Naltrexone and Disulfiram in Patients with Alcohol Dependence and Comorbid Psychiatric Disorders

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Background: *Disulfiram and naltrexone are approved by the Food and Drug Administration (FDA) for the treatment of alcoholism, but these agents have not been rigorously evaluated in dually diagnosed individuals.*

Method: *Two-hundred and fifty-four patients with an Axis I psychiatric disorder and comorbid alcohol dependence were treated for 12 weeks in an outpatient medication study conducted at three Veterans Administration outpatient clinics. Randomization included assignment to one of four groups: 1) naltrexone alone; 2) placebo alone; 3) (open-label) disulfiram and (blinded) naltrexone; or 4) (open-label) disulfiram and (blinded) placebo. Medication compliance was evaluated using the Microelectric Events Monitoring System. Primary outcomes were measures of alcohol use. Secondary outcomes included psychiatric symptoms, alcohol craving, g-GGT levels and adverse events.*

Results: *There was a high rate of abstinence across groups. Subjects treated with an active medication had significantly more consecutive weeks of abstinence and less craving than those treated with placebo, but there were no significant group differences in other measures of alcohol consumption. There was no advantage of the combination of both medications.*

Conclusions: *These data suggest a modest advantage for the use of disulfiram and naltrexone for this group of dually diagnosed alcohol-dependent individuals but did not suggest an advantage in the combination.*

Key Words: Alcohol, comorbidity, disulfiram, dual diagnosis, naltrexone

Following preclinical studies suggesting that naltrexone may be an effective pharmacologic agent in treatment of alcohol dependence, the efficacy of naltrexone in reducing alcohol use in alcohol-dependent individuals was demonstrated in two well-known clinical trials (Volpicelli et al 1992; O'Malley et al 2002). Naltrexone was subsequently the second medication approved by the Food and Drug Administration (FDA) for use in treating alcohol dependence. A meta-analysis of all published placebo-controlled trials using naltrexone up to 2000 suggested that naltrexone has a modest positive effect on alcohol consumption (e.g., effect size for percentage drinking days = –.191, $p <$ .001; Kranzler and Van Kirk 2001). Naltrexone has not been uniformly effective, however. For example, a large multisite trial in alcohol-dependent veterans failed to confirm any effect of naltrexone on drinking outcomes (Krystal et al 2001).

The safety and effectiveness of naltrexone in alcohol-dependent populations with major mental illness is an important clinical question. These individuals constitute a large number of those seeking treatment in substance abuse programs (McKellar 2003), and these patients have mostly been excluded from clinical trials evaluating pharmacotherapies for alcohol dependence. Some evidence is emerging, however. A few pilot studies including open-label reports, chart review studies, and a large safety study suggest that naltrexone is safe in patients with alcoholism and comorbid severe mental illness (Croop et al 1997; Salloum et al 1998; Maxwell and Shinderman 2000; Morris et al 2001). A small controlled clinical trial has shown naltrexone to be effective in reducing alcohol consumption and craving compared with placebo in patients with alcohol dependence and comorbid schizophrenia (Petrakis et al 2004). A large administrative review of naltrexone utilization in the Department of Veterans Affairs nationally demonstrated a low overall rate of naltrexone use (<2%), but clinicians were more likely to use it in patients with comorbid Axis I psychiatric diagnoses and in those who have had recent psychiatric inpatient hospitalization (Petrakis et al 2003). This suggests that in an ordinary clinic setting, naltrexone use is associated with comorbid Axis I psychiatric conditions, demonstrating the need for a rigorous study of its efficacy in this population.

Disulfiram, the other medication approved by the FDA for the treatment of alcohol dependence, has been used clinically in the management of patients with alcohol dependence for 50 years (Meyer 1989). Disulfiram's support from clinical trials has been mixed, with a landmark multisite study reporting that disulfiram was not superior to placebo in reducing alcohol use (Fuller et al 1986). In fact, positive clinical outcomes were found only for those individuals who complied with disulfiram. Studies in which compliance is facilitated through compliance contracts, mandates, or methadone delivery have suggested disulfiram's efficacy (Ling and Weiss 1983; O'Farrell and Bayog 1986; Chick et al 1992; Petrakis et al 2000). Like naltrexone, disulfiram has not been rigorously tested in individuals with psychiatric comorbidity. Early reports suggested disulfiram may precipitate or worsen psychosis in schizophrenia patients (Larson et al 1992), whereas other reports suggest it may be used safely in patients with comorbid psychiatric disorders (Larson et al 1992; Mueser et al 2003). To our knowledge, naltrexone and disulfiram have not been systematically compared or tested together in combination for alcohol dependence. These two medications have a very different mechanism of action, and each may have a unique contribution in the treatment of alcoholism. Self-administration, human laboratory, and retrospective patient reports from clinical trials have provided evidence for a potential mechanism of action for naltrexone. Naltrexone appears to reduce the rewarding effects of alcohol consumption and the ability of initial alcohol consumption to prime for further drinking (Swift et al 1994; Volpicelli et al 1995; Davidson et al 1996; O'Malley et al 1996, 2002). In contrast with disulfiram, naltrexone does not lead to a powerful aversive reaction if patients consume alcohol. Patients

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may thus be more willing to initiate naltrexone treatment and to continue to take the medication because they know that drinking is not prohibited. Disulfiram, on the other hand, may be more effective in promoting abstinence in individuals motivated for treatment but may appeal to fewer patients and lead to more discontinuation of treatment. Medication compliance has influenced the efficacy of both medications (Fuller et al 1986; Chick et al 1992; Volpicelli et al 1997).

