Efficacy and Tolerability of Long-Acting Injectable Naltrexone for Alcohol Dependence

A Randomized Controlled Trial

James C. Garbutt, MD
Henry R. Kranzler, MD
Stephanie S. O'Malley, PhD
David R. Gastfriend, MD
Helen M. Pettinati, PhD
Bernard L. Silverman, MD
John W. Loewy, PhD
Elliot W. Ehrich, MD
for the Vivitrex Study Group

Context Alcohol dependence is a common disorder associated with significant morbidity and mortality. Naltrexone, an opioid antagonist, has been shown to be effective for treatment of alcohol dependence. However, adherence to daily oral pharmacotherapy can be problematic, and clinical acceptance and utility of oral naltrexone have been limited.

Objective To determine efficacy and tolerability of a long-acting intramuscular formulation of naltrexone for treatment of alcohol-dependent patients.

Design, Setting, and Participants A 6-month, randomized, double-blind, placebo-controlled trial conducted between February 2002 and September 2003 at 24 US public hospitals, private and Veterans Administration clinics, and tertiary care medical centers. Of the 899 individuals screened, 627 who were diagnosed as being actively drinking alcohol-dependent adults were randomized to receive treatment and 624 received at least 1 injection.

Intervention An intramuscular injection of 380 mg of long-acting naltrexone (n = 205) or 190 mg of long-acting naltrexone (n = 210) or a matching volume of placebo (n = 209) each administered monthly and combined with 12 sessions of low-intensity psychosocial intervention.

Main Outcome Measure The event rate of heavy drinking days in the intent-to-treat population.

Results Compared with placebo, 380 mg of long-acting naltrexone resulted in a 25% decrease in the event rate of heavy drinking days ($P = .03$) and 190 mg of naltrexone resulted in a 17% decrease ($P = .07$). Sex and pretreatment abstinence each showed significant interaction with the medication group on treatment outcome, with men and those with lead-in abstinence both exhibiting greater treatment effects. Discontinuation due to adverse events occurred in 14.1% in the 380-mg and 6.7% in the 190-mg group and 6.7% in the placebo group. Overall, rate and time to treatment discontinuation were similar among treatment groups.

Conclusions Long-acting naltrexone was well tolerated and resulted in reductions in heavy drinking among treatment-seeking alcohol-dependent patients during 6 months of therapy. These data indicate that long-acting naltrexone can be of benefit in the treatment of alcohol dependence.

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ALCOHOL DEPENDENCE IS A MAjor public health problem, which worldwide is the fourth leading cause of disability.[1] Alcohol dependence is present in approximately 4% of the US adult population,[2] is common among primary care patients,[3,4] and may contribute to more than 100 000 preventable deaths per year.[5] Addiction counseling, behavioral treatments, and self-help groups (eg, Alcoholics Anonymous) are the primary interventions used to treat alcohol dependence in the United States. Although these treatments are often effective, a substantial number of patients fail to complete them or relapse.[6]

Similar to diabetes, hypertension, and asthma, alcohol dependence is increasingly recognized as a chronic disease in which genetic vulnerability and social and environmental factors are involved in the etiology and course of the disease.[7] As with other chronic diseases, long-term comprehensive man-

See also Patient Page.

Author Affiliations: Department of Psychiatry, University of North Carolina School of Medicine, Chapel Hill (Dr Garbutt), Department of Psychiatry, University of Connecticut School of Medicine, Farmington (Dr Kranzler), Department of Psychiatry, Yale University School of Medicine, New Haven, Conn (Dr O'Malley), Department of Psychiatry, Massachusetts General Hospital, Harvard Medical School, Boston (Dr Gastfriend), Department of Psychiatry, University of Pennsylvania School of Medicine, Philadelphia (Dr Pettinati), Alkermes Inc, Cambridge, Mass (Drs Silverman, Loewy, and Ehrich). Dr Gastfriend is now with Alkermes Inc.
The Vivitrex Study Group members participating in this trial are listed at the end of the article.
Corresponding Author: James C. Garbutt, MD, CB No. 7160, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599-7160 (e-mail: jc_garbutt@med.unc.edu).

