

Incorporating Alcohol Pharmacotherapies Into Medical Practice: A Review of the Literature—Updates*

A Treatment Improvement Protocol

TIP 49

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Incorporating Alcohol Pharmacotherapies Into Medical Practice.



Treatment Improvement Protocol (TIP) 49,
Incorporating Alcohol Pharmacotherapies Into
Medical Practice

Updated Findings From the Literature

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Introduction

The following updates were developed to keep current the literature review component of Treatment Improvement Protocol (TIP) 49, *Incorporating Alcohol Pharmacotherapies Into Medical Practice*, published in 2009. The literature review update period for this TIP spanned 3 years post-publication and concluded with the February–July, 2012 update. The same search methodology used in developing the literature review for TIP 49 was used for the updates.

October 1, 2007, Through October 31, 2009

No findings radically alter conclusions drawn from previous studies.

Findings on Disulfiram

Patient adherence to disulfiram treatment regimens remains a challenge. Elbreder, De Humerez, and Laranjeira (2009) conducted a transversal study of 810 subjects who were alcohol dependent (158 women) in Brazil to observe the relationship between outpatient treatment for alcohol use disorders (AUDs) and adherence to disulfiram regimens. Patients tended to have severe alcohol dependence and to belong to low socioeconomic classes. Elbreder and colleagues found that the length of outpatient treatment was directly proportional to disulfiram use; patients who remained in treatment for 1 year used more disulfiram than patients who dropped out of treatment after 1 month. The authors conclude that disulfiram should be considered a part of a holistic approach to alcoholism therapy, not the primary mode of treatment.

Findings on Oral Naltrexone

What influences efficacy?

To learn whether the efficacy of naltrexone depends on length of treatment or type of psychosocial therapy that accompanies it, Longabaugh, Wirtz, Gulliver, and Davidson (2009) hypothesized that broad-spectrum treatment (BST) and 24 weeks of naltrexone use would delay time to first heavy drinking day compared with three other treatments: 12 weeks of naltrexone with BST; 12 weeks of naltrexone with motivational enhancement therapy (MET); and 24 weeks of naltrexone with MET. For the first 12 weeks (Phase 1), all patients received naltrexone and one of the two forms of therapy. For the second 12 weeks (Phase 2), half the patients in both the MET and BST groups were given placebo instead of naltrexone. The primary measure was time to first heavy drinking day after the first 12 weeks of the study. Percentage of days abstinent (PDA) and percentage of heavy drinking days (PHDD) were secondary outcomes. (These results are reported in Davidson and colleagues, 2007.) Phase 3 measured drinking outcomes for 60 weeks following Phase 1. Researchers found that patients with 24 weeks of naltrexone and BST had relapsed to heavy drinking at 61 days compared with an average of 24 days before relapse for patients in the other three groups. However, 24 weeks of naltrexone and BST did not lead to improvement in PDA or PHDD, in general, over the course of Phase 3.

Targeted naltrexone to reduce drinking

Kranzler and colleagues (2009) conducted a 12-week, placebo-controlled study of 163 subjects to learn whether targeted naltrexone could reduce the amount of alcohol consumed (abstinence was not a goal). Subjects took naltrexone (or a placebo) daily or before an anticipated episode of heavy drinking. All patients received skills training every 2 weeks by trained counselors. The primary outcome measure was average number of drinks per day; the secondary outcome measure was average number of drinks per drinking episode. Patients with psychiatric or physical comorbidities, including clinically severe alcohol dependence, were excluded from the trial.

One hundred thirty-eight patients (84.7 percent) completed the treatment. Patients self-reported their drinking daily by telephone to an automated system. Patients who took naltrexone on a targeted basis (before a drinking episode) drank 16.5 percent less per day than those who took naltrexone daily and those who took a placebo on a targeted or daily basis. However, this effect was not significant. At week 12, patients on targeted naltrexone drank 19 percent less per drinking episode than the mean of other groups combined ($P=0.027$).

Adherence rates in practice

Kranzler, Stephenson, Montejano, Wang, and Gastfriend (2008) consulted a national prescription database to analyze patient adherence to naltrexone treatment in clinical practice, as opposed to in pharmaceutical trials. They found that, of 1,138 patients prescribed naltrexone, only 14.2 percent refilled their prescriptions for the full 6-month treatment period. The rest (85.8 percent) refilled their prescriptions for 80 percent or less of the treatment period, and more than half (51.8 percent) filled only one prescription. The percentage of patients who did not adhere to naltrexone treatment is likely higher than 86 percent, because patients prescribed naltrexone who did not fill even one prescription were not included in the database, and there was no way to determine whether patients took naltrexone after they filled their prescriptions.

Naltrexone in patients with comorbid psychiatric disorders

A small study ($N=50$) by Brown and colleagues (2009) examined the effects of naltrexone on patients with comorbid AUD and bipolar disorder. About half the patients completed the 12-week study (14 in the naltrexone group and 12 in the placebo group). The study measured average number of drinks per day and average number of drinks per drinking day. Naltrexone had a modest effect on amount of alcohol consumed in both measures, but findings did not reach significance.

Findings on Extended-Release Injectable Naltrexone

Dosing according to patient subpopulation

Dunbar, Turncliff, Hayes, and Farrell (2007) conducted a population pharmacokinetics analysis of 453 subjects to examine whether the pharmacokinetics of extended-release injectable naltrexone (XR-NTX) and 6b-naltrexol (its primary metabolite) differed across various patient subpopulations. The subpopulations were specified by age, gender, weight, health status (healthy, alcohol dependent, or alcohol and opioid dependent), smoker status, creatinine clearance, and serum levels of aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, gamma glutamyltransferase, and total bilirubin. The study found some statistically significant differences (e.g., that naltrexone clearance depends on age, weight, and health status), but no clinically significant differences were noted. The authors conclude that adjusting dosage according to patient subpopulation is unnecessary.

Onset of efficacy

Ciraulo, Dong, Silverman, Gastfriend, and Pettinati (2008) conducted a post hoc study of Garbutt and colleagues (2005) to learn the time to onset of efficacy for XR-NTX. Patients were randomized to 380 mg or 190 mg of XR-NTX or placebo, and they received 12 weeks of low-

intensity counseling (see p. 1-10 of the main literature review of TIP 49 for a different analysis of the same study). Researchers found that patients in each group reported reduced drinking immediately after treatment began (day 1). On day 2, patients receiving 380 mg of XR-NTX reported consuming fewer drinks per day than patients in the placebo group. On day 3, patients receiving 380 mg reported a reduction in drinking that was significantly lower than the placebo group (20 percent of these patients reported a heavy drinking day, compared with 35 percent of patients in the placebo group). Researchers conclude that the benefit of XR-NTX is observed in the first month of treatment and in the days immediately following initiation of treatment. The majority of patients who responded early to XR-NTX were more likely to be stable throughout the 6-month treatment period.

Findings on Acamprosate

Starting acamprosate during detoxification

A small (N=40) study that compared the effects of starting acamprosate during detoxification with those of starting acamprosate after detoxification found that there were no benefits to beginning acamprosate during detoxification (Kampman et al., 2009). In fact, compared with patients taking a placebo, patients who began acamprosate during detoxification had worse drinking outcomes at the end of the 12-week trial. The study found no significant differences between the placebo group and the acamprosate group in percentage that completed detoxification, time to achieve detoxification, Clinical Institutes Withdrawal Scale for Alcohol scores, number of 15 mg oxazepam tablets needed during detoxification, or drinking during detoxification. Acamprosate also did not improve patient retention in the rehabilitation phase, and acamprosate was associated with more drinks per drinking day and more days of heavy drinking during the rehabilitation phase, compared with a placebo.

Cue-induced craving

Hammarberg, Jayaram-Lindström, Beck, Franck, and Reid (2009) studied whether acamprosate had any effect on alcohol craving brought on by cues or priming (ingestion). In this study, patients who took acamprosate before craving tests reported less craving after consuming an alcoholic beverage than patients who took a placebo. Fifty-six patients were randomized to receive a placebo or acamprosate for 21 days. On day 21, the 42 patients who completed the initial phase of the study were given (1) an alcohol-cue session, in which they were presented with a tray of various bottles of alcohol and asked to talk about them and to select their favorite beverage; (2) a nonalcohol-cue session, in which patients followed the same procedure for juice, soda, and other nonalcoholic beverages; (3) a priming dose session, in which patients consumed as much of a standard alcoholic drink of their choice as they liked; and (4) an alcohol-choice paradigm, in which patients were asked hypothetically to choose between a drink and a small amount of money.

