Specific Substance Use Disorders

| Treatment | Alcohol | Cocaine | Opioid* | Marijuana |
|-----------|---------|---------|---------|-----------|
| CBT       | ++ (A)  | ++ (A)  | +/– (B) | + (B)     |
| MET       | ++ (A)  | +/– (B) | +/– (B) | + (B)     |
| CM        | ++ (A)  | + (A)   | + (A)   | + (B)     |
| BI        | ++ (A)  |         |         |           |
| TSF       | + (A)   | +/– (B) | +/– (B) |           |
| CET       | + (B)   |         |         |           |
| BCT       | + (B)   |         |         |           |
| CRA       | ++ (A)  |         |         |           |

NOTES: BCT = Brief Couples Therapy, BI = Brief Intervention, CBT = Cognitive-Behavioral Therapy, CET = Cue Exposure Therapy, CM = Contingency Management, CRA = Community Reinforcement Approach, MET = Motivational Enhancement Therapy, TSF = Twelve-Step Facilitation.

For level of evidence supporting the use of therapies: (–) indicates that the treatment appears not to be efficacious, (+/–) indicates conflicting results or preliminary evidence of efficacy, (+) indicates evidence of efficacy from randomized controlled trials, and (++) indicates evidence of efficacy from multiple trials and/or meta-analyses.

Evidence-based strength of recommendation taxonomy (SORT; as defined by Ebell et al. 2004): (A) Recommendation based on consistent and good-quality patient-oriented evidence. (B) Recommendation based on inconsistent or limited-quality patient-oriented evidence. (C) Recommendation based on consensus, usual practice, opinion, disease-oriented evidence, or case series for studies of diagnosis, treatment, prevention, or screening.

1 In opioid agonist therapy, patients receive a drug, such as methadone or buprenorphine, that is chemically similar to opioid drugs.

2 Contingency management is the systematic reinforcement of desired behaviors and the withholding of reinforcement or punishment of undesired behaviors.
BRENDA, which is an acronym for Biopsychosocial, Report, Empathy, Needs, Direct advice, and Assessment, has been used to provide a flexible, and practical, client-centered therapy for use in conjunction with pharmacotherapy (Garbutt et al. 2005). BRENDA, like MET, is a client-centered approach that, by building a working alliance with the patient, can act as foundation for other treatments (Pettinati et al. 2000b). BRENDA may enhance medication adherence in the treatment of alcohol dependence (Pettinati et al. 2000b).

NIAAA also has published several behavioral treatment guides and manuals (http://www.niaaa.nih.gov/Publications/EducationTrainingMaterials/guide.htm). Volume 1 of the Project COMBINE monograph series (Miller 2004), which describes combined behavioral intervention (CBI), provides detailed guidelines for a state-of-the-art counseling approach to the treatment of alcohol dependence that combines elements of CBT and MET.

Volume 2 (Pettinati et al. 2004) describes medication management (MM), an intervention that was used in the COMBINE study (Anton et al. 2006) as a minimal supportive approach to accompany medication therapy in alcohol-dependent patients. In this study, treatment with the opioid receptor antagonist3 naltrexone accompanied by MM was efficacious in achieving successful drinking outcomes. However, combining elements of multiple behavioral therapies (e.g., combining motivational interventions with CBT and clinical management) may be the most effective approach to the treatment of SUDs (Carroll 2005).

Evidence-based strength of recommendation taxonomy (SORT; as defined by Ebell et al., 2004):
- (A) Recommendation based on consistent and good-quality patient-oriented evidence.
- (B) Recommendation based on inconsistent or limited-quality patient-oriented evidence.
- (C) Recommendation based on consensus, usual practice, opinion, disease-oriented evidence, or case series for studies of diagnosis, treatment, prevention, or screening.

### Table 2. Summary of Research on Pharmacotherapies for Specific Substance Use Disorders

|            | Alcohol | Cocaine | Opioid* |
|------------|---------|---------|---------|
| Disulfiram | +/-*    | (B)     | (B)     |
| Naltrexone | ++      | (A)     | +/- (B) |
| Acamprosate| ++      | (A)     | +/- (B) |
| Topiramate | +       | (A)     | +/- (B) |
| Ondansetron| +/-**   | (C)     | +/- (C) |
| Sertraline/SSRI | +/-**    | (C)     | – (C)   |
| Carbamazepine| +      | (B)     | – (C)   |
| Valproate  | +/- (B) | +/- (B) | +/- (B) |
| Tiagabine  | +/- (B) | +/- (B) | +/- (B) |
| Aripiprazole| –       | (C)     | (B)     |
| Modafinil  | –       | (B)     | +/- (B) |
| Quetiapine | +/-**   | (C)     | (B)     |
| Olanzapine | –       | (C)     | – (C)   |
| Lithium    | –       | (C)     | – (C)   |
| Baclofen   | +/- (B) | +/- (B) | – (C)   |
| Buprenorphine| ++      | (A)     | (A)     |
| Methadone  | ++ (A)  | (A)     | (A)     |

NOTES: For level of evidence supporting the use of therapies: (–) indicates that the treatment appears to be ineffective, (+/-) indicates either conflicting results or preliminary/potential evidence of efficacy, (+) indicates support from randomized controlled trials, (+++) indicates support for efficacy from multiple trials and/or meta-analyses.

*Effective in highly motivated patients that will adhere. ** May be effective in certain subtypes of alcohol dependence, or in dually-diagnosed individuals.

Evidence-based strength of recommendation taxonomy (SORT; as defined by Ebell et al., 2004):
- (A) Recommendation based on consistent and good-quality patient-oriented evidence.
- (B) Recommendation based on inconsistent or limited-quality patient-oriented evidence.
- (C) Recommendation based on consensus, usual practice, opinion, disease-oriented evidence, or case series for studies of diagnosis, treatment, prevention, or screening.

### Pharmacotherapies

Table 2 summarizes the current research findings on the efficacy of pharmacologic treatments for SUDs. This section will review the relevant findings on treatments for alcohol, cocaine, opioid, and cannabis dependence.

**Alcohol Dependence.** Despite progress in pharmacotherapy research, medications approved to treat alcohol dependence are underutilized (Mark et al. 2003).

**Disulfiram.** This medication causes flushing, nausea, nervousness, and other unpleasant physiologic effects when combined with alcohol. It was approved by the U.S. Food and Drug Administration (FDA) in 1949, making it the first medication approved for treating alcohol dependence. Disulfiram was approved before implementation of the FDA requirement that a medication have demonstrated efficacy as well as safety. In a multicenter trial that included more than 600 male veterans, disulfiram failed to increase the likelihood of abstinence during a 1-year treatment period (Fuller et al. 1986). However, among individuals who drank, a 250-mg dose of disulfiram reduced drinking days relative to a 1-mg dose of disulfiram or a placebo. Note though, the potentially serious adverse effects produced by the medication when combined with alcohol argue for its use in abstinence-oriented treatment rather than for harm reduction.

Patients who are likely to respond well to disulfiram treatment are older; have a longer drinking history; greater social stability, impulsivity, and motivation for recovery; attend Alcoholics Anonymous meetings; and are cognitively intact (Fuller and Gordis 2004; Suh et al. 2006). When disulfiram ingestion in a clinical trial was supervised by an individual designated by the patient, the drug was shown to increase abstinent days and decrease overall drinking relative to a placebo (Chick et al. 1992). Based on these and other findings, the efficacy of disulfiram may depend upon supervised...
administration of the drug (Hughes and Cook 1997; Suh et al. 2006).