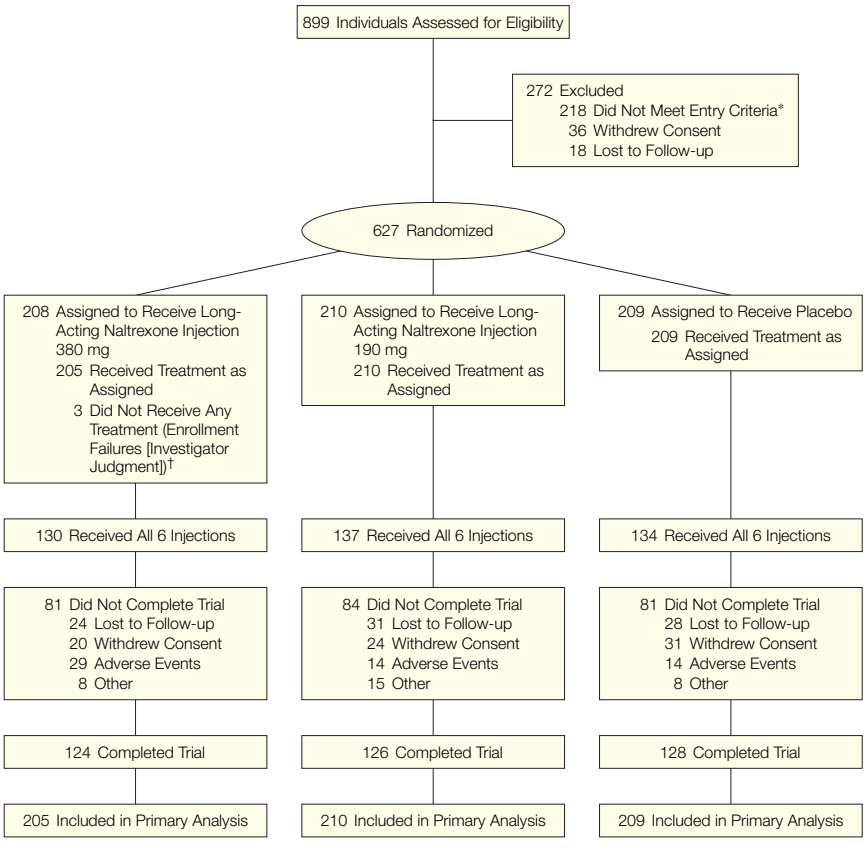
agement strategies are necessary to achieve and sustain the benefits of alcohol dependence treatment. Pharmacotherapy represents an emerging treatment option that could be used by primary care practitioners and addiction specialists.[8]

In 1994, naltrexone was approved by the US Food and Drug Administration to treat alcohol dependence after the medication was shown to reduce drinking frequency and the likelihood of relapse to heavy drinking.[9,10] Naltrexone, an opioid antagonist, is thought to reduce the reinforcing subjective or behavioral response to alcohol.[11,12] In about 3200 alcohol-dependent patients in at least 19 published controlled studies, oral naltrexone, compared with placebo, has shown efficacy in the treatment of alcohol dependence although some studies have reported no or minimal effectiveness.[13-18] Despite substantial evidence of efficacy, clinical use of naltrexone has been limited, in part because of the heterogeneity in treatment response.[19]

One documented reason for the heterogeneity of response across naltrexone trials has been poor adherence to the daily medication regimen.[20-23] Adherence to a daily oral medication regimen is a general problem in medicine.[7] Additional challenges to adherence in the context of substance abuse include variable patient motivation toward treatment; impaired cognitive function, particularly executive function; and denial.[24] As a prototypical addictive disorder, alcohol dependence is thought to involve dysfunction of the brain's reward system with attendant impaired control over drives and motivation.[25] Moreover, treatment may directly conflict with the behaviors and rewards associated with the abused substance.[26]

Since the 1970s, several efforts have been made to develop a parenteral extended-release naltrexone,[27-29] and 1 formulation has reported an effect on abstinence.[29] Recently, a new polylactide-co-glycolide (PLG)–based, long-acting naltrexone formulation that releases naltrexone for 1 month following a single injection was developed.[30] We conducted a 6-month, multicenter, randomized, double-blind, placebo-controlled study of the efficacy and safety of 2 dosing levels of this long-acting injectable formulation of naltrexone in combination with a low-intensity psychosocial intervention for treatment of alcohol dependence.

Figure 1. Trial Flow Diagram



*The most common reasons for screening failures included a clinically significant medical condition, active hepatitis (aspartate transaminase [AST] or alanine transaminase [ALT] >3 times the upper limit of normal), failure to meet an average of 2 episodes of heavy drinking per week for the 30 days before randomization, and clinically significant psychiatric disease.
†Enrollment failures due to investigator judgment were from seizure; an ongoing unresolved, unstable medical condition; and planned surgery to include opiate analgesia.

METHODS

This study was conducted at 24 US public hospitals, private and Veterans Administration clinics, and tertiary care medical centers. Of 899 individuals who were screened, 627 were determined eligible and were randomly assigned to receive treatment during the period of February 2002 to September 2003 (FIGURE 1). All patients provided written, informed consent, which, along with the protocol, was approved by each center's institutional review board.

Screening and Eligibility Criteria

Participants were male or nonpregnant nonlactating female outpatients aged 18 years or older with a current diagnosis of alcohol dependence defined by the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*).[31] Patients also had a minimum of 2 episodes of heavy drinking (≥5 standard drinks/d for men and ≥4 standard drinks/d for women) per week during the 30 days before screening. Race determination was based on the participant's response during the screening interview. Although race was

used to compare medication groups at baseline, there was no a priori hypothesis about race and treatment effect.