The primary subjective measure of craving was measured using the Desire for Alcohol Questionnaire (DAQ) short form and the Visual Analog Scale (VAS). Following the alcohol-cue session, there were no significant differences in DAQ or VAS scores between the two groups. Following the alcohol priming session, only patients on placebo had raised DAQ and VAS

scores. There were no differences between the two groups in the amount of alcohol consumed in the priming session.

Findings on Combined Medication Therapy

Zweben and colleagues (2008) looked at COMBINE data among the 1,226 patients randomized to 8 medication or placebo groups to analyze the relationship between adherence rates and drinking outcomes (PDA and time to first heavy drinking day, defined as 5 or more drinks for men and 4 or more for women). Adherence was defined as taking 80 percent or more of the prescribed medication or placebo.

Researchers found that a combination of medications resulted in lower adherence rates: Patients taking both naltrexone and acamprosate had lower overall adherence rates than patients taking only a placebo, and patients taking naltrexone and acamprosate had lower adherence than those taking only naltrexone. Patients who did not take their medications regularly were more likely than patients who adhered to treatment to stop taking medications altogether. Adding combined behavioral interventions (CBI) to medical management (MM) treatment did not increase adherence.

As predicted, patients who adhered to medications or placebo had better PDA outcomes than patients who did not adhere (82 percent and 72 percent, respectively). Among patients who adhered to treatment, the highest PDAs were among patients treated with naltrexone and MM only (no CBI) (80 percent), and the worst PDAs were among patients treated with placebo and MM only (74 percent).

Adherence to treatment also increased time to first heavy drinking day outcomes. Forty percent of patients who adhered to treatment of placebo and MM only avoided relapse to heavy drinking during the study period, compared with 10 percent of patients in the same treatment group who did not adhere. For placebo-treated patients who did not adhere, the addition of CBI increased rates of avoiding relapse for 25 percent.

Among patients assigned naltrexone and MM only, those who adhered avoided relapse at nearly twice the rate of those who did not adhere (42 percent versus 22 percent, respectively). The addition of CBI did not significantly increase adherence or reduce relapse rates among patients treated with naltrexone.

Donovan, Anton, Miller, Longbaugh, Hosking, and Youngblood (2008) studied the effects of COMBINE interventions for 1 year after treatment (weeks 16–68) by measuring PDA and time to first heavy drinking day. PDA was determined in each 4-week period throughout the year, starting with data gathered at the end of week 16. Followup rates were comparable across treatment groups. Across all treatment conditions (including placebo groups), overall good clinical outcomes (defined as no drinking or moderate drinking with no problems) were 71 percent at week 16, 54 percent at week 26, 42 percent at week 52, and 46 percent at week 68. The only significant association with good clinical outcome was CBI; this finding contrasts with findings of the value of CBI during the 16-week treatment phase. Patients who had received CBI were 20 percent more likely to have good outcomes at week 68, although the effects of CBI diminished over the study period after treatment.

Patients tended to drink more (reduced PDA) from weeks 16 to 68 regardless of medication group. The combined average PDA of treatment groups was 68 percent at week 26 and 63 percent at week 68. Regarding time to first heavy drinking day, patients who had received naltrexone during the treatment period were less likely to relapse or took longer to relapse to heavy drinking than patients in the placebo group. No significant effects of acamprosate were found.

A 2009 study by Bogenschutz, Tonigan, and Pettinati using COMBINE data to match patient to treatment is described below.

Matching Patient to Treatment

Data remain mixed on whether the modest results seen to date on pharmacologic treatment for alcoholism could be improved by matching patients to treatment.

Type of alcoholism

Bogenschutz, Tonigan, and Pettinati (2009) looked at COMBINE data to determine whether patients with Type B alcohol dependence responded better to naltrexone treatment than patients with Type A alcohol dependence. (These types are described in the main literature review, p. 1-4.) The study sample included patients randomized to four treatment groups (MM and naltrexone, MM and naltrexone plus acamprosate, MM and naltrexone plus CBI, and MM and naltrexone plus acamprosate and CBI). Patients provided enough information to be confidently assigned to an alcoholism type. Data for the 618 patients who met the criteria were taken from the 16-week measures collected at the end of active treatment.

Researchers found that the benefits of naltrexone were limited to patients with Type A alcohol dependence who received MM but not CBI. For these patients, PDA was 25 percent for patients treated with naltrexone compared with 36 percent for those treated with a placebo. PHDD was 18 percent for patients treated with naltrexone compared with 32 percent for those treated with a placebo. Results for patients with Type B alcohol dependence did not reach significance. Researchers also found that adherence to medication did not alter the findings (c.f. Zweben et al., 2008, above).

Gender

Baros, Latham, and Anton (2008) looked at why Garbutt and colleagues (2005) and Hernandez-Avila and colleagues (2006) reported that women do not respond as well to naltrexone compared with men and hypothesized that small sample size of women and endpoint measures may have caused that finding. Baros and colleagues combined data from two similar placebo-controlled trials (Anton et al., 1999, 2005) to improve the ratio of women to men. Subjects were administered naltrexone or a placebo, and both groups received cognitive-behavioral therapy. The combined studies yielded 211 people (57 women, 27 percent). Baros and colleagues found that women on naltrexone had significantly higher PDAs than women on placebo. However, when compared with the larger sample size, only men showed significant effects on PDA, PHDD, drinks per drinking day, and other measures.

Genes

Using a sample from a previous study (Ooteman, Koeter, Verheul, Schippers, & Van den Brink, 2007), Ooteman and colleagues (2009) studied the effects of acamprosate and naltrexone on cue-induced craving and its association with genetic indicators. They hypothesized that naltrexone would primarily benefit patients motivated by reward drinking (mediated by the dopaminergic and opioidergic genotypes), whereas acamprosate would primarily benefit patients motivated by negative reinforcement or relief drinking (GABAergic and glutamatergic genotypes). Patients received 3 weeks of acamprosate or naltrexone. Of the 108 patients who completed the study, most had moderate to severe alcohol dependence. Craving was measured on the day before medication began and on day 21, and differences were computed. Craving was measured by patient report (using the VAS) and heart rate (using electrocardiogram). The tested polymorphisms for reward drinking were OPRM1 (alleles A118G), DRD1 (alleles D21403D1), and DRD2 (alleles TaqI A1/A2). Polymorphisms for relief drinking were GRIN2B (alleles C2664T), GABRA6 (alleles T1519C), GABRAB2 (alleles C1412T), and GABRG2 (alleles C2664T).

Significant effects on induced craving were found for three of the seven genotypes (DRD2, GABRA6, and GABRAB2), and effects were related to specific polymorphism. Although this study did not completely support the hypothesis, the researchers conclude that genetic matching holds promise for increased medication effectiveness and warrants further study.

Using DNA from 1,013 participants in the COMBINE study, Anton and colleagues (2008) found that patients with at least one copy of the A118G allele had an 87-percent chance of a good outcome if randomized to naltrexone. Ooteman and colleagues (2009) also reported a trend for the OPRM1 polymorphism.

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Findings on Disulfiram

Two studies added to the literature on disulfiram. A Danish study randomized 39 subjects to disulfiram and cognitive-behavioral therapy (CBT) or to a placebo and CBT (Ulrichsen, Nielsen, & Ulrichsen, 2010). After 6 months of supervised treatment, researchers found no significant differences between the two groups in abstinence from alcohol intake during the study period, time to first drink, number of alcohol-free days, or completion of CBT.

Diehl and colleagues (2010) retrospectively compared the long-term effectiveness of disulfiram and acamprosate in 353 subjects, who had been alcohol dependent an average of 13.5 years. Thirty-eight percent had a co-occurring psychiatric disorder, such as depression or anxiety. The 108 subjects in the disulfiram group tended to be younger, less educated, and employed less than subjects in the acamprosate group (n=245). In addition, subjects in the disulfiram group had had an alcohol use disorder (AUD) for more years, consumed higher amounts of alcohol daily, and had been in detoxification programs more often than those in the acamprosate group. Another significant difference was that 20.4 percent of patients in the disulfiram group had other substance use disorders (SUDs) in addition to alcohol dependence, compared with 9.8 percent in the acamprosate group.