Naltrexone. Several meta-analyses support the efficacy of oral naltrexone (at a daily dosage of 50 mg) in the treatment of alcohol dependence (see Spanagel and Zieglsangberger 1997 and table 3 for the putative mechanism of action of the medication). Naltrexone has been shown most consistently to be effective in reducing the risk of relapse to heavy drinking, with less consistent evidence that it reduces the percentage of drinking days or increases the likelihood of total abstinence (Bouza et al. 2004; Srisurapanont and Jarusuraisin 2005). One long-acting formulation of naltrexone has been shown to be effective in reducing heavy drinking among alcohol-dependent patients and may offer enhanced adherence, at least early in treatment, which can be a critical time in the process of recovery for AODUD patients (Garbutt et al. 2005). Based on the findings from that study, the FDA approved long-acting naltrexone for the treatment of alcohol dependence. A second injectable formulation of naltrexone reduced the number of drinking days and increased the likelihood of total abstinence compared with a placebo injection (Kranzler et al. 2004).

Acamprosate. Acamprosate is an amino acid derivative that affects the brain signaling molecules (i.e., neurotransmitters) γ-aminobutyric acid (GABA) and glutamate (Spanagel and Zieglsangberger 1997). The mechanism of action of acamprosate (Johnson 2008; Littleton and Zieglsangberger 2003; Spanagel and Zieglsangberger 1997) is shown in table 3.

Meta-analyses of European clinical trials have shown that acamprosate nearly doubles the likelihood of abstinence and reduces the risk of heavy drinking (Bouza et al. 2004; Chick et al. 2003; Mann et al. 2004). Based on these studies, later age of onset of alcohol dependence, the absence of a family history of alcohol dependence, and the presence of physiologic dependence and higher levels of anxiety are associated with a beneficial response to acamprosate (Johnson et al. 2007; Verheul et al. 2005). Based on three pivotal trials from Europe, the FDA approved acamprosate to treat alcohol dependence (Kranzler and Gage 2008). However, two recent studies (Anton et al. 2006b; Mason et al. 2006) of acamprosate conducted in the United States show the drug to be no better than placebo, when a standard, intent-to-treat analysis was used.

Two studies (Kiefer et al. 2003; Anton et al. 2006b) of naltrexone plus acamprosate versus either agent alone for the treatment of alcohol dependence did not show a clear advantage of the combination. Kiefer and colleagues (2003) found that the combination treatment was superior to acamprosate alone but was not better than naltrexone alone. In the COMBINE study (Anton et al. 2006b), treatment with the combination of naltrexone and acamprosate was no better than placebo treatment.

Anticonvulsant Medications. Topiramate is the best studied of the anticonvulsant medications that have been evaluated for the treatment of alcohol dependence. It has been shown to be effective in reducing a variety of drinking outcomes among alcohol-dependent patients (see table 3 for mechanism of action) in both a single-site study (Johnson et al. 2003) and in a randomized, placebo-controlled, double-blind, multicenter trial (Johnson et al. 2007). Studies of other anticonvulsants, including carbamazepine and valproate, also have shown some evidence of efficacy for the treatment of alcohol dependence and may be especially useful in patients with co-occurring bipolar disorders (Brady et al. 2002; Mueller et al. 1997; Salloum et al. 2005).

Disulfiram. Some of the initial research with disulfiram was conducted in study participants with alcohol and cocaine dependence and is discussed below. Disulfiram probably reduces cocaine use in cocaine-dependent individuals. Disulfiram also reduces drinking among individuals with alcohol dependence and has no effect on drinking among those with cocaine dependence. However, two recent studies (Anton et al. 2006a; Brown et al. 2005; Guardia et al. 2004; Kampman et al. 2007; Monnelly et al. 2004; Johnson et al. 2000; Kranzler et al. 1996, 2006; Kranzler and Ciraulo 2005; Pettinati et al. 2000a). Lithium does not appear efficacious for the treatment of alcohol dependence and has not been adequately tested among patients with co-morbid alcohol dependence and bipolar disorder (see Cerullo and Strakowski 2007 and Frye and Salloum 2006 for reviews). In a recent randomized, placebo-controlled clinical trial (Addolorato et al. 2007), baclofen, a GABA<sub>b</sub> receptor agonist, was shown to be safe and effective for the treatment of alcohol dependence. However, given the possibility of misuse and other complications from baclofen, which have been noted in the medical literature (e.g., withdrawal, psychosis, and delirium), more research with this medication is needed before it can be recommended as a safe and effective treatment for SUDs (Auger and Potash 2005; May 1983; McDonald et al. 2001; Perry et al. 1998).

Cocaine Dependence. Although many medications have been evaluated to treat cocaine dependence, few agents have shown efficacy. Currently, disulfiram, tiagabine, topiramate, and modafinil are the most promising of the available treatments (Karila et al. 2007; Vocci and Elkashef 2005).

Other Medications. A thorough discussion of serotonergic medications (e.g., selective serotonin reuptake inhibitors [SSRIs], ondansetron) and other medications (e.g., atypical antipsychotics, lithium) is beyond the scope of this review. Currently, there is not sufficient evidence to recommend the use of these agents for the treatment of primary SUDs. Ongoing research may clearly define a role for such medications in treating SUDs, particularly in certain subgroups of alcohol-dependent patients and those with co-occurring psychiatric illness (Anton et al. 2006a; Brown et al. 2005; Guardia et al. 2004; Kampman et al. 2007; Monnelly et al. 2004; Johnson et al. 2000; Kranzler et al. 1996, 2006; Kranzler and Ciraulo 2005; Pettinati et al. 2000a).
| Name            | Main Mechanism                                                                 | Pharmacologic Action                                                                                                                                                                                                 |
|-----------------|--------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Disulfiram      | Aversive therapy: consumption of alcohol within up to 2 weeks of ingesting the medication produces the disulfiram–ethanol reaction, consisting of flushing, palpitations, increased heart rate, decreased blood pressure, nausea/vomiting, sweating, dizziness, among other possible symptoms. Anticipating these effects averts drinking. Also may diminish the “high” produced by cocaine, reducing cocaine craving. It also directly reduces cocaine use independent of the patient’s level of drinking. | For alcohol dependence: inhibits the action of the metabolic enzyme aldehyde dehydrogenase, resulting in a buildup of acetaldehyde during ethanol metabolism. May also indirectly modulate receptors for the neurotransmitter glutamate. For cocaine dependence: inhibits the function of the enzyme dopamine β-hydroxylase, thus inhibiting metabolism of the neurotransmitter dopamine, thereby increasing the unpleasant effects of cocaine. Also increases cocaine plasma concentrations. |
| Naltrexone      | Attenuates the rewarding effects of alcohol in the brain and also may reduce the conditioned anticipation of those effects, as manifested in the urge to drink. | Is an opioid receptor antagonist; it blocks the effects of increased endogenous opioids (caused by alcohol) on dopaminergic transmission in the nucleus accumbens.                                                                 |
| Acamprosate     | Postulated to reduce relapse risk by reducing the urge to drink and the drive to experience the negative reinforcing effects of alcohol. | Essentially a modulator of glutamatergic transmission; has a complex mechanism of action that involves the modulation of certain glutamate (NMDA) receptors, calcium channels, and other downstream intracellular molecular events. |
| Topiramate      | Postulated to reduce the rewarding effects of drinking and the conditioned anticipation of those effects, as manifested in the urge to drink. | Multiple pharmacologic effects; facilitates some chemical connections in the brain and inhibits others. Indirectly attenuates dopaminergic transmission in the nucleus accumbens in response to drinking and directly attenuates neuronal glutamatergic hyperexcitability in the absence of alcohol. Mechanism in reducing cocaine use is unknown but is perhaps related to its GABAergic and glutamatergic effects. |
| Modafinil       | Attenuates the rewarding effects of cocaine, perhaps reducing the urge to use as well. Acts as a “functional partial agonist,” meaning that it has stimulant-like effects but also reduces cocaine self-administration and euphoria. | Unknown mechanism of action; thought to have minimal abuse potential and limited euphoric effects.                                                                                                                                                                               |
| Buprenorphine   | Blocks the rewarding effects of opioids, reduces withdrawal and the urge to use the drugs. | Partial agonist at μ-opioid receptors, blocks κ-opioid receptors. Unknown mechanism in reducing cocaine use in opioid-dependent patients.                                                                                                                                 |
| Methadone       | Blocks the rewarding effects of opioids, reduces withdrawal and urge to use the drugs. | Agonist at μ-opioid receptors; has unique pharmacokinetic and pharmacodynamic properties, including a long latency to peak blood concentrations (thereby minimizing its euphoric effects), a long half-life (reducing acute withdrawal symptoms), and opioid cross-tolerance (reducing euphoria from heroin and other short-acting opioids). Unknown mechanism in reducing cocaine use in opioid-dependent patients. |