Exclusion criteria included evidence of liver failure; alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels greater than 3 times the upper limit of normal; any clinically significant medical condition that in the opinion of the investigator would adversely affect safety or study participation; major depression with suicidal ideation, psychosis, or bipolar disorder (patients with treated depression and stable pharmacotherapy for at least 8 weeks were not excluded); dependence within the past year on benzodiazepines, opiates, or cocaine; more than 7 days of inpatient treatment for substance abuse in the month before screening; or use of opiates, oral naltrexone, or disulfiram in the 2 weeks before screening. A negative urine test result for opiates and methadone was required on the day of randomization. Detoxification prior to randomization was performed only if medically indicated. Use of benzodiazepines was prohibited during the week before the first dose of study medication. Important selection features were that inclusion did not require intent to abstain and ongoing active drinking was not a cause for exclusion. A subpopulation of lead-in abstinent patients was defined as those who reported no drinking during the 7 consecutive days preceding the first dose of study medication.

Randomization Procedures

Patients were randomized to 1 of 3 treatment groups: long-acting injectable naltrexone 380 mg (4 mL), long-acting injectable naltrexone 190 mg (2 mL), or placebo (half of this group received 4-mL injections of microspheres without naltrexone, and the other half received 2-mL injections). The study used a dynamic randomization procedure based on the biased coin principle[32] to optimally balance the allocation of participants based on 4 characteristics: sex, patient-specified goal of total abstinence, self-reported abstinence for the 7-day lead-in period prior, and study site.

Study Procedures and Outcome Definitions

Over 24 weeks, patients received at 4-week intervals intramuscular gluteal injections of the study medication on alternating sides. Injections were prepared in amber-colored syringes to mask a slight color difference between the active and placebo microspheres. To preserve the blind, injections were administered by individuals who were not involved in any of the safety or efficacy assessments or psychosocial treatments. Treatment assignment was blinded to all other study personnel.

All patients received standardized supportive therapy (12 sessions) using the Biopsychosocial, Report, Empathy, Needs, Direct advice, and Assessment (BRENDA) model,[33] a 6-stage, low-intensity intervention designed to facilitate direct feedback of addiction-related consequences. During this trial, BRENDA sessions were administered by psychologists, nurses, therapists, counselors, and physicians at the study sites. At each study visit, patients were systematically asked whether any adverse events had occurred and injection sites were inspected.

The number of standard drinks consumed per day was recorded using the timeline follow back method, which uses calendars and recall of drinking patterns to yield reliable and valid reports by patients.[34] To maximize the accuracy of self-report, such data were collected only when breath alcohol levels were 0.02 g/dL or less. Patients who discontinued study drug treatment prematurely were allowed to remain in the study, continue to follow the established visit and procedure schedule, and receive BRENDA treatment. At the end of the study or at early termination, participants were referred for appropriate alcoholism treatment as determined by the site research team.

Study Formulation

The naltrexone long-acting injection used in this study consisted of microspheres (approximately 100-μm diameter) composed of naltrexone and PLG polymeric matrix. PLG is a common biodegradable medical polymer with an extensive history of human use in absorbable sutures and extended-release pharmaceuticals. Following injection, naltrexone is released from the microspheres, yielding peak concentrations within 3 days. Thereafter, by a combination of diffusion and erosion, naltrexone is released for more than 30 days.[30,35]

Definition of Outcomes

The primary efficacy end point was the event rate, which combines the frequency and pattern of heavy drinking days over the 24 weeks of treatment. The definition of heavy drinking (≥5 drinks per day for men and ≥4 drinks per day for women) is consistent with that used in previous trials of oral naltrexone.[9,10,13,36] Overall, the event rate of heavy drinking is the number of heavy drinking days divided by the number of days at risk for heavy drinking. On each day, the treatment group event rate was contrasted with the placebo group event rate by forming the event rate ratio. The method of analysis estimates the average event rate ratio over time taking into account patient discontinuation.

Secondary end points included the event rate of "risky" drinking days (>2 drinks per day for men and >1 drink per day for women) adapted from the National Institute on Alcohol Abuse and Alcoholism[37] and the event rate of any drinking days. Exploratory end points included changes in serum γ-glutamyl transferase concentration over time and time to study discontinuation. Adverse events were coded using the preferred terminology of the Medical Dictionary for Regulatory Activities.[38] Serious adverse events (SAEs) were defined as any untoward medical occurrence that at any dose results in death, is life-threatening, requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect. Serious adverse events could also be identified by the investigator if the events would have jeopardized the patient or required in-

tervention to prevent one of the other outcomes listed previously.

Statistical Methods

The primary analysis for the primary and secondary end points was performed on the intention-to-treat population. The primary objective was to determine whether either dosage of long-acting naltrexone decreased the event rate of heavy drinking days compared with placebo. Statistical methods to analyze multiple drinking episodes in alcoholism treatment clinical trials have been described by Wang et al.[39]

The primary analysis for the end point was performed using a stratified Andersen-Gill recurrent-event Cox model with robust variance estimation.[40,41] The model estimated the treatment effects of naltrexone 190 mg vs placebo and naltrexone 380 mg vs placebo.