Nevertheless, compared with the acamprosate group, subjects in the disulfiram group had significantly longer times until relapse (1 month versus 3.5 months, respectively). Subjects in the disulfiram group also attended outpatient treatment significantly longer than subjects in the acamprosate group (14.9 months, compared with 2.7 months). The disulfiram group was abstinent an average of 9.75 months, compared with 2 months for the acamprosate group. The authors attribute part of the success seen in the disulfiram group to the high frequency of contact required to treat subjects with disulfiram.

Findings on Oral Naltrexone

One new trial on oral naltrexone compared treatments for subjects with alcohol dependence and co-occurring depression (Pettinati et al., 2010). Subjects (N=170) were randomized into one of four groups to receive 14 weeks of naltrexone plus an antidepressant (sertraline), sertraline plus a placebo, naltrexone plus a placebo, or a double placebo. All subjects received weekly CBT. Subjects excluded from the trial included those with other SUDs (besides tobacco), as well as those with bipolar affective disorder, schizophrenia, or other psychiatric diseases. The study compared depression scores (using the Hamilton Depression Rating Scale [HAM-D]), days abstinent, and time to relapse among the groups.

Subjects were largely white and male and had an average of 14 years of education. The average length of AUD was 21 years. At the beginning of the study, the average number of drinks on any drinking day was 12, and the HAM-D score averaged 23.

Across the 14 weeks, adherence rates averaged 87 percent and did not differ significantly among groups. Subjects in the naltrexone plus antidepressant group had significantly better drinking

outcomes than subjects in the other three groups. More subjects (53.7 percent) in the naltrexone plus antidepressant group were abstinent for the 14 weeks than subjects in the other groups combined. Subjects in the naltrexone plus antidepressant group also drank less heavily and had longer time to relapse relative to subjects in other groups. The percentage of subjects who were not depressed at the end of treatment was significantly greater in the naltrexone plus antidepressant group when compared with all other groups combined, although there was no statistical difference when comparing depression scores across all groups (Pettinati et al., 2010).

Ray and Oslin (2009) looked at COMBINE data to assess the effectiveness of naltrexone in African Americans. Of the 1,383 participants enrolled in the COMBINE study, 100 were African American. Of these, 51 received naltrexone (with or without acamprosate) and 49 received a placebo. Participants were largely male (70 percent), and the average age was 44. Data analysis showed no significant difference in percentage of days abstinent or time to first heavy drinking day for African-American subjects treated with naltrexone. These findings cannot be generalized to imply that no African Americans will benefit from naltrexone; more studies are needed.

Findings on Extended-Release Injectable Naltrexone

Lee and colleagues (2010) studied the feasibility of using extended-release injectable naltrexone (XR-NTX) coupled with medical management (MM) in a primary care setting. The open-label study was conducted at two primary care clinics in lower Manhattan. The average age of subjects was 46, most were white and male, and 93 percent were binge drinkers. MM was provided at the time of the subjects' monthly XR-NTX injection. Physicians were trained on MM concepts and recorded progress on a standardized form, but MM delivery itself was not standardized in this study. No incentives were offered to patient for their participation; however, those who returned for the final data collection visit (month 4) received \$20. Sixty-five subjects started the trial and received the first injection, 49 received the second injection, and 40 received all three injections. Subjects who received all three injections decreased drinks consumed per day from a median of 4.1 to 0.5. The authors conclude that retention rates and success rates suggest that primary care settings may be a feasible venue for XR-NTX treatment.

Findings on Acamprosate

A small (N=56) study in Sweden contributed to the debate on whether acamprosate reduces craving for alcohol (as opposed to alcohol consumption) in people with AUDs (Hammarberg et al., 2009). Subjects were randomized to 21 days of treatment with acamprosate or a placebo. Craving was measured through a self-report tool (Obsessive Compulsive Drinking Scale) at baseline and at day 21, and results were compared. At day 21, both groups reported a significant reduction in craving, but the difference was greater for subjects treated with acamprosate.

Kennedy and colleagues (2010) published a review of acamprosate trials from 1995 through 2009. Their key conclusions are as follows:

- Acamprosate is a safe and effective medication to help subjects maintain abstinence from alcohol; most side effects are mild.
- U.S. studies failed to show the benefit of acamprosate over a placebo. Unlike European trials that showed efficacy, U.S. trials (including the COMBINE study) enrolled subjects

who used substances in addition to alcohol and who were not required to be abstinent or to have withdrawn from alcohol dependence before participating in the studies.

- In meta-analyses, acamprosate has been shown to be more beneficial than a placebo.
- The combination of naltrexone and acamprosate is not more effective than treatment with acamprosate alone.
- Acamprosate may be more beneficial if prescribed in combination with psychosocial treatments.

Findings on Combined Medication Therapy

Gueorguieva and colleagues (2010) reassessed COMBINE data using a trajectory model to better understand the effects of naltrexone, acamprosate, and combined behavioral intervention (CBI) on drinking trajectories. For subjects who reported any drinking, the data were organized into six trajectories: (T1) abstainers, (T2) infrequent drinkers, (T3) frequent to infrequent drinkers, (T4) increasing to frequent, (T5) increasing to nearly daily, and (T6) nearly daily drinkers. The trajectory for abstainers did not mean that subjects did not drink at all during the study period; rather it meant that the odds of drinking on any given day approached zero. Results of the analysis supported findings from the original COMBINE study. There was no significant association with acamprosate (alone or in combination with other therapies) on the likelihood of being in a positive trajectory (T1–T3). Nevertheless, naltrexone decreased the possibility of being in the (T4) increasing to frequent and (T6) nearly daily drinkers trajectories. CBI decreased the probability of being in the (T5) increasing to nearly daily trajectory. Naltrexone and CBI in combination increased the chances of being in the (T1) abstainer trajectory and in the (T3) frequent to infrequent category.

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June 11, 2010, Through December 31, 2010

General Findings

During the period covered in this literature review update, the American Society for Addiction Medicine (ASAM) published *ASAM Patient Placement Criteria: Supplement on Pharmacotherapies for Alcohol Use Disorders* (Fishman, Shulman, Kolodner, Mee-Lee, & Wilford, 2010). This book provides guidance on treatment placement for patients with alcohol use disorders (AUDs), and reviews the use of medications used to treat AUD. The journal, *Current Pharmaceutical Design*, published a special issue in 2010 that focused on pharmacotherapy for AUDs.

Zahm (2010) summarized articles about physiological, pharmacological, biochemical, and molecular biological bases of substance use disorders (SUDs), in general, as well as some of the medications used to treat AUDs. Some medications show a slight to moderate level of effectiveness. Medications that change the activity of the part, or parts, of the brain involved in substance abuse and craving complement, but do not replace, long-term behavior modification or other psychosocial approaches. The author concluded that, with instances of severe addictions to substances, the most effective long-term approaches are long-term behavior modification, cognitive behavioral therapy, and, particularly, mutual help groups. The advances made in understanding the pathophysiology involved in SUDs may help in the development of medications that specifically target the areas of the brain that have been changed by substance abuse. The author stated that relapse and relapse prevention remain the most persistent challenges in substance abuse treatment.

Findings on Disulfiram

Krampe and Ehrenreich (2010) summarized the literature on disulfiram published between 1937 and 2000, and reviewed 13 clinical trials published between 2000 and 2008. The authors stated that the 13 clinical trials found that, when taking disulfiram under supervised conditions (referred to as supervised disulfiram), and when combined with psychotherapy, the medication was effective in treating AUDs. The authors also found that, in the majority of studies that compared supervised disulfiram, acamprosate, topiramate, gamma-hydroxy butyrate, supervised disulfiram was as or more effective than the other medications. According to the authors, psychotherapy to accompany supervised disulfiram should include psychoeducation regarding how disulfiram works, the importance of continuing to take it, and its role in treatment. The authors also emphasized the need for a medical professional to administer the medication. The authors noted that patient adherence is a major problem with disulfiram. Two studies cited in the review included some of the reasons why patients discontinued taking disulfiram: to resume drinking, and the belief that the individual could remain abstinent without it. The authors surmised that psychotherapy could improve medication adherence by addressing these two issues, and helping the client work through them.