NOTE: An agonist is a substance that binds to a specific receptor and triggers a response in the cell. For references see text, as well as Kranzler and Ciraulo 2005.
individuals by producing an aversive reaction to the drug and also may reduce the euphoria produced by the drug, although some studies note an increase in subjective “highs” (see table 3 for more details on the putative mechanism of action) (Baker et al. 2007; Sofuoglu and Kosten 2005; Voci and Elkashef 2005). Disulfiram also may delay the high from cocaine, decreasing its reinforcement value. Combined with associated increases in plasma concentrations of cocaine, patients may experience greater nervousness and increased cardiovascular strain, which are aversive (Hameedi et al. 1995; McCance-Katz et al. 1998). However, similar to what is seen in the treatment of alcohol dependence with disulfiram, adherence limits the utility of this medication in the treatment of cocaine dependence. Practical approaches to dealing with this problem include making access to a desired treatment (e.g., methadone for co-occurring opioid dependence) contingent on adherence or using social reinforcers (e.g., an agreement or contract between patient and spouse requiring adherence).

**Tiagabine.** A GABA reuptake inhibitor, tiagabine has yielded mixed results for the treatment of cocaine dependence (Gonzalez et al. 2007; Winhusen et al. 2005, 2007). In 2005, a black-box warning was added to the label for tiagabine, warning physicians of new-onset seizures that were noted in some patients (without a history of epilepsy) taking the medication (Gabatril® package insert).

**Modafinil.** Of particular interest in the treatment of cocaine dependence is modafinil because it has a mild stimulant-like effect and produces a mild euphoria (the exact nature of which has been debated in the literature). The drug appears to blunt the desirable effects and the craving associated with cocaine use and reduces cocaine use in a human laboratory setting, with little or no abuse potential (Hart et al. 2007; O’Brien et al. 2006).

**Naltrexone.** Most of the findings concerning the effects of naltrexone on cocaine dependence come from studies of patients with co-occurring alcohol and cocaine dependence (see below), although one study (Schmitz et al. 2001) evaluated its use in patients with only cocaine dependence. This study evaluated the effects of naltrexone in a prospective, randomized trial that compared four groups receiving placebo or naltrexone (50 mg) combined with either relapse prevention therapy or standard drug counseling. The group that received naltrexone combined with relapse prevention treatment outperformed the other three groups, supporting its use, but only in combination with that specific psychosocial intervention.

**Baclofen.** Some evidence of efficacy in treating cocaine dependence also has been shown with the use of baclofen (Shoptaw et al. 2003).

**Other Medications.** Antipsychotic medications do not appear useful for treating cocaine dependence (Amato et al. 2007). A vaccine that causes patients to develop antibodies to cocaine in the blood is in development and has shown promise in treating cocaine dependence (Martell et al. 2005).

**Opioid Dependence.** Opioid dependence in the United States is most often treated with behavioral treatment approaches combined with maintenance therapy with the opioid agonists methadone or buprenorphine. Considerable evidence supports the efficacy of these agents for opioid dependence treatment (Barnett et al. 2001; Connock et al. 2007; Johansson et al. 2007; Martick et al. 2003, 2004; Van den Brink and Haasen 2006). Although some patients are able to maintain abstinence from opioids following detoxification through involvement in self-help groups such as Narcotics Anonymous, many patients require treatment with opioid agonist medications, and some require maintenance treatment indefinitely. Methadone treatment of opioid dependence is available only through licensed methadone programs that monitor patients’ drug and alcohol use and sometimes provide treatment for co-occurring psychiatric disorders.

Opioid antagonists, including naltrexone (which is FDA approved for this indication), also can be used to treat opioid dependence in patients who are able to transition from physiologic dependence to abstinence. To avoid precipitating acute withdrawal, a patient should be free of opioid use for a minimum of 7 days before being treated with an opioid antagonist (Nunes et al. 2006). In a recent meta-analysis of naltrexone treatment of opioid dependence (Johansson et al. 2006), retention in treatment was a significant moderator of a beneficial effect of the drug. This likely reflects the key problem of adherence to naltrexone that is seen in treatment populations. However, behavioral therapies such as contingency management may appear to improve naltrexone adherence and treatment retention in this population (Nunes et al. 2006). Patients should be warned that death by overdose can occur despite opioid receptor blockade by naltrexone or after recent treatment with naltrexone (Gibson and Degenhardt 2007; Gibson et al. 2007).

Baclofen, which has shown some promise in the treatment of alcohol and cocaine dependence (see above), also has been evaluated as a maintenance treatment for opioid dependence (Assadi et al. 2003). In a 12-week, randomized, double-blind, placebo-controlled trial, baclofen was superior to placebo on treatment retention, opioid withdrawal symptoms, and depressive symptoms. However, there was no significant difference in terms of opioid use, alcohol use, opioid craving, or side effects.

**Cannabis Dependence.** There are no medications that have demonstrated efficacy for the treatment of cannabis dependence (Nordstrom and Levin 2007).

---

5 Tiagabine inhibits the reuptake of GABA by neurons, thus providing increased GABA availability.
TREATMENT OF AODUDS

As reviewed above, most studies have focused on the treatment of individual SUDs rather than co-occurring disorders. Although studies conducted specifically in AODUD populations are limited, the evidence to date suggests that approaches similar to those used to treat the individual SUDs may be effective. As with the treatment of dependence on individual substances, behavioral therapies provide the “backbone” or main component of treatment for patients with AODUDs. In addition, because the studies evaluating pharmacotherapies in AODUD patients almost always include at least one behavioral therapy component, this review does not examine these types of therapy separately. Table 4 summarizes the evidence for various individual treatments for AODUDs.

Contingency management has been shown to increase treatment retention and improve outcomes across a spectrum of addictive disorders, irrespective of psychiatric severity. Hence, contingency management may serve effectively as a platform for the treatment of AODUDs (Weinstock et al. 2007). A review of treatments for alcoholic methadone patients suggested that making methadone treatment contingent on disulfiram ingestion may effectively reduce drinking and alcohol-related adverse outcomes (Bickel et al. 1987). Along similar lines, contingency management using both prizes and vouchers has been shown to be beneficial for co-occurring opioid and cocaine/stimulant use disorders, as well as other co-occurring substance dependence disorders, including alcohol dependence (Peirce et al. 2006; Petry et al. 2000; Petry and Martin 2002; Prendergast et al. 2006).

Co-Occurring Alcohol and Cocaine Dependence

Similarities in the pathophysiology of cocaine and alcohol dependence suggest that these disorders may respond to the same medications (Johnson 2005). Carroll and colleagues (1998) examined the effects of disulfiram, CBT, and 12-step facilitation (TSF) on drinking and cocaine use in patients with these co-occurring disorders. Compared with no medication, disulfiram was efficacious in reducing the use of both drugs, and both CBT and TSF were superior to supportive counseling. In a 1-year follow-up, the effects of disulfiram on cocaine use persisted, but no effects were found on drinking behavior (Carroll et al. 2000). Other studies (Carroll et al. 2004; Nich et al. 2004) of disulfiram in cocaine-dependent subjects have shown that co-occurring alcohol use and dependence, as well as female gender, may actually limit the efficacy of the medication.

