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

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49

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Updated Findings From the Literature, October 2009

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Updated Findings From the Literature, October 2009

This update includes findings from October 1, 2007, through October 10, 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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