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

Update

Reviews Literature From July 1, 2011, Through January 31, 2012

Treatment Improvement Protocol (TIP) Series

49

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UPDATED FINDINGS FROM THE LITERATURE, JANUARY 2012

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Updated Findings From the Literature, January 2012

This Treatment Improvement Protocol (TIP) Literature Review Update includes findings published between July 1, 2011, and 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 Oral Naltrexone

No articles were published on this topic that met the selection criteria.

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.

Methodology

The same methodology used in developing the literature review for TIP 49 was used for this update.

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