Hersh and colleagues (1998) found no advantage for naltrexone (50 mg/day) over placebo in the treatment of people with co-occurring cocaine and alcohol use disorders. In a randomized, controlled trial in which alcohol- and cocaine-dependent subjects received either naltrexone (50 mg/day) or placebo, combined with either relapse prevention or drug counseling psychotherapy, Schmitz and colleagues (2004) also found no effects of the medication. In a recent, 11-week comparison of disulfiram, naltrexone, or a combination of the two for the treatment of cocaine and alcohol dependence, study participants receiving disulfiram (alone or in combination) had

---

Table 4 Summary of Research on Treatments for AODUDs

|                | Alcohol/Cocaine | Alcohol/Opioid | Cocaine/Opioid |
|----------------|-----------------|----------------|----------------|
| Disulfiram     | +/- (B)         | +/- (B)**      | + (B)          |
| Naltrexone     | +/- (B)         | * (C)          | * (C)          |
| Buprenorphine  | + (B)           |               |               |
| Methadone      | +/- (C)         | + (B)          |               |
| Desipramine    | * (C)           | + (B)          |               |
| Topiramate     | * (C)           |               |               |
| Baclofen       | * (C)           |               |               |
| Tiagabine      | +/- (B)         |               |               |
| CBT            | + (B)           |               |               |
| CM             | +/- (B)         | + (B)          |               |
| TSF            | +/- (B)         |               |               |

NOTES: AODUDs = Alcohol and other drug use disorders, CBT = cognitive-behavioral therapy, CM = contingency management, TSF = twelve-step facilitation.

- * = recommendation synthesized from studies performed in primarily alcohol or cocaine dependent subjects, not specifically in the dually dependent group
- ** = may only be effective when continued opioid agonist therapy is made contingent on disulfiram ingestion.

For level of evidence supporting the use of therapies: (−) indicates that the treatment appears to be ineffective, (+/−) indicates conflicting results or preliminary evidence of efficacy, (+) indicates evidence of efficacy from randomized controlled trials, (++) indicates evidence of efficacy from multiple trials and/or meta-analyses.

Evidence-based strength of recommendation taxonomy (SORT; as defined by Ebell et al., 2004):
- (A) Recommendation based on consistent and good-quality patient-oriented evidence.
- (B) Recommendation based on inconsistent or limited-quality patient-oriented evidence.
- (C) Recommendation based on consensus, usual practice, opinion, disease-oriented evidence, or case series for studies of diagnosis, treatment, prevention, or screening.
higher rates of combined abstinence (to both alcohol and cocaine) than those on placebo (Pettinati et al. 2008b). The combination of disulfram and naltrexone was superior to either drug given alone, or placebo, on a secondary outcome measure (i.e., the achievement of 3 weeks of continuous abstinence). All the patients received concurrent CBT as a behavioral regimen. A study of 12 patients with co-occurring alcohol and cocaine dependence showed significant reductions in the use of both substances with the addition of naltrexone (50 mg/day) or disulfram (400 mg/day) to CBT, compared with CBT alone (Grassi et al. 2007).

Because topiramate (at a target dose of 300 mg/day) has demonstrated efficacy in studies of alcohol dependence (Johnson et al. 2003, 2007) and preliminary evidence of efficacy in studies of cocaine dependence (at a target dose of 200 mg/day) (Kampman et al. 2004), it may be an ideal candidate for the treatment of these disorders when they co-occur. Further, topiramate can be safely prescribed to patients taking buprenorphine or methadone, so it could be combined with other treatments for alcohol and drug dependence.

Although modafinil appears to be effective for reducing cocaine use in cocaine-dependent patients, a recent study showed that those with co-occurring alcohol dependence may not experience this benefit (Karila et al. 2007; Vocci and Elkashef 2005). Because alcohol use disorders may have a negative effect on outcomes for cocaine abuse treatment, particularly when patients continue to drink after initiating cocaine abuse treatment, addressing the use of both substances through combined treatment approaches may be optimal (Poling et al. 2007).

**Co-Occurring Opioid and Cocaine Dependence**

Buprenorphine appears dose-dependently to reduce cocaine use in opioid-dependent patients, although it does not appear to be any more effective than methadone for that purpose (Montoya et al. 2004, Oliveto et al. 1994; Schottenfeld et al. 1993, 1997). The addition of disulfram to buprenorphine or methadone may augment or facilitate abstinence from cocaine and opioids in patients dependent on both substances (Kosten et al. 2003, 2005; Oliveto et al. 1999).

Interestingly, in a placebo-controlled study comparing disulfram alone or in combination with contingency management in buprenorphine-maintained patients, the combined group did significantly better than the other groups on measures of cocaine use (Kosten et al. 2003). High-dose tiagabine (24 mg/day), in addition to methadone, also was superior to placebo in reducing cocaine use in patients dependent on both opioids and cocaine (Gonzalez et al. 2003, 2007). A double-blind, randomized, placebo-controlled trial of disulfram in methadone-maintained patients with co-occurring dependence on cocaine found that disulfram significantly decreased cocaine use in these patients (Petakis et al. 2000). George and colleagues (2000) also found disulfram to reduce cocaine use and increase the number of weeks of cocaine abstinence in buprenorphine-maintained patients with co-occurring cocaine dependence.

Two randomized controlled studies of bupropion in methadone-maintained patients have shown a possible role for the medication in the treatment of cocaine dependence. Margolin and colleagues (1995) compared bupropion with placebo in a 12-week study of 149 methadone-maintained patients with cocaine dependence. Although there was no overall difference in cocaine use between the two groups, a subgroup of patients that was depressed at the beginning of the study showed a significant reduction in cocaine use. Poling and colleagues (2006) conducted a 6-month trial of bupropion and contingency management in methadone-maintained patients with cocaine dependence. These investigators found that bupropion combined with contingency management reduced cocaine use. Although in this population bupropion on without contingency management has not been shown to be efficacious, combining the medication with contingency management may have a synergistic effect. No serious adverse events were reported in either study. However, as with cocaine, bupropion can lower the seizure threshold.

**Co-Occurring Opioid and Alcohol Dependence**

Preliminary research suggests that adequate dosing of methadone during maintenance treatment (achieved by increasing the dose until urine screens are negative for all opioids and benzodiazepines) may be effective in reducing both drug and alcohol use in patients with a co-occurring alcohol use disorder (Maremmani et al. 2007). As mentioned above, disulfiram appears to be efficacious in reducing drinking in this population but probably only when continued methadone maintenance is made contingent on disulfiram ingestion (Bickel et al. 1987).

Naltrexone, in both the oral and long-acting injectable forms, has been shown to be effective in treating detoxified opioid-dependent patients and thus can be considered for use in highly motivated individuals (Comer et al. 2006; Johansson et al. 2006; Nunes et al. 2006). However, the high cost of the only long-acting naltrexone formulation available in the United States, combined with reports of patient deaths from opioid overdose stemming from efforts to overcome the blockade produced by naltrexone, require that practical and ethical concerns be evaluated before this approach can be recommended widely to treat opioid dependence (Gibson and Degenhardt 2007; Gibson et al. 2007). Nonetheless, the use of naltrexone for selected patients (e.g., physicians) with opioid dependence appears justified. The use of naltrexone therapy in patients with alcohol dependence and a less severe form of co-occurring opioid use disorder (i.e., abuse rather than dependence, with no history of intravenous use) also may be a viable option because it does not present as great a risk of opioid overdose as may be present in...
patients with moderate to severe opioid dependence.