Rieckmann and colleagues (2010) reported on a nationwide longitudinal survey of Single State Authorities (SSAs), or their representatives, from all States and the District of Columbia (DC). The survey was designed to determine SSAs' perceptions of the use of medication-assisted

treatment (MAT) in SUD treatment in their States. This survey used quantitative and qualitative methods and used data obtained through recorded telephone interviews. Of the medications approved by the U.S. Food and Drug Administration (FDA) to treat AUDs, disulfiram was the only medication included in the survey.

Results of the survey found that disulfiram was used in 36 States and DC. Reported barriers to use of MAT in general included:

- Public, provider, and client resistance to MAT.
- Limited infrastructure for providing medications, including funding, required shifts in organizational procedures, and staff development.
- Legislation, policies, and regulations preventing implementation.
- Prevailing public attitudes that medications should not be used to treat addiction, based on a perception that a drug should not be treated by using another drug.

The researchers concluded that access to medication is a priority for SSAs, but that such access is slow to be implemented.

Findings on Oral Naltrexone

Garbutt (2010) reviewed the effectiveness and tolerability of naltrexone in the treatment of AUDs. This review revealed that naltrexone is effective in reducing relapse to *heavy* drinking, but only modestly effective in enhancing complete abstinence. In the studies cited by Garbutt, the medication's effect ranged from small to moderate, but still showed a statistically significant effect on patients' drinking. The author expressed concern that naltrexone's lack of effectiveness in certain studies may discourage clinicians from using it, even though the medication could be an important component of a treatment program. The article included information about two tolerability issues: risk of liver damage, and side effects. At the usual dose of 50 mg, naltrexone was found to have no adverse effect on the liver. The medication produced few serious side effects. The most common side effects reports were nausea, headache, dizziness, fatigue, insomnia, and nervousness. The author identified two areas in which further research is needed: to determine the effects that naltrexone may have on long-term outcomes, and to learn which patients are most likely to benefit from naltrexone treatment.

Findings on Extended-Release Injectable Naltrexone

A study of extended-release injectable naltrexone (XR-NTX) attempted to determine if it could be successfully used in a primary-care setting (Lee et al., 2010). The researchers assessed the use of XR-NTX in conjunction with medical management. The 3-month observational cohort study evaluated treatment retention, patient satisfaction, and alcohol use among individuals in need of treatment for AUDs at two medical clinics at urban public hospitals. The treatment offered consisted of medical management (MM) and three monthly XR-NTX injections. Physician-delivered MM stressed alcohol abstinence, medication effects, attendance at mutual-help groups, and counseling. The physicians helped patients who wanted additional support locate mutual-help groups or outpatient treatment programs. Of the 72 patients who enrolled in the study, 90 percent (65 of 72) received the first XR-NTX injection; 75 percent (49 of 65) received the second XR-NTX injection; 62 percent (40 of 65), received the third XR-NTX injection.

The researchers noted that few participants remained abstinent for the 3-month duration of the study. The 40 participants who completed the program reported fewer drinks per day, fewer drinking days per month, and fewer heavy drinking days per month. This improvement was correlated with retention, which was, in turn, correlated with participation in Alcoholics Anonymous (AA, a mutual-help group), outpatient treatment, or a combination of the two. The researchers concluded that XR-NTX and MM, delivered in a primary care setting, appeared feasible and acceptable to patients.

Findings on Acamprosate

Koeter and colleagues (2010) performed a meta-analysis of 11 clinical trials to determine the influence of early and late adherence to acamprosate on treatment attendance and duration of abstinence in the treatment of AUD. The authors examined data from 11 randomized controlled trials comparing acamprosate ($n = 1,128$) with placebo ($n = 1,177$) in studies published between 1985 and 2006. The meta-analysis confirms that nonadherence remains a serious problem; the early discontinuation of acamprosate may compromise the medication's effectiveness, because of its delayed onset of action. Conversely, treatment with disulfiram or oral naltrexone yields immediate pharmacological actions. The study confirmed that a person's motivation to become abstinent significantly affects treatment adherence and improves medication efficacy. Therefore, providing motivational interventions early in treatment can improve the likelihood of a person's adherence in taking medication, and thus the prospect of long-term abstinence.

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January 1, 2011, Through June 30, 2011

General Findings

Numerous studies have shown that negative mood is often a strong predictor of alcohol relapse and that alcohol craving mediates the relationship between negative mood and drinking. A study by Witkiewitz, Bowen, and Donovan (2011) sought to determine whether targeting craving during treatment could reduce the association between negative mood and drinking. The investigators conducted a secondary analysis of data from the Combining Medications and Behavioral Interventions for Alcoholism (COMBINE) Study, a large, multisite randomized clinical trial (RCT) that combined medication with cognitive-behavioral intervention for treating alcohol use dependence (AUD). The researchers assessed the effectiveness of the Coping With Cravings and Urges module. More than half (432 persons) of those who received a cognitive-behavioral intervention also received this module, which consists of several components, including:

- A description of how urges and cravings are predictable and controllable.
- An assessment of the cues or situations that lead to cravings or urges.
- An urge-monitoring homework assignment.
- Psychoeducational strategies for coping with external triggers.
- An urge-surfing exercise to deal with internal triggers, such as a negative mood.

Primary outcome measures in the COMBINE Study examined alcohol use by the percentage of days abstinent and the number of days until the first period of heavy drinking. This study also assessed negative mood and craving. The authors found that using the Coping With Cravings and Urges module reduced the impact of negative mood on days of heavy drinking. In addition, results suggest a change in craving may have altered the relationship between negative mood and heavy drinking. As a result, the study provides preliminary support for including this module in behavioral interventions for people with alcohol dependence and comorbid mood disorders.

Several factors limited the study, most notably:

- Participants were not randomly assigned to the craving module, so other client or therapist characteristics not measured in the COMBINE Study may have influenced the therapists' decisions regarding who should receive the module. It may also explain the differences that were observed.
- This study exclusively used the total Obsessive Compulsive Drinking Scale (OCDS) core; future research could examine whether the craving module yields different effects on specific aspects of craving.
- The craving module consists of several components, including urge-surfing, the rationale behind urges and cravings, an assessment of cues or situations that increase cravings, urge-monitoring assignments, and psychoeducation. As a result, investigators could not isolate which components were most effective in reducing negative mood, craving, or drinking.

- The study relied entirely on self-reports; the findings could be strengthened if they were validated by physical or behavioral indicators of mood, craving, or drinking behavior.

Findings on Oral Naltrexone

Previous studies have found that naltrexone (ReVia) is more effective among men than among women and among those with a family history of alcohol use disorders (FHAUD). Capone and colleagues (2011) conducted a multilevel modeling study that examined FHAUD using first-degree relatives (parents, siblings, and children) and gender as moderators to assess the effects of naltrexone on three outcomes: (1) percentage of days abstinent; (2) drinks per drinking day; and (3) percentage of heavy drinking days. This study reviewed patient report records from the COMBINE Study. Specifically, 603 COMBINE Study participants were randomized into 4 groups involving combined pharmacotherapy and medical management. As with the larger sample, 69 percent were male and the average age was 44.2 years. About one-quarter ($M = 0.26$, $SD = 0.23$) reported first-degree relatives with alcohol problems, and more than half (59 percent) indicated that one or two parents had a history of alcohol problems. The study found that FHAUD affected drinking behavior, but neither gender nor FHAUD affected naltrexone's efficacy. Although this study was built on the strength and validity of the COMBINE Study and a multilevel modeling approach, the fact that the FHAUD measure in COMBINE used first-degree relatives may only be a limitation, as may be the fact that data from the sample are based on self-reports.

Flórez et al. (2011) conducted a 6-month naturalistic, randomized, and open-label trial to determine whether topiramate or naltrexone yielded better outcomes after 3 and 6 months of treatment. The sample included 182 patients who had been drinking heavily during the past month. The assessment of each patient at enrollment provided a baseline for comparison. Results were measured by using tools that assessed alcohol intake, cravings, disability, and quality of life. The trial also used changes in biomarkers of alcohol intake. Although the study found no difference between topiramate and naltrexone in terms of treatment compliance, which was high in both groups, a mean dose of 200 mg/day of topiramate yielded better results than a 50 mg/day dose of naltrexone in the treatment of alcohol dependence during the first 6 months of treatment. The authors also observed reduced nicotine use among those taking topiramate, underscoring the efficacy of this medication in treating patients with both alcohol and nicotine dependence. The topiramate group reported higher rates of negative side effects at 3 months, but these symptoms disappeared by the 6-month marker.