The analysis was performed on all heavy drinking events between the first treatment and 30 days following the last dose. In the case of dropouts, last-day drinking data were collected. Analyses of the primary end point were performed for each of the predefined stratification variables (sex, goal of abstinence, 7-day period of abstinence prior to treatment). No imputations were performed for days in which drinking data were unavailable. Retention rate comparability between treatment groups was evaluated by generating Kaplan-Meier curves for the time-to-study discontinuation. A log-rank test was used to examine treatment group differences. Furthermore, to adjust for the impact of participant discontinuation during the study while measuring the treatment effect on heavy drinking, a pattern mixture-model approach was implemented in the generalized Andersen-Gill recurrent-event Cox model.[42] We used SAS version 8.2 statistical software (SAS Institute Inc, Cary, NC). We considered $P<.05$ (2-tailed) to be statistically significant.

RESULTS

Between February 2002 and September 2003, 627 patients were randomly assigned to one of the treatment groups. Three patients did not receive their first injection based on investigator decision, leaving 624 patients who received treatment and constituted the intention-to-treat population for analyses (Figure 1). Four hundred twenty-three patients (68%) were men and 521 (83%) were white. The mean age was 45 years (range, 19-74 years). The mean (SD) of heavy drinking days in the 30 days before randomization was 20 (8) days. Overall, 53 (8.8%) of patients were abstinent in the 7 days before receiving the first injection, and 270 (43%) of the patients had a treatment goal of total abstinence. Pretreatment characteristics of the patients in the 3 treatment groups were similar although women differed from men on several measures, including being more likely to use antidepressant medication and less likely to smoke (TABLE 1).

In 401 patients (64%), all 6 injections were administered, and 463 (74%) received at least 4 injections. Time to discontinuation was similar among groups. The median rate of therapy sessions completed was 92% (11 of 12 possible), and 267 (43%) of patients attended all therapy sessions. The number of therapy sessions and the percentage of patients attending all sessions were similar among treatment groups.

Adverse events occurring in at least 10% of the patients during treatment with long-acting injectable naltrexone are listed in TABLE 2. The most common adverse events were nausea, headache, and fatigue. Nausea was mild or moderate in approximately 95% of cases; however, the large majority of these episodes occurred only during the first month of treatment. Nausea and decreased appetite occurred more frequently in patients treated with long-acting naltrexone 380 mg.

The most common injection site reaction was tenderness, occurring after 15.9% of 380-mg and 13.6% of 190-mg naltrexone doses and after 17.6% of 4-mL placebo and 9.2% of 2-mL placebo injections. Seven patients (about 1%) discontinued injections due to site reactions: 4 in the 380-mg naltrexone and 2 in the 190-mg naltrexone groups and 1 in the 4-mL placebo group.

Study discontinuation secondary to adverse events occurred in 29 (14.1%) in the 380-mg naltrexone, 14 (6.7%) in the 190-mg naltrexone and 14 (6.7%) in the placebo groups ($P = .01$, 380 mg vs 190 mg and placebo; the group difference being accounted for by a greater number of adverse events of nausea, injection site reaction, and headache). The percentage of patients who experienced SAEs during treatment was similar among the treatment groups: 11 (5.4%) for 380-mg and 10 (4.8%) for 190-mg naltrexone and 15 (7.2%) for placebo. The most common SAE was hospitalization for alcohol detoxification. Two SAEs (eosinophilic pneumonia and interstitial pneumonia) were judged by the investigator to be possibly related to study medication. Both events occurred in patients treated with naltrexone 380 mg and resolved with treatment. These complications have not been reported previously with either naltrexone or the PLG microspheres.

Mean AST and ALT levels did not change significantly over the course of treatment or with medication. Furthermore, there was no effect of medication on the proportion of patients in the different groups who had AST or ALT elevations higher than 3 times the upper limit of normal.

Analyses of primary and secondary efficacy variables measured during the 6-month treatment period are listed in TABLE 3. Patients treated with long-acting naltrexone 380 mg experienced approximately a 25% greater reduction in the rate of heavy drinking relative to placebo-treated patients ($P = .03$; FIGURE 2 and FIGURE 3). Patients treated with naltrexone 190 mg reported a 17% greater reduction in the rate of heavy drinking than placebo-treated patients ($P = .07$). Neither the rate of National Institute on Alcohol Abuse and Alcoholism risky drinking nor the rate of any drinking was significantly lower with either dose of long-acting naltrexone (Table 3). Consistent with observed reductions in heavy drinking, there was a 15% reduction in γ-glutamyl trans-