We conducted a multicenter controlled trial of the efficacy of naltrexone and disulfiram alone and in combination in individuals with major Axis I disorders and comorbid alcohol dependence in a general clinic (i.e., nonresearch) setting. In this 12-week outpatient study, individuals were randomized to one of four groups: 1) naltrexone alone; 2) placebo alone; 3) disulfiram and naltrexone; or 4) disulfiram and placebo. The use of a placebo control condition for disulfiram may lead to the temptation for individuals to sample alcohol to "test" the blind, leaving questions about the safety and the ability to have a true medication blind using this design. Therefore, individuals were randomized to either disulfiram or no disulfiram, and disulfiram was dispensed in an open-label fashion. The dispensing of naltrexone was placebo-controlled and double-blind. We evaluated the following hypotheses: 1) either medication condition would yield superior drinking outcomes when contrasted with inactive medication, 2) naltrexone would be superior to disulfiram in indices of patient acceptance and craving and would result in fewer heavy drinking days, and 3) combination treatment would be superior to either treatment alone because it would combine the abstinence-initiating effect of disulfiram with the antipriming effects of naltrexone. Furthermore, because disulfiram was dispensed in an open fashion, we could evaluate the relative acceptability and efficacy of each treatment because patients in the combined medication group could discontinue disulfiram while still complying with naltrexone treatment if they planned to drink.

Methods

Subjects

This study was approved by the Human Subjects Subcommittee of the VA Connecticut Healthcare System and the Northampton and Bedford, Massachusetts, VAs, which are all affiliated with the New England Mental Illness and Research Education Clinical Center (MIRECC). Subjects were recruited from the patients who were treated in clinics at these MIRECC facilities. Subjects met current DSM-IV criteria for a major Axis I disorder and current DSM-IV criteria for alcohol dependence. These diagnoses were determined by structured clinical interview (Spitzer et al 1992). Subjects had been abstinent no more than 29 days. Those subjects on psychiatric medications had to be on a stable regimen for at least 2 weeks before randomization. Exclusion criteria were unstable psychotic symptoms or serious current psychiatric symptoms, such as suicidal or homicidal ideation, or medical problems that would contraindicate the use of naltrexone and disulfiram, including liver function tests $>$ 3 times the normal level. Those subjects on psychiatric medications had to be on a stable regimen (no medication changes) for at least 2 weeks before randomization. Subjects were also required to be abstinent for 3 days before randomization, and the stated goal of the study was complete abstinence.

Because subjects were recruited from the clinics at the three VA sites, participants in the trial continued to receive psychiatric treatment as usual. All three clinics have intensive substance abuse treatment programs that include an intensive rehabilitation program with aftercare and supported housing options for patients in treatment. Most subjects were already enrolled in the clinics before signing informed consent, although a few responded to advertisements and entered treatment as a result of entering into the trial.

After providing written informed consent, subjects completed an intake assessment, which included a physical examination, laboratory assessments, and an interview with a psychiatrist. Of the 567 patients meeting initial eligibility criteria, 313 declined to participate or were deemed ineligible, and 254 were randomized. As shown in Figure 1, of those who were not randomized, the most common reasons were an unwillingness to be randomized (n = 98) or take the study medications (n = 78). In addition, 43 individuals had medical conditions that precluded participation, 43 did not have a current comorbid Axis I psychiatric disorder, 18 did not meet criteria for alcohol dependence, 33 individuals could not maintain the 3-day sobriety requirement before randomization, 24 individuals were using opiates, 23 were deemed as cognitively impaired and unable to participate, and 9 were psychiatrically unstable. Other reasons included no reliable transportation (n = 36), moving within the next 6 months (n = 15), facing possible incarceration (n = 15), or not eligible for VA services (n = 9). Individuals may have had more than one reason for exclusion from participation.

Treatments

Following completion of these baseline assessments, 254 subjects were randomized to one of four groups for a 12-week trial. Randomization included 1) open randomization to disulfiram 250 mg or no disulfiram, and 2) randomization to naltrexone 50 mg or placebo in a double-blind fashion. This resulted in the following groups: naltrexone alone, placebo alone, disulfiram and naltrexone, or disulfiram and placebo.

The randomization was done simultaneously, and those subjects who were on disulfiram were given two study bottles and started both medications on the first day of randomization. Medications were stored in separate bottles for each study medication and clearly labeled as "disulfiram" or "naltrexone study medication." Medication compliance was assessed using Microelective Events Monitoring (MEMS) caps at each visit. All subjects were informed of how their medication compliance would be monitored and also received weekly Clinical Management/Compliance Enhancement therapy (Carroll et al 1998) administered by research personnel.

Assessments

Primary outcomes were measures of alcohol use. The Substance Abuse Calendar, based on the Timeline Follow-Back Interview (Sobell and Sobell 1992), was administered by a research assistant at each weekly visit to collect a detailed self-report of alcohol and other substance use throughout the 84-day treatment period as well as for the 90-day period before randomization. Although data on alcohol consumption was available for the 90-day period before randomization occurred, most patients decreased their alcohol use because they had already entered treatment. Therefore, the first 30 days of this baseline period is more representative of their actual baseline alcohol consumption. Craving was assessed weekly using the Obsessive Compulsive Drinking Scale (OCDS; Anton et al 1996).

Psychiatric symptoms were assessed using the Brief Symptoms Inventory (BSI; Derogatis and Melisaratos 1983) administered by the research staff at the baseline and biweekly during