There were limitations to the study. For example, the trial was not blinded, nor did it include a placebo group. Furthermore, trial criteria excluded persons with physical or mental illnesses, those who lived alone, and those with a current diagnosis of dependence or abuse of other substances except nicotine. Trial participants had a good prognosis, which should be taken into account when comparing the results with those of other studies. Patient questionnaires were corroborated by significant others, but it would have been more accurate to use a urinary marker. Finally, although this study assessed the 6-month treatment period, it did not assess efficacy in relapse prevention.

Laaksonen, Lahti, Sinclair, Heinälä, and Alho (2011) used multiple linear regression analyses to explore possible associations between sweet preference and naltrexone treatment efficacy for

AUD. The sample included 78 participants (56 men and 22 women) with diagnosed AUD after a 32-week treatment period with naltrexone (n = 45) or placebo (n = 33). Patients in the naltrexone group received 50 mg of naltrexone per day for 12 weeks, after which they received naltrexone only as needed for 20 weeks, along with therapy to help them cope with either moderate drinking or abstinence. None of the study participants had undergone detoxification. During the last 20 weeks of the treatment period, sweet testing of 6 different concentrations was conducted at 5 different times for a total of 30 tests per participant. After each sweet test, patients were asked, “How much do you like the taste?” All sweet tests were administered by the same person at least 1.5 hours after breakfast and at least 1 hour after smoking and teeth brushing. Patients, the sweet tester, and the investigator were blind to the study. Patient reactions to the question determined how the preference for each solution was calculated, and the correlation’s accuracy increased with the number of solutions tested.

Each participant recorded his or her alcohol drinking in a drinking diary starting 1 week before naltrexone or placebo administration, and each participant was contacted 10 times during the 32-week clinical trial. Alcohol craving was assessed at baseline, 12 weeks, and 32 weeks. Naltrexone efficacy was determined across three outcome measures: (1) the number of contacts without relapse to heavy drinking, which was defined as 5 or more drinks on one occasion at least once since the previous contact with an investigator; (2) reduction in alcohol use from the mean at baseline; and (3) reductions in OCDS scores.

The authors found that most subjects (67 percent) improved while on naltrexone and that lower sweet scores significantly predicted relapse to heavy drinking. Of the 15 patients who increased drinking, 12 (80 percent) had low sweet scores. All seven participants who increased drinking by more than 100 g/week had low sweet scores, and four had the lowest possible score. There was no such association in the placebo group. Although there was no major difference in the correlation between sweet scores, changes in alcohol drinking, or OCDS results between the naltrexone and placebo groups, analysis of the naltrexone group revealed that lower sweet scores significantly predicted higher weekly alcohol consumption in weeks 13–32. A major factor in the significant difference between the two groups was that those in the placebo group with higher sweet scores tended, though not significantly, not to succeed in treatment. This study suggests that higher sweet preference had a strong relationship to improved treatment outcomes with naltrexone and may be a predictor for better treatment outcomes for persons with alcohol dependence.

The study revealed one possible explanation—lower sweet preference—why naltrexone is not effective for all patients. The authors acknowledge evidence suggesting that reduced sweet preference may be a side effect of naltrexone treatment. The study also did not measure alcohol use in the week before the sweet-testing period, so it is possible that some participants reduced or increased their drinking more than others. Yet, these findings indicate that persons with AUD and a low sweet preference may have less successful naltrexone treatment outcomes, whereas their counterparts with high sweet preference are more likely to achieve successful treatment outcomes with naltrexone. However, additional large-scale clinical studies are needed.

Yoon and colleagues (2011) examined the short-term safety, tolerability, and feasibility of taking a larger dose of naltrexone (150 mg/day, compared with the standard dose of 50 mg/day) to treat AUDs among persons with strong alcohol craving. During an 8-week open-label pilot study, 24

patients received this larger dose. Patients were not required to be abstinent to participate. The study provided only medication management; counseling or intensive psychosocial interventions were not provided. The study protocol follows:

- For the first 2 days of the study, patients received only 25 mg/day to minimize nausea.
- For the next 5 days, the dose was increased to 50 mg/day. To minimize nausea, patients received 10 mg of prochlorperazine daily as needed during the first 3 days.
- During the second week of the study, patients received 100 mg/day (50 mg in the morning and 50 mg in the afternoon).
- In the third week and throughout the remainder of the study, patients received 150 mg/day (i.e., 100 mg in the morning and 50 mg in the afternoon).

Of the 24 subjects who started the study, 6 did not finish. None left the study because of naltrexone-related issues or adverse effects.

The investigators assessed safety and tolerability each week. Liver function tests were conducted at baseline, at three points during the study, and after the study. Primary patient outcome measures were the percentage of drinking days and number of drinks consumed each drinking day. The study found that the larger dose of naltrexone was safe and tolerated well, yielding no serious side effects. The most common side effects reported early in the study were nausea, dizziness, and drowsiness; however, these side effects were mild to moderate in severity and decreased over time. The study also found that gamma glutamyltransferase levels improved and liver function remained stable. This finding could be the result of the study's novel approach of restricting concurrent use of over-the-counter analgesics such as acetaminophen, aspirin, or ibuprofen.

In terms of outcomes, high-dose naltrexone significantly reduced the percentage of drinking days and the number of drinks consumed per drinking day. Subjects also reported that their craving for alcohol was weaker and that they experienced less pleasure while consuming alcohol.

The investigators acknowledge that these findings should be considered preliminary because this was an open-label, nonrandomized trial with no comparison group. Long-term safety and efficacy beyond 8 weeks merit additional exploration in future trials that could replicate these results in a larger sample. It also should be noted that these findings may be relevant only to patients with strong alcohol craving. Finally, the authors warn that safety cannot be guaranteed by restricting over-the-counter analgesics for patients on high-dose naltrexone. The study suggests that high-dose naltrexone may be a useful treatment alternative for patients with strong alcohol craving. However, double-blind, placebo-controlled trials of high-dose naltrexone are necessary to verify the safety and efficacy of high-dose naltrexone.

Findings on Acamprosate

Rösner et al. (2011) reviewed 24 RCTs with 6,915 participants who met the selection criteria for the review. Most of these RCTs were conducted in Europe, two in the United States, and one each in South Korea, Australia, and Brazil. All RCTs provided outpatient treatment with the exception of one trial that provided inpatient treatment to adolescents. The purpose of this review was to compare the effectiveness of acamprosate (Campral) to placebo and naltrexone and to

identify any side effects using individual patient data meta-analyses to verify the primary effectiveness outcomes. The reviewers found that, compared with placebo, acamprosate combined with psychosocial treatment strategies significantly reduced the risk of any drinking and increased cumulative abstinence duration. Specifically, acamprosate reduced the risk of any drinking after detoxification to 86 percent of the risk in the placebo group and increased the number of abstinent days by approximately 3 days per month.

Secondary outcomes (gamma glutamyltransferase and heavy drinking) were not statistically significant. The only side effect reported from acamprosate was diarrhea. The reviewers found no significant differences in outcomes between acamprosate and naltrexone or between industry-sponsored trials and nonprofit-funded trials. Furthermore, they found that acamprosate appears to be a safe, effective treatment for patients with AUD that supports continued abstinence after detoxification. Although its effectiveness is moderate in its magnitude, it is important, given the common occurrence of relapse in this population and the limited treatment alternatives.

Further review of the above study by McNeely and Sherman (2011) concluded that the findings were based mostly on results of efficacy studies and on the fact that acamprosate's effectiveness may be much less in real-world settings. As an example, the authors note that all patients received counseling, which is not always available. In addition, posttreatment data for 10 RCTs indicated reduced effects for acamprosate and that 3 doses per day may inhibit medication adherence, suggesting that other treatment alternatives (e.g., naltrexone) may produce better outcomes. McNeely and Sherman recommend that patients with AUD should be referred for specialty treatment, and if a patient refuses, then the primary care provider and patient should discuss various treatment options, including counseling, medications, and followup.