Table 1. Baseline Characteristics of the Patients

Characteristics	Long-Acting Naltrexone						Placebo (n = 209)		
	380 mg (n = 205)			190 mg (n = 210)					
	Overall	Men	Women	Overall	Men	Women	Overall	Men	Women
Demographics									
Age, mean (SD), y*	45.0 (10.1)	45.4 (10.9)	44.2 (8.3)	44.6 (10.8)	44.6 (11.5)	44.6 (9.3)	44.7 (10.8)	44.7 (11.2)	44.6 (10.0)
Sex, No. (%)	205	138 (67.3)	67 (32.7)	210	142 (67.6)	68 (32.4)	209	143 (68.4)	66 (31.6)
White, No. (%)	172 (83.9)	113 (81.9)	59 (88.1)	169 (80.5)	112 (78.9)	57 (83.8)	180 (86.1)	119 (83.2)	61 (92.4)
Weight, mean (SD), kg*	84.2 (20.7)	90.5 (19.2)	71.1 (17.5)	82.7 (19.8)	88.7 (19.2)	70.5 (15.3)	81.6 (17.0)	86.1 (15.5)	71.9 (16.2)
Employed ≥20 h/wk, No. (%)	144 (70.2)	98 (71.0)	46 (68.7)	149 (71.0)	105 (73.9)	44 (64.7)	151 (72.2)	103 (72.0)	48 (72.7)
Other drug use, No. (%)									
Current smoker*	99 (48.3)	73 (52.9)	26 (38.8)	106 (50.5)	76 (53.5)	30 (44.1)	88 (42.1)	65 (45.5)	23 (34.8)
Antidepressants	62 (30.2)	30 (21.7)	32 (47.8)	55 (26.3)	30 (21.3)	25 (36.8)	61 (29.2)	35 (24.5)	26 (39.4)
Liver enzyme levels, mean (SD), U/L†									
AST*	30.0 (13.1)	32.5 (14.3)	24.7 (8.0)	32.7 (17.4)	35.7 (18.6)	26.4 (12.5)	31.9 (18.1)	33.8 (18.5)	27.7 (16.5)
ALT*	31.9 (19.2)	37.3 (20.5)	20.8 (8.6)	32.9 (20.6)	38.2 (22.1)	21.8 (10.9)	34.0 (21.8)	38.1 (22.4)	25.0 (17.6)
GGT*	58.6 (60.8)	67.7 (63.8)	39.8 (49.7)	73.5 (86.4)	86.6 (90.5)	46.1 (70.3)	75.6 (113.9)	87.2 (127.3)	50.5 (72.0)
Drinking behavior									
Abstinence goal, No. (%)	90 (43.9)	65 (47.1)	25 (37.3)	90 (42.9)	59 (41.5)	31 (45.6)	90 (43.1)	65 (45.5)	25 (37.9)
Abstinence for 7 d before randomization, No. (%)	17 (8.3)	13 (9.4)	4 (6.0)	17 (8.1)	10 (7.0)	7 (10.3)	19 (9.1)	15 (10.5)	4 (6.1)
Self-help group attendance, No. (%)*	24 (11.7)	18 (13.0)	6 (9.0)	22 (10.5)	17 (12.0)	5 (7.4)	23 (11.0)	19 (13.3)	4 (6.1)
% Heavy drinking in 30 d before randomization, mean (SD)‡	64.0 (25.9)	63.5 (26.5)	65.0 (24.8)	65.6 (26.4)	64.6 (25.4)	67.7 (28.4)	65.2 (24.8)	65.2 (24.5)	65.2 (25.5)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyltransferase.
*$P<.05$ (significant difference between men and women in the overall study population [N = 624]).
†The normal enzyme level ranges are sex and age specific: ALT: women 18 to 69 years is 6 to 34 U/L; >69 years, 6 to 32 U/L; men 18 to 69 years, 6 to 43 U/L; >69 years, 6 to 35 U/L; AST: women ≥18 years, 9 to 34 U/L, men ≥18 years, 11 to 36 U/L; GGT: women, 18 to 59 years, 4 to 49 U/L and >59 years, 5 to 50 U/L; men 18 to 59 years, 10 to 61 U/L; and >59 years, 10 to 50 U/L.
‡Heavy drinking is defined in the "Methods" section.

ferase observed during the study for the overall sample. The rate of nausea was not related to the event rate of heavy drinking.

Treatment × factor interactions were examined for the 3 predefined randomization factors: sex, lead-in abstinence, and treatment goal of abstinence. Treatment × factor interactions with long-acting naltrexone demonstrated significant effects for sex ($P = .002$) and lead-in abstinence ($P = .02$). The treatment goal of abstinence did not demonstrate a significant interaction with treatment. To further explore the observed treatment × factor interactions, treatment effects were calculated for the individual subgroups defined by the factors (Table 3). The results indicate that the treatment effect among men taking 380-mg naltrexone vs placebo was highly significant (hazard ratio [HR], 0.56, $P<.001$), whereas the treatment effect was not significant in women (HR, 1.23, $P = .28$). Significant treatment effects were observed with long-acting naltrexone 380 mg vs placebo irrespective of whether patients were abstinent during lead-in; however, treatment effects were greater for patients with lead-in abstinence (HR, 0.20, $P = .005$) compared with patients who drank during the lead-in period (HR, 0.79,