**TREATMENT Recommendations for Patients With AODUDs**

For patients with alcohol and cocaine dependence, disulfiram has better empirical support than any other medication. Less compelling evidence exists for the use of either naltrexone or topiramate, but these also should be considered for treatment of these co-occurring disorders. A daily dose of more than 50 mg of naltrexone is needed to treat these disorders but may not be efficacious for women with co-occurring alcohol and cocaine dependence. Topiramate has not yet been studied in AODUD patients, but its safety and efficacy have been demonstrated in patients with alcohol or cocaine dependence. Although the optimal dosage has not yet been determined, preliminary findings suggest that 200 to 300 mg per day, increased gradually over 6 to 8 weeks, is required. Second-line therapies may be effective in patients with cocaine dependence but not alcohol dependence (i.e., modafinil and tiagabine) or vice versa (i.e., acamprosate). Baclofen also could be considered for use in select patients based on evidence of its efficacy in alcohol or cocaine dependence. In addition to an absence of data on the efficacy of these medications in co-occurring alcohol and cocaine dependence, it is unclear whether these medications should be used alone or combined with first-line or other second-line agents. There is limited evidence to support combining disulfiram and naltrexone to treat co-occurring alcohol and cocaine dependence; further research on the combination is needed before it can be recommended as offering an advantage over the use of either medication alone.

For alcohol-dependent patients on methadone maintenance, optimizing the dosage of methadone may help to reduce drinking. Stabilizing opioid withdrawal symptoms and illicit opioid use with methadone or buprenor-

---

**Summary of General Treatment Recommendations**

Although the treatment literature is rapidly growing for individual SUDs, there is a paucity of systematic research on treatments for AODUDs. The existing literature shows that, as with DUDs alone, combined behavioral and psychopharmacological treatments for patients with AODUDs are likely to be optimal. At a minimum, patients should be encouraged to participate in a 12-step program and are likely to benefit from the addition of group or individual therapies that use motivational enhancement and cognitive-behavioral techniques. When available, the use of contingency management is likely to enhance outcomes for patients with AODUDs. The use of medications to improve outcomes in AODUD patients has shown initial promise, particularly for co-occurring alcohol and cocaine dependence.

Treatment planning for patients with AODUDs should include medical and psychiatric evaluations and integrated treatment to address co-occurring substance use and psychiatric disorders. Given the burden of psychopathology, patients with AODUDs often may require a higher level of care (e.g., inpatient rehabilitation, psychiatric partial hospital or intensive outpatient “dual diagnosis” programs) for initial stabilization. Medications with beneficial effects on drinking behavior and other drug use should be used in combination with behavioral interventions. In short, treatment for patients with AODUDs should start with a motivational intervention, with a focus on developing a therapeutic alliance. In these efforts, the clinician should be mindful of the patient’s stage of change and level of motivation, utilize empathic listening and expression, address the patient’s goals and needs, emphasize and promote self-regulation skills, utilize multiple treatment modalities, actively address co-occurring medical and psychiatric illness, and promote adherence to the treatment program.
ACKNOWLEDGMENTS

Supported by NIAAA grants P50 AA03510 and K24 AA13736.

FINANCIAL DISCLOSURE

Dr. Kranzler has received research support from Bristol-Myers Squibb and Ortho-McNeil Pharmaceuticals; consulting fees from Ortho-McNeil Pharmaceuticals, H. Lundbeck A/S, Forest Pharmaceuticals, elbion NV, Sanofi-Aventis, Solvay Pharmaceuticals, and Alkermes, Inc.; and honoraria from Forest Pharmaceuticals and Alkermes, Inc.

REFERENCES

ADDOLORATO, G.; LEGGIO, L.; FERRULLI, A.; ET AL. Effectiveness and safety of baclofen for maintenance of alcohol abstinence in alcohol-dependent patients with liver cirrhosis: Randomised, double-blind controlled study. Lancet 370(9603):1915–1922, 2007. PMID: 18068515

AMATO, L.; MINOZZI, S.; PANI, P.P.; AND DAVOLI, M. Antipsychotic medications for cocaine dependence. Cochrane Database of Systematic Reviews (3):CD006306, 2007. PMID: 17636840

American Society of Addiction Medicine. PPC-2R: ASAM Patient Placement Criteria for the Treatment of Substance-Related Disorders, S.E.-R. Chevy Chase, MD: American Society of Addiction Medicine, 2001.

ANTON, R.; BREDER, C.; HAN, J.; ET AL. Antipiriprazole in the treatment of alcohol dependence: Results from a multi-site study. Neuropsychopharmacology 31(S1): S200, 2006a.

ANTON, R.F.; O’MALLEY, S.S.; CIRAULO, D.A.; ET AL. Combined pharmacotherapies and behavioral interventions for alcohol dependence: The COMBINE study: A randomized controlled trial. JAMA: Journal of the American Medical Association 295(17):2003–2017, 2006a. PMID: 16670409

ASSADI, S.M.; RADGOODARZI, R.; AND AHMADI-ABBARI, S.A. Baclofen for maintenance treatment of opioid dependence: A randomized double-blind placebo-controlled clinical trial. BMC Psychiatry 3:16, 2003. PMID: 14627003

AUGER, R.R.; AND POTHAS, J.B. Delirium from baclofen withdrawal after suicide attempt. Psychosomatics 46(2):151–152, 2005. PMID: 15774955

BAKER, J.R.; JATLOW, P.; AND MCCANCE-KATZ, E.F. Disulfiram effects on responses to intravenous cocaine administration. Drug and Alcohol Dependence 87(2–3):202–209, 2007. PMID: 16979847

BARNETT, P.G.; ZARIC, G.S.; AND BRANDEAU, M.L. The cost-effectiveness of buprenorphine maintenance therapy for opiate addiction in the United States. Addiction 96(9):1267–1278, 2001. PMID: 11672491

BICKEL, W.K.; MARION, I.; AND LOWINSON, J.H. The treatment of alcoholic methadone patients: A review. Journal of Substance Abuse Treatment 4(1):15–19, 1987. PMID: 3302285

BOUZA, C.; ANGELES, M.; MUNOZ, A.; AND AMATE, J.M. Efficacy and safety of naltrexone and acamprosate in the treatment of alcohol dependence: A systematic review. Addiction 99(7):811–828, 2004. PMID: 15200577

BRADY, K.T.; MYRICK, H.; HENDERSON, S.; AND COFFEY, S.F. The use of divalproex in alcohol relapse prevention: A pilot study. Drug and Alcohol Dependence 67(3):323–330, 2002. PMID: 12127203

BROWN, E.; GARZA, M.; AND CARMODY, T. A randomized, double-blind, placebo-controlled trial of quetiapine in bipolar disorder and alcohol dependence (Abstract). Alcohol: Clinical and Experimental Research 31 (Suppl. 6):204:259A, 2007.

BROWN, E.S.; JEFFRESS, J.; LIGGIN, J.D.; ET AL. Switching outpatients with bipolar or schizoaffective disorders and substance abuse from their current antipsychotic to aripiprazole. Journal of Clinical Psychiatry 66(6):756–760, 2005. PMID: 15960570

CARROLL, K.M. Recent advances in the psychotherapy of addictive disorders. Current Psychiatry Report 7(5):329–336, 2005. PMID: 16216150

CARROLL, K.M., AND ONKEN, L.S. Behavioral therapies for drug abuse. American Journal of Psychiatry 162(8):1452–1460, 2005. PMID: 16055766

CARROLL, K.M.; FENTON, L.R.; BALL, S.A.; ET AL. Efficacy of disulfiram and cognitive behavior therapy in cocaine-dependent outpatients: A randomized placebo-controlled trial. Archives of General Psychiatry 61(3):264–272, 2004. PMID: 14993114

CARROLL, K.M.; NICH, C.; BALL, S.A.; ET AL. One-year follow-up of disulfiram and psychotherapy for cocaine-alcohol users: Sustained effects of treatment. Addiction 95(9):1335–1349, 2000. PMID: 11048353

CARROLL, K.M.; BERNDT, L.; BALL, S.A.; ET AL. Treatment of cocaine and alcohol dependence with psychotherapy and disulfiram. Addiction 93(5): 713–727, 1998. PMID: 9692270

CESELLO, M.A., AND STRAKOWSKI, S.M. The prevalence and significance of substance use disorders in bipolar type I and II disorder. Substance Abuse Treatment, Prevention, and Policy 2:29, 2007. PMID: 17908301

CHICK, J.; GOUGH, K.; FALKOWSKI, W.; ET AL. Disulfiram treatment of alcoholism. British Journal of Psychiatry 161:84–89, 1992. PMID: 1638335

CHICK, J.; LEHERT, P.; AND LANDRON, F. Does acamprosate improve reduction of drinking as well as aiding abstinence? Journal of Psychopharmacology 17(4):397–402, 2003.