The international research program on acamprosate involved 6,500 patients who were participating in this randomized, double-blind, placebo-controlled trial that documented extensive baseline and followup data. From this group, Lejoyeux and Leher (2011) used an individual patient data meta-analysis of 3,354 patients participating in 11 studies in 10 different countries to study predictors and correlates of depression in patients with AUDs after detoxification and during outpatient treatment with acamprosate. Of these patients, 1,743 were not depressed, 491 had mild depression, and 1,120 had moderate-to-severe depression. Patients with AUDs and moderate-to-severe depression exhibited a profile consisting of five predictors, including being female, younger (participants were compared across three age groups—younger than 30 years, 30 to 50 years, and older than 50 years), unemployed, living alone, and drinking alcohol episodically. Female gender was the most dominant predictor of AUDs and depression. However, patients of both genders with both AUDs and depression were less likely to start treatment or adhere to it.

Acamprosate treatment achieved similar results for patients with depression and those without depression. However, the authors found that acamprosate improved abstinence and had an indirect positive effect on depression by improving abstinence. Sustained abstinence was the key factor in reducing depression; patients with depression were 7.58 times more likely to overcome depression if they remained continuously abstinent. The study suggests systematically identifying patients with depression among those with AUDs but treating the alcohol dependence first because improved abstinence often led to depressive disorder remission.

The meta-analysis, however, has limitations. The original studies were not planned with the objective of measuring depression in patients with AUDs, so different measures of alcohol use, impairment, depression, and treatment participation were combined into single measures in the meta-analysis. None of the studies were designed for epidemiological purposes. However, it is important to note that these patient data were obtained from possibly the largest database of patients, making it possible to compare depression and nondepression among patients with AUDs.

Umhau et al. (2011) conducted a randomized, double-blind laboratory study of subjects seeking alcohol treatment who were in the early stages of abstinence. The study examined whether yohimbine or meta-chlorophenylpiperazine (mCPP) induced alcohol craving. It also evaluated the predictive ability of this approach by evaluating acamprosate's ability to modulate stimuli-induced craving. The primary outcome measure was craving in response to yohimbine, mCPP, or placebo saline solution infusions. Secondary outcome measures included anxiety and plasma levels of prolactin, adrenocorticotrophic hormone (ACTH), and cortisol. A total of 35 patients, mostly adult men, met the inclusion criteria, successfully completed the telephone screening, and were admitted to the National Institutes of Health (NIH) Clinical Research Center. After withdrawal, if any, patients received 2 weeks of medication (either 999 mg of acamprosate every 8 hours or a matching placebo). The NIH Clinical Center pharmacy randomized the subjects, to which the investigators and clinical staff were blind. The double-blind was made possible by encapsulating acamprosate that was obtained commercially and by manufacturing a matching placebo. Subjects then participated in three challenge sessions with yohimbine, mCPP, or saline infusion. Challenge sessions were conducted in counterbalanced order at least 5 days apart. Primary measures were cravings, anxiety, and biochemical measures. Craving was measured using the Penn Alcohol Craving Scale and the Alcohol Urges Questionnaire, the latter of which allowed investigators to compare results with the findings of previous studies.

Twenty-five subjects completed the three sessions. Both the yohimbine and mCPP challenges produced modest but significant increases in craving, compared with the saline infusion, and both yielded strong ACTH, cortisol, and prolactin responses. The mCPP significantly increased anxiety ratings, whereas yohimbine did not.

The authors observed a significant association between cravings and alcoholism severity. However, acamprosate did not reduce craving. The authors admit that 2 weeks of acamprosate may not have been enough to mitigate craving and that either an interaction occurred between the acamprosate and the drug used to induce craving or that acamprosate acts independently of stress-induced stimuli. They also suggest that it may be possible to increase craving via other stimuli or combinations of stimuli. Nonetheless, the authors argue that pharmacologically induced craving continues to be a useful surrogate marker approach to creating new treatments for alcoholism, but it may have to be augmented with psychological stimuli and customized to the ways in which specific medications work.

Findings on Combined Medication Therapy

Guardia et al. (2011) completed a double-blind, RCT to determine whether combined quetiapine and naltrexone treatment was more effective than naltrexone alone among patients with alcohol dependence. Eligible patients were randomized into two groups; one group (n = 30) received

both naltrexone (50 mg/day) and quetiapine (25–200 mg/day), whereas the other group (n = 32) received the same dose of naltrexone with placebo. The treatment period lasted 12 weeks, followed by 4 additional weeks of naltrexone-only treatment. Efficacy measures included percentage of days abstinent, drinks per drinking day, and relapse rate. Eleven patients in the combination group and four patients in the placebo group withdrew before completing 12 weeks of treatment.

The combination of quetiapine and naltrexone did not improve drinking outcomes. The authors note that this finding seems, at least to some degree, inconsistent with a recent, randomized, placebo-controlled trial that explored quetiapine only as a treatment for alcohol dependence. That trial found that quetiapine was more effective than placebo across several drinking measures—and especially among individuals with more severe AUDs. Perhaps quetiapine is more effective as a monotherapy than when prescribed in combination.

The authors also note that the quetiapine dosage used in this study (127.5 mg/day) was lower than the dosage for the aforementioned randomized trial (300 mg/day) and the recommended dose for other psychiatric indications. This lower dosage may have inhibited quetiapine's effectiveness on drinking outcomes. A placebo-only group would have strengthened this study by determining whether both treatments were effective. The high attrition rate also was a serious problem that may have biased the results in favor of quetiapine. It also is possible that the high attrition rate may have been related to tolerability problems. However, the tolerability analysis of those who completed the study found no differences between the two groups.

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July 1, 2011, Through January 31, 2012

General Findings

Abraham, Knudsen, and Roman (2011) conducted structured, face-to-face interviews with a national sample of 223 administrators of privately funded substance abuse treatment programs to examine patterns of disulfiram (Antabuse) and tablet naltrexone (ReVia) adoption over a 2-year period. This study was limited to disulfiram and tablet naltrexone because they were the only medications for alcohol use disorder (AUD) treatment approved by the Food and Drug Administration at baseline. In addition, the authors sought to identify any predictors of sustainability, later adoption, discontinuation, and persistent nonadoption.

Researchers collected data at two points (Wave 1 and Wave 2) during a nationally representative longitudinal study of private treatment programs participating in the National Treatment Center Study. Wave 1 involved collecting baseline data from 2002 to 2004. Wave 2 consisted of collecting followup data from 2007 to 2008. Programs that met inclusion criteria were divided into four groups for each medication:

- *Sustainers* that offered medication at both baseline and 2-year followup
- *Later adopters* that did not offer these medications at baseline but did at followup
- *Nonadopters* that did not offer medication at either baseline or followup
- *Discontinuers* that offered medication at baseline but not at followup

The following exhibit details the results of the four groups for each medication.

Exhibit 1 Disulfiram and Tablet Naltrexone by Treatment Program Category

Program Category	Disulfiram	Tablet Naltrexone
Sustainers	16.6%	19.3%
Later adopters	13.0%	17.9%
Nonadopters	55.2%	50.2%
Discontinuers	15.2%	12.6%

As shown in Exhibit 1, most administrators reported that they never provided either disulfiram or tablet naltrexone in their programs. This finding was “striking,” according to the authors, because of the promotional efforts made throughout several levels of government, and by leaders in the treatment field, encouraging the use of alcohol pharmacotherapies. For both medications, the authors observed that having a physician on staff increased the likelihood that a program would be either a sustainer or later adopter; however, given that more than 70 percent of programs in the study had access to at least one physician at followup, it was clear that having a physician on staff does not necessarily translate into adoption of alcohol pharmacotherapy. Some of the potential reasons are explained below.

Those administrators whose programs offered these treatments to clients with AUDs at baseline but later stopped were asked why they discontinued disulfiram or tablet naltrexone treatment. These findings are relevant because the data generated by this study are among the first to measure AUD medication discontinuation within treatment programs. Some programs stopped offering these treatments altogether because of the loss of a staff physician, changes in State regulations that prohibited prescribing medications for AUDs, difficulties involving medication costs or reimbursement, concerns over legal liability, concerns regarding the safety or efficacy of the medications, or because of a determination that medications were not consistent with the program's treatment philosophy. Other programs replaced either disulfiram or tablet naltrexone with a newer AUD medication, such as acamprosate, injectable naltrexone, or both. Interestingly, while some of the programs that had offered disulfiram switched to tablet naltrexone, none of the programs that had offered tablet naltrexone switched to disulfiram.

The authors also found that a higher percentage of criminal justice referrals had a negative impact on sustained adoption over time. This could be rectified, the authors suggest, by amending criminal justice contracts to include AUD medication use.