Table 2. Adverse Events During Treatment Occurring in 10% or More of Patients

Adverse Event	No. (%) of Patients*			*P* Value	
	380 mg (n = 205)	190 mg (n = 210)	Placebo (n = 209)	380-mg Naltrexone vs Placebo	380-mg vs 190-mg Naltrexone
Nausea	68 (33)	53 (25)	23 (11)	<.001	.08
Headache	45 (22)	33 (16)	34 (16)	.17	.13
Fatigue	41 (20)	34 (16)	23 (11)	.01	.37
Insomnia	28 (14)	27 (13)	25 (12)	.66	.89
Vomiting	28 (14)	22 (11)	12 (6)	.20	.65
Decreased appetite	26 (13)	12 (6)	3 (1)	<.001	.02
Diarrhea	26 (13)	23 (11)	18 (9)	.20	.65
Dizziness	26 (13)	23 (11)	8 (4)	.001	.65
Injection site pain	24 (12)	18 (9)	19 (9)	.04	.42
Nasopharyngitis	22 (11)	32 (15)	24 (12)	>.99	.19
Upper respiratory tract infection	21 (10)	15 (7)	18 (9)	.62	.30

*Percentages are based on the number of patients in the intent-to-treat population (dosed at least once). Fisher exact test was used for association of treatment by adverse event; pairwise comparisons with 2 × 2 tables. Other adverse events, that occurred in less than 10% of patients but more frequently in the long-acting naltrexone patients ($P<.05$) included the following: abdominal pain ($P = .01$), injection site induration ($P = .03$), injection site pruritus ($P = .01$), and decreased libido ($P = .01$). Adverse event rates were similar for men and women except for nausea, which was significantly higher in women at 190 mg only, and for decreased libido, which was limited to men.

$P = .05$). The subset of patients with lead-in abstinence also showed a significant treatment effect with long-acting naltrexone 190 mg vs placebo (HR, 0.05, $P < .001$). However, due to small numbers in certain of the individual subgroups, these and the following analyses should be interpreted with caution.

Table 3. Analyses of Primary and Secondary Efficacy Outcomes*

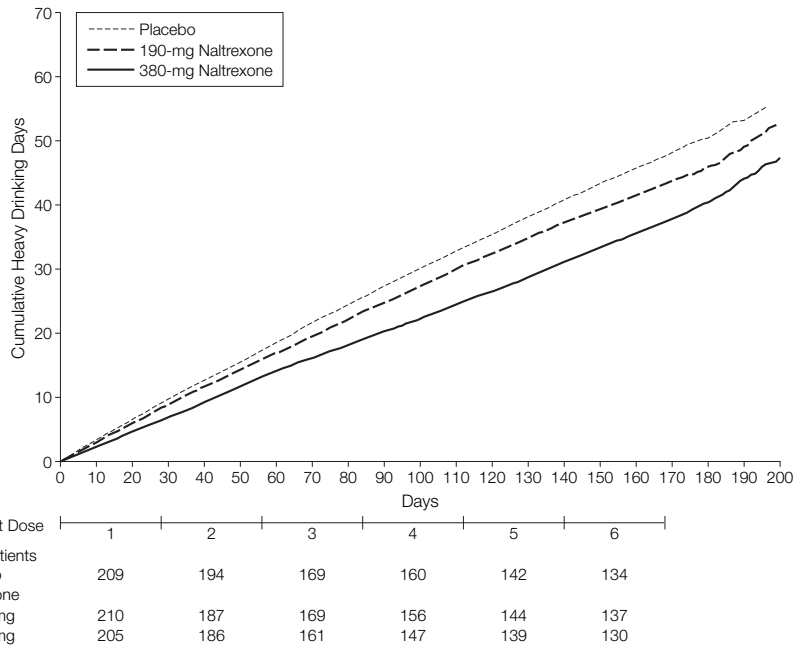
	Population	Naltrexone 380 mg vs Placebo		Naltrexone 190 mg vs Placebo	
		Hazard Ratio (95% CI)	*P* Value	Hazard Ratio‡ (95% CI)	*P* Value
Primary outcome					
Heavy drinking	624	0.75 (0.60-0.94)	.03	0.83 (0.68-1.02)	.07
Sex					
Men	423	0.56 (0.41-0.77)	<.001	0.83 (0.64-1.07)	.16
Women	201	1.23 (0.85-1.78)	.28	1.07 (0.73-1.58)	.72
Goal of total abstinence					
Yes	270	0.72 (0.48-1.08)	.11	0.88 (0.61-1.28)	.50
No	354	0.79 (0.59-1.05)	.10	0.91 (0.70-18)	.48
Lead-in drinking					
Yes	571	0.79 (0.62-1.00)	.05	0.93 (0.75-1.15)	.48
No	53	0.20 (0.07-0.62)	.005	0.05 (0.02-0.15)	<.001
Secondary outcomes					
Risky drinking†	624	0.90 (0.76-1.07)	.23	0.95 (0.81-1.13)	.58
Nonabstinent days	624	0.96 (0.83-1.11)	.58	0.98 (0.85-1.14)	.80

*For the primary end point (heavy drinking), the Hochberg method was used to adjust multiple comparisons. As specified a priori, the secondary outcomes (drinking more than the National Institute on Alcohol Abuse and Alcoholism–specified level of risky drinking and nonabstinent days) are included for informational purposes, and no adjustments were made.