COMER, S.D.; SULLIVAN, M.A.; YU, E.; ET AL. Injectable, sustained-release naltrexone for the treatment of opioid dependence: A randomized, placebo-controlled trial. Archives of General Psychiatry 63(2):210–218, 2006. PMID: 16461865

CONNOCK, M.; JUAREZ-GARCIA, A.; JOWETT, S.; ET AL. Methadone and buprenorphine for the management of opioid dependence: A systematic review and economic evaluation. Health Technology Assessment 11(9):1–171–iii–iv, 2007. PMID: 17313907

DAKE, R.E.; MUISER, K.T.; BRUNNETTE, M.F.; AND MCHugh, G.J. A review of treatments for people with severe mental illnesses and co-occurring substance use disorders. Psychiatric Rehabilitation Journal 27(4):360–374, 2004. PMID: 15222148

FREY, M.A., AND SALLOUM, I.M. Bipolar disorder and co-morbid alcoholism: Prevalence rate and treatment considerations. Bipolar Disorders 8(6):677–685, 2006. PMID: 17156154

FULLER, R.K.; BRANCHEY, L.; BRIGHTWELL, D.R.; ET AL. Disulfiram treatment of alcoholism: A Veterans Administration cooperative study. JAMA: Journal of the American Medical Association 256(11):1449–1455, 1986. PMID: 3528541

FULLER, R.K., AND GORDIS, E. Does disulfiram have a role in alcoholism treatment today? Addiction 99(1):21–24, 2004. PMID: 14678055

GARBUTT, J.C.; KRUNZLER, H.R.; O’MALLEY, S.S.; ET AL. Efficacy and tolerability of long-acting injectable naltrexone for alcohol dependence: A randomized controlled trial. JAMA: Journal of the American Medical Association 293(13):1617–1625, 2005. PMID: 15811981

GIBSON, A.E., AND DEGENHARDT, L.J. Mortality related to pharmacotherapies for opioid dependence: A comparative analysis of coronial records. Drug and Alcohol Review 26(4):405–410, 2007. PMID: 17564876

GIBSON, A.E.; DEGENHARDT, L.J.; AND HALL, W.D. Opioid overdose deaths can occur in patients with naltrexone implants. Medical Journal of Australia 186(3):152–153, 2007. PMID: 17309046

GONZALEZ, G.; SEVARINO, K.; SOFUOGLU, M.; ET AL. Tiagabine increases cocaine-free urines in cocaine-dependent methadone-treated patients: Results of a randomized pilot study. Addiction 98(11):1625–1632, 2003. PMID: 14616189

GONZALEZ, G.; DESAI, R.; SOFUOGLU, M.; ET AL. Clinical efficacy of gabapentin versus tiagabine for reducing cocaine use among cocaine dependent methadone-treated patients. Drug and Alcohol Dependence 87(1):1–9, 2007. PMID: 16930857

GRASSI, M.C.; CROCE, A.M.; GIUDICI, F.D.; ET AL. Short-term efficacy of disulfiram or naltrexone in
reducing positive urination for both cocaine and coacethylen in cocaine abusers: A pilot study. *Pharmacological Research* 55(2):117–121, 2007. PMID: 1714102

Gualdría, J.; Segura, L.; Gonzalo, B.; et al. A double-blind, placebo-controlled study of olanzapine in the treatment of alcohol-dependence disorder. *Alcoholism: Clinical and Experimental Research* 28(5):736–745, 2004. PMID: 15166648

Hameedi, F.A.; Rosen, M.L.; McCance-Katz, E.F.; et al. Behavioral, physiological, and pharmacological interaction of cocaine and disulfiram in humans. *Biological Psychiatry* 50(3):560–563, 1995. PMID: 7619981

Hart, C.L.; Haney, M.; Vosburg, S.K.; et al. Olanzapine in the treatment of alcohol-dependence disorder. *Neuropsychopharmacology* 33(4):761–768, 2008. PMID: 17568397

Hersh, D.; Van Kirk, J.R.; and Kranzler, H.R. Naltrexone treatment of co-morbid alcohol and cocaine use disorders. *Psychopharmacology (Berlin)* 139(1–2):44–52, 1998. PMID: 9765841

Hughes, J.C., and Cook, C.C. The efficacy of disulfiram: A review of outcome studies. *Addiction* 92(4):381–395, 1997. PMID: 9177060

Johansson, B.A.; Berglund, M.; and Lindgren, A. Efficacy of maintenance treatment with naltrexone for opioid dependence: A meta-analytical review. *Addiction* 101(4):491–503, 2006. PMID: 16548929

Johansson, B.A.; Berglund, M., and Lindgren, A. Efficacy of maintenance treatment with methadone for opioid dependence: A meta-analytical study. *Nordic Journal of Psychiatry* 61(4):288–295, 2007. PMID: 17763122

Johnson, B.A. Recent advances in the development of treatments for alcohol and cocaine dependence: Focus on topiramate and other modulators of GABA or glutamate function. *CNS Drugs* 19(10):873–896, 2005. PMID: 16185095

Johnson, B.A. Update on neuropharmacological treatments for alcoholism: Scientific basis and clinical findings. *Biochemical Pharmacology* 75(1):34–56, 2008. PMID: 17880925

Johnson, B.A.; Roache, J.D.; Javors, M.A.; et al. Onandetron for reduction of drinking among biologically predisposed alcoholic patients: A randomized controlled trial. *JAMA: Journal of the American Medical Association* 284(8):963–971, 2000. PMID: 10944641

Johnson, B.A.; Ait-Daoud, N.; Bowden, C.L.; et al. Oral topiramate for treatment of alcohol dependence: A randomised controlled trial. *Lancet* 361(9350):1677–1685, 2003. PMID: 12767733

Johnson, B.A.; Rosenthal, N.; Capece, J.A.; et al. Topiramate for treating alcohol dependence: A randomized controlled trial. *JAMA: Journal of the American Medical Association* 298(14):1641–1651, 2007. PMID: 17925516

Kampman, K.M.; Pettinati, H.; Lynch, K.G.; et al. A pilot trial of topiramate for the treatment of cocaine dependence. *Drug and Alcohol Dependence* 75(3):233–240, 2004. PMID: 15283944

Kampma, K.M.; Pettinati, H.M.; Lynch, K.G.; et al. A double-blind, placebo-controlled pilot trial of quetiapine for the treatment of type A and type B alcoholism. *Journal of Clinical Psychopharmacology* 27(4):344–351, 2007. PMID: 17632217

Karila, L.; Gorelick, D.; Weinstein, A.; et al. New treatments for cocaine dependence: A focused review. *International Journal of Neuropsychopharmacology* 11(3):425–438, 2008. PMID: 17927843

Kiefer, F.; Jain, H.; Tarnaske, T.; et al. Comparing and combining naltrexone and acamprosate in relapse prevention of alcoholism: A double-blind, placebo-controlled study. *Archives of General Psychiatry* 60(1):92–99, 2003. PMID: 12511176

Kleber, H.D.; Weiss, R.D.; Anton, R.F., Jr.; et al. Treatment of patients with substance use disorders, second edition. *American Psychiatric Association. American Journal of Psychiatry* 164(Suppl. 4):5–123, 2007. PMID: 17569411

Kosten, T.; Olveto, A.; Feinberg, A.; et al. Desipramine and contingency management for cocaine and opiate dependence in buprenorphine maintained patients. *Drug and Alcohol Dependence* 70(3):315–325, 2003. PMID: 12757969

Kosten, T.; Soffooglu, M.; Poling, J.; et al. Desipramine treatment for cocaine dependence in buprenorphine- or methadone-treated patients: Baseline urine results as predictor of response. *American Journal on Addictions* 14(1):8–17, 2005. PMID: 15804873

Kranzler, H.R., and Ciraulo, D.A., eds. *Clinical Manual of Addiction Psychopharmacology*. Washington, DC: American Psychiatric Publishing, 2005.