Fewer than 20 percent of programs successfully sustained the provision of AUD medications throughout the duration of the study. Organizational characteristics of the programs that were associated with sustained adoption of both medications included being located in a hospital setting, having a sufficient number of medical staff trained in AUD medication use, and using selective serotonin reuptake inhibitors at baseline. These findings suggest that better integration of medical staff and resources into treatment programs—such as partnering with primary care practitioners or local hospitals to provide medical services, including AUD medications—is critical to sustained adoption. Additional characteristics that were associated with sustained adoption included program accreditation by the Joint Commission or the Commission on Accreditation of Rehabilitation Facilities, and increased revenues from private insurance. Furthermore, large treatment programs were more likely to sustain use of tablet naltrexone, suggesting that small treatment programs may benefit from additional funding earmarked for AUD medication use.

According to the authors, these findings suggest that accrediting bodies, relationships with primary care physicians, medication-specific medical staff training, increased availability of AUD medication funding resources, and modifications of criminal justice contracts to include AUD medication use can all have a positive effect on a program's adoption of AUD medications as a part of an overall treatment program.

The study had several limitations. Most important, the small number of programs that adopted or sustained AUD medication use precluded further analysis via multivariate statistical techniques. Second, because the two data collection periods occurred 4 years apart, the results may not have identified more dynamic adoption patterns. Third, data were obtained via administrator self-report, so the data were subject to recall bias. Finally, these findings were limited to private sector treatment programs and may not be generalizable to public sector treatment programs that benefit from more steady funding streams (e.g., Federal block grants or State contracts).

Findings on Disulfiram

Jørgensen, Pedersen, and Tønnesen (2011) reviewed the effectiveness of disulfiram in treating persons with AUDs. Their review included 11 randomized controlled trials that involved 1,527 participants and compared disulfiram with placebo, no treatment, or other abstinence-supportive treatments. These studies averaged 8 months in duration. Of the 11 trials, 6 studies found that disulfiram treatment yielded significantly better abstinence outcomes. Six of nine studies measuring secondary outcomes (e.g., days until relapse, number of drinking days) found that disulfiram treatment resulted in significantly more days until relapse and fewer drinking days. The authors concluded that supervised disulfiram treatment has some positive effect on short-term abstinence, days until relapse, and number of drinking days compared to placebo, no treatment, or other treatment.

The review has several limitations. First, the quality of the studies included in the review, according to the authors, was moderate. Second, the methods lacked uniformity (e.g., differences in how relapse and abstinence were defined, whether the administration of disulfiram was supervised or unsupervised). Third, most of the studies included in the review were short in duration, and only three studies lasting 12 months observed significant reductions in days until relapse and/or drinking days. The authors noted the many challenges to doing disulfiram research and called for more homogenous, high-quality studies with sufficient sample sizes that will permit a more complete assessment of disulfiram treatment efficacy.

Findings on Extended-Release Injectable Naltrexone

Pettinati et al. (2011) conducted post-hoc analyses of data from 624 individuals with relatively severe alcohol dependence who participated in a 6-month, multicenter, double-blind, placebo-controlled, randomized trial to examine the effectiveness of injectable extended-release naltrexone (XR-NTX). Participants received 380 mg of XR-NTX once per month for 24 weeks. All participants received 12 sessions of low-intensity psychosocial counseling during the trial. The authors analyzed treatment effects among participants who exhibited higher alcohol use severity at baseline as measured by the Alcohol Dependence Scale (ADS) or by having undergone medical detoxification in the week before randomization. They also examined efficacy via the relationship between severity indices prior to treatment and reporting at least 4 days of lead-in abstinence prior to treatment. (In the original study, 4 days of lead-in abstinence emerged as a major predictor of “good” outcomes.)

The authors found that, for persons with relatively higher severity of alcohol dependence, XR-NTX 380 mg treatment, combined with low-intensity psychosocial counseling, reduced heavy drinking and helped maintain abstinence compared to placebo. Specifically, among participants with higher severity of alcohol dependence as determined by ADS scores ($ADS > 16$), those who received XR-NTX ($n=50$) had significantly fewer drinking days compared to the placebo group ($n=47$). In addition, the average number of heavy drinking days within the treatment group decreased by an average of 37.3 percent compared to 27.4 percent for the placebo group. Among the small number of participants who underwent detoxification immediately before randomization, the treatment group ($n=11$) reduced their heavy drinking days by 48.9 percent compared to 30.9 percent for the placebo group ($n=15$). Furthermore, participants who were abstinent for at least 4 days before treatment ($n=82$), compared to those who had not been

abstinent ($n=542$), actually had much higher pretreatment ADS scores and were more likely to need detoxification before randomization. Participants with lead-in abstinence were more successful at achieving both initial and 6-month abstinence. These findings contradicted previous studies which suggested that XR-NTX treatment be limited to individuals with low-severity alcohol dependence.

The study had several limitations. First, the analyses were conducted post hoc using only a subsample from the original trial, thus reducing the statistical power of the findings due to a smaller sample size. Second, because the study excluded participants with unstable major depressive disorders, bipolar disorder, psychosis, or past-year dependence on benzodiazepines, opiates, or cocaine, these results may not be generalizable to the broader population of persons with alcohol dependence. Third, the authors point out that the lack of a detoxification does not always indicate low severity of dependence, and some individuals with high-severity dependence may not have had access to detoxification care. Additional research is needed to clarify optimal XR-NTX treatment duration and its relationship to other variables (i.e., severity of dependence, initial abstinence, attrition from treatment, and drinking outcomes).

Findings on Acamprosate

Wölwer et al. (2011) conducted a randomized, controlled, multisite trial to determine the efficacy of combined treatment with acamprosate and integrated behavior therapy (IBT) on drinking behavior among individuals with alcohol dependence who had completed detoxification. Their hypothesis was that acamprosate treatment combined with IBT would yield better drinking outcomes than either a combination of IBT and placebo or a combination of treatment as usual (meaning supportive counseling once each week) and acamprosate. IBT consists of relapse prevention, social skills training, and motivational and cognitive methods over 4 modules that include 24 sessions held once a week for 6 months in groups of 2 to 9 participants.

The sample consisted of 371 participants between the ages of 25 and 60 who had been dependent on alcohol for the past 6 months and had adequate German language skills. Exclusion criteria included additional substance use disorders (except for nicotine), psychotic disorders, those taking an antidepressant, persons with mental retardation or brain damage, an unstable medical condition, known hypersensitivity to acamprosate, and women who were pregnant or nursing.

After inpatient detoxification, participants were randomly assigned to one of three groups for 6 months of outpatient treatment. The first group received IBT plus acamprosate ($n=124$). The second group received IBT plus placebo ($n=125$). The third group received treatment as usual plus acamprosate ($n=122$). Participants were assessed before treatment, after 3 months in the study, at the end of treatment, and 3 and 6 months post-treatment. Since maintaining abstinence is the primary goal of the German healthcare system, success in this study was defined as those who had remained abstinent or those who had reduced drinking behavior. Relapsing participants were excluded from the study treatment and IBT group sessions. Relapse was defined as those who drank alcohol for 7 consecutive days or those who missed more than three consecutive therapy sessions without notice.

Contrary to their original hypothesis, the authors found that the combination of acamprosate and IBT did not yield better drinking outcomes than treatment with either IBT plus placebo or

acamprosate plus treatment as usual. The treatment success rate was 47.6 percent for IBT plus acamprosate, 37.7 percent for treatment as usual plus acamprosate, and 48.0 percent for IBT plus placebo. During the 6-month treatment period, 54.7 percent of participants either discontinued treatment or were excluded due to relapse or missing more than three consecutive therapy sessions. There were no significant differences between the three groups in the amount of time participants remained in the study until dropout. Furthermore, there was no significant difference in treatment success for the three groups at followup. However, the authors indicate that the roughly 10 percent difference between groups that received acamprosate, though not statistically significant, may be a clinically relevant finding and may suggest that a more comprehensive psychosocial intervention could achieve better results. The authors note this with some level of caution because statistically proven results supporting such a conclusion are lacking.

The authors noted some study limitations. First, treatment as usual may not have been the control it was intended to be because it did in fact include some principles and techniques of motivational interviewing. Second, any missing data were classified as relapse and may have inflated the percentage of participants who relapsed. Finally, three of the authors disclosed potential conflicts of interest in terms of advisory board memberships or previous research or symposia support from study funders. The lead author and the remaining 11 authors reported no potential conflict of interest.