†National Institute on Alcohol Abuse and Alcoholism–specified level of risky drinking is more than 2 drinks per day for men and more than 1 drink for women.

‡Treatment effect size is derived from the estimate of the hazard ratio (HR) for each individual treatment relative to placebo: HR = 1 indicates no treatment effect (ie, treatment effect size = 0); HR = 0.75 is a 25% reduction of heavy drinking relative to placebo (ie, treatment effect size relative to placebo = 0.25); HR = 1.25 is a 25% increase of heavy drinking relative to placebo (ie, treatment effect size relative to placebo = 1.25).

Figure 2. Primary Efficacy Analysis: Mean Heavy Drinking Event Rate



Intention-to-treat analysis shows the cumulative mean event rate of heavy drinking during the study by treatment group. The participant retention rates are shown at 4-week intervals through 24 weeks, which was the intended duration of the treatment.

To explore factors that could be influential alone and in combination with treatment for heavy drinking outcomes in women, 9 factors were examined including age, lead-in drinking, attendance at self-help group meetings, treatment goal, employment status, body mass index, use of antidepressants, race, and history of depression. Each factor was dichotomized, and efficacy analyses for each subgroup of women were performed. These either showed no difference between subgroup pairs or yielded subgroup sizes that were too small for meaningful interpretation. In addition, the treatment effects of naltrexone 380 mg vs placebo in women and in the overall sample were not influenced by adjusting for smoking status.

Patients in all 3 treatment groups substantially reduced the number of heavy drinking days compared with their pretreatment levels. Figure 3 shows the change from pretreatment in the median number of heavy drinking days per month by treatment group and sex.

It was found that time to subject discontinuation was comparable for all treatment groups (log-rank test, $P = .92$). When the exposure times between treated and control groups are comparable, bias of the estimated treatment effect (as a result of dropouts) may be of less concern.[39]

The pattern mixture model analysis indicated that the treatment effect of long-acting, injectable naltrexone 380 mg compared with placebo was significant ($P = .001$). These results argue against there being a bias toward an effect of long-acting naltrexone treatment as a result of the pattern of participant discontinuation.

The patients enrolled in this study predominantly were actively drinking, with only 8.3% abstinent for the 7-day lead-in period. The number of patients who maintained complete abstinence during the trial was 14 (7%) in the 380-mg naltrexone group, 13 (6%) in the 190-mg naltrexone group, and

11 (5%) in the placebo group. Among patients with lead-in abstinence, the rate of total abstinence was 41% in the 380-mg naltrexone group, 35% in the 190-mg naltrexone group, and 17% in the placebo group. Group differences on these measures did not reach significance.

Headache did not show a clear dose-response relationship with medication; a relationship between drinking outcomes and headache was not a preplanned analysis.

COMMENT

This study demonstrated that a long-acting injectable formulation of naltrexone in conjunction with psychosocial treatment significantly reduced heavy drinking in a large geographically varied sample of treatment-seeking patients with alcohol dependence. Treatment effects were influenced by sex and prerandomization abstinence from alcohol. The efficacy of the 380-mg dose was evident within the first month after the initial injection and was maintained over the 24-week treatment period. Naltrexone injections were well tolerated, few serious adverse events were reported, and there was no evidence of hepatotoxicity.

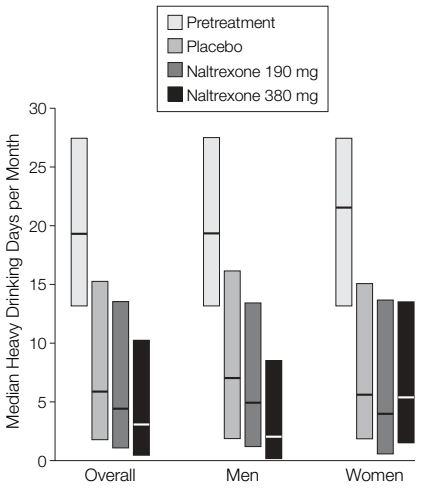
The primary outcome measure in this study—heavy drinking—is the sine qua non of alcoholism and is both clinically meaningful and of public health importance. Of the various measures of drinking behavior, heavy drinking shows the highest correlation with negative life consequences such as impaired driving, interpersonal problems, and injuries.[43] Reductions in heavy drinking, as observed in this study with long-acting naltrexone, can be expected to lead to improvements in various areas of health and in the quality of life in alcohol-dependent patients although direct evaluation of these outcomes is needed. The 25% relative reduction in the heavy drinking event rate with the 380-mg dose reflects the average reduction in drinking events within the treatment group. However, the average reduction in events is disproportionately weighted by participants who were drinking at the highest levels during the study. These patients contributed a greater number of events to the overall analysis and thus had a greater impact on the average. As can be seen in Figure 3, the 48% reduction in the median percentage of days of heavy drinking reflects the response by the typical individual patient in the study. Analyses assessing the relationship between alcohol consumption and disease risk indicate increased risk for a variety of adverse health consequences that are detectable with each additional alcoholic drink per day.[44] In addition, since no single treatment will reduce completely the risk of heavy drinking among all alcohol-dependent patients, we believe that an important clinical benefit of long-acting naltrexone is that it provides a firm basis for combination with other treatments, including psychotherapy, other medications, or both.