Kranzler, H.R., and Gage, A. Acamprosate efficacy in alcohol-dependent patients: Reanalysis of results from 3 pivotal trials. *American Journal on Addictions*, 2008. In press.

Kranzler, H.R.; Burleson, J.A.; Brown, J.; and Babor, T.F. Fluoxetine treatment seems to reduce the beneficial effects of cognitive-behavioral therapy in type B alcoholics. *Alcoholism: Clinical and Experimental Research* 20(9):1534–1541, 1996.

Kranzler, H.R., and Ciraulo, D.A., eds. *Targeted naltrexone for early problem drinkers*. Washington, DC: American Psychiatric Publishing, 2005.

Mann, K.; Lehter, P.; and Morgan, M.Y. The efficacy of acamprosate in the maintenance of abstinence in alcohol-dependent individuals: Results of a meta-analysis. *Alcoholism: Clinical and Experimental Research* 28(1):51–63, 2004. PMID: 14745302

Maremmani, I.; Pani, P.P.; Mellini, A.; et al. Alcohol and cocaine use and abuse among opioid addicts engaged in a methadone maintenance treatment program. *Journal of Addictive Diseases* 26(1):61–70, 2007. PMID: 17439869

Margolin, A.; Kostern, T.R.; Avants, S.K.; and et al. A multicenter trial of bupropion for cocaine dependence in methadone-maintained patients. *Drug and Alcohol Dependence* 40(2):125–131, 1995. PMID: 8745134

Mark, T.L.; Kranzler, H.R.; Song, X.; et al. Physicians’ opinions about medications to treat alcoholism. *Addiction* 98(5):617–626, 2003. PMID: 12751979

Martell, B.A.; Mitchell, E.; Poling, J.; et al. Vaccine pharmacotherapy for the treatment of cocaine dependence. *Biological Psychiatry* 58(2):158–164, 2005. PMID: 16038686

May, C.R. Baclofen overdose. *Annals of Emergency Medicine* 12(3):171–173, 1983. PMID: 6829997

McCance-Katz, E.F.; Kostern, T.R.; and Jatlow, P. Disulfiram effects on acute cocaine dependence. *Clinical Psychopharmacology and Neuroscience Reviews* (2):CD002207, 2003. PMID: 12804430

McCance-Katz, E.F.; Kostern, T.R.; and Jatlow, P. Disulfiram effects on acute cocaine administration. *Drug and Alcohol Dependence* 52(1):27–39, 1998. PMID: 9788003

McCauley, M.E., and Petry, N.M. The role of psychosocial treatments in pharmacotherapy for alcoholism. *American Journal on Addictions* 12 (Suppl. 1):S41–S52, 2003. PMID: 14972779

McDonald, N.J.; Festa, M.S.; and Wilkins, B. Teenage coma. *Journal of Pediatric and Child Health* 37(4):395–396, 2001. PMID: 11532062
Miller, W.R., ed. COMBINE Monograph Series, Volume I: Combined Behavioral Intervention Manual: A Clinical Research Guide for Therapists Treating People With Alcohol Abuse and Dependence. DHHS Publication No. (NIH) 04–5288. Bethesda, MD: NIAAA, 2004.

Minkoff, K., and Cline, C.A. Changing the world: The design and implementation of comprehensive continuous integrated systems of care for individuals with co-occurring disorders. *Psychiatric Clinics of North America* 27(4):727–743, 2004. PMID: 15550290

Monnelly, E.P.; Ciraulo, D.A.; Knapp, C.; et al. Qtetiapine for treatment of alcohol dependence. *Journal of Clinical Psychopharmacology* 24(5):532–535, 2004. PMID: 15349010

Montesos, J.R.; Flannery, B.A.; Pettinati, H.M.; et al. Predicting treatment response to naltrexone: The influence of craving and family history. *American Journal on Addictions* 10(3):258–268, 2001. PMID: 11579624

Montoya, I.D.; Gorelick, D.A.; Preston, K.L.; et al. Randomized trial of bupropion for treatment of concurrent opiate and cocaine dependence. *Clinical Pharmacology and Therapeutics* 75(1):34–48, 2004. PMID: 14749690

Mueller, T.T.; Stout, R.L.; Rudd, S.; et al. A double-blind, placebo-controlled pilot study of carbamazepine for the treatment of alcohol dependence. *Alcoholism: Clinical and Experimental Research* 21(1):86–92, 1997. PMID: 9046378

National Association of State Mental Health Program Directors/National Association of State Alcohol and Drug Abuse Directors. The New Conceptual Framework for Co-Occurring Mental Health and Substance Use Disorders. Washington, DC: National Association of State Mental Health Program Directors/National Association of State Alcohol and Drug Abuse Directors, 1998.

Nich, C.; McCance-Katz, E.F.; Petrakis, I.L.; et al. Sex differences in cocaine-dependent individuals’ response to disulfiram treatment. *Addictive Behaviors* 29(6):1123–1128, 2004. PMID: 15236812

Nordstrom, B.R., and Levin, F.R. Treatment of cannabis use disorders: A review of the literature. *American Journal on Addictions* 16(5):331–342, 2007. PMID: 17882603

Nunes, E.V.; Rothenberg, J.L.; Sullivan, M.A.; et al. Behavioral therapy to augment oral naltrexone for opioid dependence: A ceiling on effectiveness? *American Journal of Drug and Alcohol Abuse* 32(4):503–517, 2006. PMID: 17127538

O'Brien, C.P.; Dackis, C.A.; and Kampman, K. Does modafinil produce euphoria? *American Journal of Psychiatry* 163(6):1109, 2006. PMID: 16741217

Olvetto, A.; Kosten, T.; Schottenfeld, R.; et al. Cocaine use in buprenorphine- vs methadone-maintained cocaine users. *American Journal on Addictions* 3:43–48, 1994.

Olvetto, A.H.; Feingold, A.; Schottenfeld, R.; et al. Desipramine in opioid-dependent cocaine abusers maintained on buprenorphine vs methadone. *Archives of General Psychiatry* 56(9):812–820, 1999. PMID: 12884887

Oslin, D.W.; Pettinati, H.M.; Volpicelli, J.R.; et al. The effects of naltrexone on alcohol and cocaine use in dually addicted patients. *Journal of Substance Abuse Treatment* 16(2):163–167, 1999. PMID: 10023615

Peirce, J.M.; Petry, N.M.; Sitter, M.L.; et al. Effects of lower-cost incentives on stimulant abstinence in methadone maintenance treatment: A National Drug Abuse Treatment Clinical Trials Network study. *Archives of General Psychiatry* 63(2):201–208, 2006. PMID: 16461864

Perry, H.E.; Wright, R.O.; Shannon, M.W.; and Woolf, A.D. Baclofen overdose: Drug experimentation in a group of adolescents. *Pediatrics* 101(6):1045–1048, 1998. PMID: 9606233

Petrakis, I.L.; Carroll, K.M.; Nich, C.; et al. Disulfiram treatment for cocaine dependence in methadone-maintained opioid addicts. *Addiction* 95(2):219–228, 2000. PMID: 10723850