Findings on Combined Medication Therapy

Anton et al. (2011) examined whether gabapentin, when used in combination with oral naltrexone, was more effective than naltrexone treatment alone in helping to prevent early relapse.

This randomized controlled clinical trial used a double dummy, placebo-controlled medication design and included 150 individuals with alcohol dependence who had abstained from alcohol for at least 4 consecutive days before randomization. All participants met the criteria for alcohol dependence based on the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV) (American Psychiatric Association, 1994). Exclusion criteria were strictly defined and included many medical and psychosocial variables (e.g., meeting criteria for any other DSM-IV, Axis I disorder; taking opioid, psychotropic, anticonvulsant, or study-related medications; having pending legal charges).

Participants were randomly assigned to 3 groups of 50 participants each. One group received naltrexone plus active gabapentin, one group received naltrexone plus placebo gabapentin, and one group received placebo naltrexone and placebo gabapentin. Participants received 25 mg of naltrexone or its matching placebo for the first 2 days and then 50 mg/day for up to 16 weeks. Gabapentin (300 mg capsules) or its matching placebo was given to participants in increasing dosages: one capsule at night on day 1 (300 mg/day); one capsule in the morning and one at night on day 2 (600 mg/day); one capsule in the morning, at noon, and at night on days 3 and 4 (900 mg/day); and one capsule in the morning, one at noon, and two at night (1,200 mg/day) on days 5 through 42 (6 weeks). All participants received medical management to evaluate physical complaints and encourage medical adherence. Participants also were provided up to 16 sessions of combined behavioral intervention therapy based on the treatment manual from the Combining

Medications and Behavioral Interventions study, which combined cognitive–behavioral therapy, motivational interviewing, and 12-step techniques.

Across the three groups, there were no demographic or drinking variable differences. Most participants were in their mid-40s, most were male (over 80 percent), most were Caucasian (over 85 percent), and most drank 12–13 drinks per drinking day on about three-quarters of the 90 days before randomization.

During the first 6 weeks, researchers observed a longer delay in heavy drinking in the naltrexone/gabapentin group than the naltrexone alone group or the placebo group. The naltrexone/gabapentin group also had fewer drinking days than the other two groups. However, these findings faded once the naltrexone/gabapentin group stopped receiving gabapentin. These findings indicate that the addition of gabapentin to naltrexone treatment improved drinking outcomes during the first 6 weeks of the study compared to those who received naltrexone only or placebo. It is also important to note that naltrexone (alone) was not superior to placebo in this study. In fact, it yielded less desirable results than the placebo on some measures.

Study limitations included the fact that it was a single-site study with a fairly small and demographically limited sample. In addition, participants did not have significant mental health problems other than alcohol dependence, were not taking psychiatric medications, were in fairly good health, and were mostly motivated to achieve abstinence. Last, this study did not examine the potential effect of gabapentin use independent of naltrexone on drinking outcomes, which the authors argue merits further study.

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February 1, 2012, Through July 31, 2012

General Findings

Litten et al. (2012) explored whether the antipsychotic medication quetiapine (Seroquel) may be useful in treating heavy drinking. The authors designed a double-blind, placebo-controlled trial that included 224 individuals—179 men and 45 women ages 18 to 64—at 5 clinical sites who had been diagnosed with alcohol dependence and who reported heavy drinking. All study participants received either quetiapine or placebo, which were dispensed to participants for 3 months in a double-blind manner. Participants in both groups also received Medical Management, a minimally intensive intervention that assesses side effects, educates participants about heavy drinking, advises participants about abstinence, promotes adherence to the medication regimen, supports recovery, and urges participants to attend mutual-help groups like Alcoholics Anonymous. In addition, the study design stratified participants by gender, site location, and reduction in drinking before randomization. The primary outcome measure for the study was the weekly percentage of heavy drinking days during weeks 3 through 11 of the study.

In general, quetiapine was well-tolerated by participants. It also significantly reduced depressive symptoms and improved sleep. It did not, however, improve the primary drinking outcome or any secondary drinking outcomes except among a subgroup of participants who already had reduced their drinking prior to randomization. This subgroup of individuals achieved better drinking outcomes during the maintenance phase of the study. Nevertheless, the clinical trial ultimately showed that quetiapine did not reduce alcohol consumption compared to placebo, so the authors could not recommend quetiapine to treat individuals with alcohol dependence.

Findings on Oral Naltrexone

Morgenstern et al. (2012) sought to test 4 treatment conditions among 200 men who have sex with men with problem drinking behaviors who wanted to reduce their drinking but not quit drinking completely. Most participants were approximately 40 years old, Caucasian, single, had received at least some college education, reported a baseline weekly consumption of 43.1 drinks, and drank slightly more than 8 drinks per drinking day. The study used urn randomization to assign participants to 4 treatment conditions: naltrexone only ($n=51$); placebo only ($n=48$); modified behavioral self-control therapy (MBSCT) alone ($n=50$); and naltrexone plus MBSCT ($n=51$). All participants also received a brief medication compliance intervention.

The study lasted 12 weeks followed by a 1-week assessment period. Specifically, the authors wanted to examine two primary outcomes—the weekly sum of drinks consumed and the weekly number of heavy drinking days. They were also interested in a secondary outcome—the percentage of those who successfully reduced their drinking to nonhazardous levels.

The study found no benefit of adding naltrexone to MBSCT. In fact, MBSCT alone demonstrated better efficacy than naltrexone alone. Also, MBSCT participants, regardless of medication condition, reduced their number of heavy drinking days from approximately 3.5 heavy drinking days per week pretreatment to approximately 1 day of heavy drinking per week at the end of treatment. Naltrexone, when used with a minimal medication compliance

intervention, was more effective than placebo on only one important clinical indicator—achieving nonhazardous drinking. Naltrexone also was more effective than placebo on one clinically descriptive outcome—negative consequences of drinking.

The study has some limitations. Internal validity of the data may have been limited in that the assessment of medication compliance and drinking behaviors was based on participant self-report. External validity may have been limited by the use of research assessments that might influence drinking behaviors, the recruitment and treatment of participants from non-primary-care (academic) settings, the relevance of these findings to populations other than men who have sex with men, and the absence of posttreatment followup services.

Peters et al. (2012) examined young adults who use both marijuana and alcohol to determine whether marijuana use increases the risk of heavy drinking. The study recruited 122 (70 percent men) young adults ages 18 to 25 to participate in an 8-week, randomized, double-blind, placebo controlled clinical trial of naltrexone used in combination with brief motivational counseling to reduce heavy drinking.

At intake, participants reported their alcohol use, negative consequences of alcohol use, motivation to reduce drinking, trait impulsivity, expectancies for alcohol-induced disinhibition, cigarette use, and history of not adhering to treatment regimens.

Of the 122 study participants, 71 (58 percent) reported no marijuana use in the past 3 months, 27 (22 percent) reported using marijuana once per week in the past 3 months, and 24 (20 percent) reported using marijuana at least twice per week in the past 3 months. Due to the relatively small sample size, the authors compared the 51 participants who reported at least weekly marijuana use during the past 3 months to the 71 participants who reported no marijuana use in the past 3 months.

A significantly larger percentage of those who reported marijuana use also reported both unintentional and intentional nonadherence to medical regimens, as well as a history of cigarette smoking, compared to those who reported no marijuana use. Regardless of whether a participant reported co-occurring marijuana use, univariate tests revealed no difference in alcohol consumption, negative alcohol-related consequences, motivation to reduce drinking, or demographic characteristics.

In multivariate tests that controlled for demographic characteristics, the authors found that co-occurring marijuana use and heavy drinking was strongly associated with impulsivity and a history of both unintentional and intentional nonadherence to medication. Based on these findings, the authors suggested that young adults who use marijuana and also drink heavily constitute a high-risk clinical profile and may benefit from interventions focused on increasing treatment adherence.

One limitation of the study is the cross-sectional nature of data collection from a fairly small clinical sample of young adults participating in a pharmacotherapy treatment trial. Another limitation is that data were collected via self-report and did not include lifetime use of marijuana. Finally, this study did not demonstrate that young adults with co-occurring marijuana use and

heavy drinking behaviors reported worse treatment outcomes than those who reported no marijuana use; however, these data will be available for future study.

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