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

Update

Reviews Literature From January 2011 Through June 2011

Treatment Improvement Protocol (TIP) Series

49

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UPDATED FINDINGS FROM THE LITERATURE, JUNE 2011

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Updated Findings From the Literature, June 2011

This Treatment Improvement Protocol (TIP) Literature Review Update includes findings published between January 1, 2011, and 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 Disulfiram

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

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 Extended-Release Injectable Naltrexone

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

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 Lehert (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, adrenocorticotropic 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.

Methodology

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

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