Petry, N.M., and Martin, B.; Cooney, J.L.; and Kranzler, H.R. Give them prizes and they will come: Contingency management for treatment of alcohol dependence. *Journal of Consulting and Clinical Psychology* 68(2):250–257, 2000. PMID: 10780125

Petry, N.M., and Martin, B. Low-cost contingency management for treating cocaine- and opioid-abusing methadone patients. *Journal of Consulting and Clinical Psychology* 70(2):398–405, 2002. PMID: 11952198

Pettinati, H.M.; Kampman, K.M.; Lynch, K.G.; et al. A double blind, placebo-controlled trial that combines disulfiram and naltrexone for treating co-occuring cocaine and alcohol dependence. *Addictive Behaviors* 33(5):651–667, 2008a. PMID: 18079068

Pettinati, H.M.; Kampman, K.M.; Lynch, K.G.; et al. Gender differences with high-dose naltrexone in the patients with co-occurring cocaine and alcohol dependence. *Journal of Substance Abuse Treatment* 34(4):378–390, 2008a. PMID: 17664051

Pettinati, H.M.; Volpicelli, J.R.; Kranzler, H.R.; et al. Sertraline treatment for alcohol dependence: Interactive effects of medication and alcoholic subtype. *Alcoholism: Clinical and Experimental Research* 24(7):1041–1049, 2000a. PMID: 10924008

Pettinati, H.M.; Volpicelli, J.R.; Pierce, J.D.; et al. and O'Brien, C.P. Improving naltrexone response: An intervention for medical practitioners to enhance medication compliance in alcohol dependent patients. *Journal of Addictive Diseases* 19(1):71–83, 2000b. PMID: 10772604

Pettinati, H.M.; Weiss, R.D.; Miller, W.R.; et al. COMBINE Monograph Series, Volume 2: Medical Management Treatment Manual: A Clinical Research Guide for Medically Trained Clinicians Providing Pharmacotherapy as Part of the Treatment for Alcohol Dependence. DHHS Publication No. (NIH) 04–5289. Bethesda, MD: NIAAA, 2004.

Polog, J.; Kosten, T.R.; and Sofuoglu, M. Treatment outcome predictors for cocaine dependence. *American Journal of Drug and Alcohol Abuse* 33(2):191–206, 2007. PMID: 17497542

Poling, J.; Olvetto, A.; Petry, N.; et al. Six-month trial of bupropion with contingency management for cocaine dependence in a methadone-maintained population. *Archives of General Psychiatry* 63(2):219-228, 2006. PMID: 16461866

Prendergast, M.; Poskus, D.; Finney, J.; et al. Contingency management for treatment of substance use disorders: A meta-analysis. *Addiction* 101(11):1546–1560, 2006. PMID: 17034434

Rubio, G.; Ponce, G.; Rodriguez-Jimenez, R.; et al. Clinical predictors of response to naltrexone in alcoholic patients: Who benefits most from treatment with naltrexone? *Alcohol and Alcoholism* 40(3):227–233, 2005. PMID: 15797885

Saloum, I.M.; Cornelius, J.R.; Daley, D.C.; et al. Efficacy of valproate maintenance in patients with bipolar disorder and alcoholism: A double-blind placebo-controlled study. *Archives of General Psychiatry* 62(1):37–45, 2005. PMID: 15630071

Schmitz, J.M.; Stotts, A.L.; Sayre, S.L.; et al. Treatment of cocaine-alcohol dependence with naltrexone and relapse prevention therapy. *American Journal on Addictions* 13(4):333–341, 2004. PMID: 15370932

Schottenfeld, R.S.; Pakes, J.; Ziedonis, D.; and Kosten, T.R. Buprenorphine: Dose-related effects on cocaine and opioid use in cocaine-abusing opioid-dependent humans. *Biological Psychiatry* 34(1–2):66–74, 1993. PMID: 8373940

Schottenfeld, R.S.; Pakes, J.R.; Olvetto, A.; et al. Buprenorphine vs methadone maintenance treatment for concurrent opioid dependence and cocaine abuse. *Archives of General Psychiatry* 54(8):713–720, 1997. PMID: 9283506

Schmitz, J.M.; Stotts, A.L.; Richers, H.M.; and Gerakowski, J. Naltrexone and relapse prevention treatment for cocaine-dependent patients. *Addictive Behaviors* 26(2):167–180, 2001. PMID: 11316375

Shoptaw, S.; Yang, X.; Rotheram-Fuller, E.J.; et al. Randomized placebo-controlled trial of baclofen for cocaine dependence: Preliminary effects for individuals with chronic patterns of cocaine use. *Journal of Clinical Psychiatry* 64(12):1440–1448, 2003. PMID: 14728105

Sofuoglu, M., and Kosten, T.R. Novel approaches to the treatment of cocaine addiction. *CNS Drugs* 19(1):13–25, 2005. PMID: 15651902

Spanagel, R., and Ziegglansberger, W. Anti-craving compounds for ethanol: New pharmacological tools to study addictive processes. *Trends in Pharmacological Sciences* 18(2):54–59, 1997. PMID: 9090311

Srisurapanont, M., and Jarusurasin, N. Opioid antagonists for alcohol dependence.
Treatment of Co-Occurring AODUDs

Cochrane Database of Systematic Reviews
(1):CD001867, 2005. PMID: 15674887

STINSON, F.S.; GRANT, B.F.; DAWSON, D.A.; ET AL. Co-morbidity between DSM-IV alcohol and specific drug use disorders in the United States: Results from the National Epidemiologic Survey on Alcohol and Related Conditions. Drug and Alcohol Dependence 80(1):105–116, 2005. PMID: 16157233

SUH, J.J.; PETTINATI, H.M.; KAMPMAN, K.M.; O’BRIEN, C.P. The status of disulfiram: A half of a century later. Journal of Clinical Psychopharmacology 26(3):290–302, 2006. PMID: 16702894

VAN DEN BRINK, W., AND HAASEN, C. Evidence-based treatment of opioid-dependent patients. Canadian Journal of Psychiatry 51(10):635–646, 2006. PMID: 17052031

VERHEUL, R.; LEHERT, P.; GEERLINGS, P.J.; ET AL. Predictors of acamprosate efficacy: Results from a pooled analysis of seven European trials including 1485 alcohol-dependent patients. Psychopharmacology (Berl) 178(2–3):167–173, 2005. PMID: 15322728

VOCCI, F.J., AND ELMASHEF, A. Pharmacotherapy and other treatments for cocaine abuse and dependence. Current Opinions in Psychiatry 18(3):265–270, 2005. PMID: 16639150

VOLPICELLI, J.R.; VOLPICELLI, L.A.; AND O’BRIEN, C.P. Medical management of alcohol dependence: Clinical use and limitations of naltrexone treatment. Alcohol and Alcoholism 30(6):789–798, 1995. PMID: 8679021

WEINSTOCK, J.; ALESSI, S.M.; AND PETRY, N.M. Regardless of psychiatric severity the addition of contingency management to standard treatment improves retention and drug use outcomes. Drug and Alcohol Dependence 87(2–3):288–296, 2007. PMID: 17005329

WINHUSEN, T.; SOMOZA, E.; CRAULIO, D.A.; ET AL. A double-blind, placebo-controlled trial of tiagabine for the treatment of cocaine dependence. Drug and Alcohol Dependence 91(2–3):141–148, 2007. PMID: 17629631

WINHUSEN, T.M.; SOMOZA, E.C.; HARRER, J.M.; ET AL. A placebo-controlled screening trial of tiagabine, sertraline and donepezil as cocaine dependence treatments. Addiction 100 (Suppl.1):68–77, 2005. PMID: 15730351

ZANIS, D.A.; MCELLEN, A.T.; ALTERMAN, A.I.; AND CNAAN, R.A. Efficacy of enhanced outreach counseling to reenroll high-risk drug users 1 year after discharge from treatment. American Journal of Psychiatry 153(8):1095–1096, 1996. PMID: 8678182