In contrast to the majority of clinical investigations of oral naltrexone use that have required patients to be abstinent prior to starting medication, the current study did not impose such a requirement; rather, the majority of patients enrolled were drinking heavily. Thus, the study demonstrates the efficacy of directly initiating long-acting, injectable naltrexone treatment in patients who are actively drinking but who are motivated to reduce their drinking—circumstances that are commonly seen in general medical practice.

Although not required for efficacy, the results suggest that this medication formulation is also compatible with an abstinence orientation. Patients who entered treatment with a goal of abstinence had a greater degree of drinking reduction than those who only intended to reduce their drinking, and both groups derived the same added advantage from injectable naltrexone vs placebo. However, patients who were abstinent when they began treatment benefited to a greater degree from the active agent than those who were still drinking at the time of the first injection.

Men comprised the majority (68%) of patients in this study, which is consistent with the prevalence pattern of alcohol dependence in the United States,[2] and showed a substantial treatment effect. Although it may be tempting to speculate that naltrexone may not work for women, such a conclusion is not justified because the study was not designed to answer this question, the women who participated may not be representative of women with alcohol dependence in the general population, and the number of women studied was small. Moreover, men and women in this study differed on a number of important variables, including the prevalence of smoking and antidepressant use, weight, and commitment to abstinence. Although these variables did not explain the sex differences in naltrexone efficacy, the men and women in this sample may have differed on other variables that may positively influence naltrexone response but were not assessed in this study, such as family history of alcoholism. In addition, alcohol-dependent women have been shown to respond better than men to a variety of psychosocial interventions,[45-47] making it difficult to demon-

Figure 3. Median Heavy Drinking Days per Month for Each Treatment Group Overall and by Sex



In addition to injections of study treatment, all patients received standardized, low-intensity psychosocial support. This represents an intention-to-treat analysis with the last observation carried forward. The bars represent interquartile range.

strate an added effect of medication. An important aim of future studies should be to seek a better understanding of the response by alcohol-dependent women to naltrexone.

The pharmacokinetic profile of long-acting injectable naltrexone differs substantially from that of the oral formulation. The new preparation has no daily naltrexone peaks and a reduced ratio of 6-β-naltrexol to the parent compound.[30,48] The implications, if any, of these pharmacokinetic differences from oral naltrexone for efficacy and tolerability in alcohol dependence need further study.

Our study has limitations. This trial was designed to study a broad range of alcohol-dependent patients by including patients from both public and private treatment settings and also from specialty and nonspecialty practices. However, clinical trials may enroll patients with a greater degree of motivation for change than is seen among patients who are treated in traditional outpatient settings. Although treatment attendance was relatively high in this study, dropouts reduce the extent to which the findings generalize to the population of all alcoholics. Furthermore, drinking data for dropouts were not obtained once they left the study, so it is not known how these drinking outcomes would have affected the results. Factors that potentially mitigate the impact of dropouts include the observations that dropout rates were equivalent across the 3 treatment groups and that the effects of long-acting naltrexone were noted before many participants dropped out. An important strength of the study is, in fact, that the multiple time-to-event analysis allowed information from early discontinuation to be captured in the overall efficacy analysis.

Additional research is needed to determine the optimal duration of treatment with long-acting naltrexone, as well as indicators that treatment can be discontinued. The utility of long-acting naltrexone in special populations (such as individuals with alcohol dependence and a major mental disorder or those who are in the criminal justice system) remains to be examined.

In summary, the results from this trial, with one of the largest samples ever treated with a medication for alcohol dependence, indicate that long-acting injectable naltrexone is well tolerated and is associated with a significant reduction in heavy drinking in a population of actively drinking patients. The long-acting formulation has the potential to improve intervention strategies for alcohol dependence by providing a predictable pharmacological foundation for treatment. In addition to their utility for alcohol dependence, long-acting formulations may prove to be an important treatment strategy for a variety of addictive disorders.

Author Contributions: Dr Garbutt had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Kranzler, Silverman, Loewy, O'Malley, Ehrich.
Acquisition of data: Garbutt, Kranzler, O'Malley, Gastfriend, Pettinati.
Analysis and interpretation of data: Garbutt, Kranzler, Gastfriend, Pettinati, Silverman, Loewy, O'Malley Silverman, Ehrich.
Drafting of the manuscript: Garbutt, Kranzler, O'Malley, Gastfriend, Pettinati, Silverman, Loewy, Ehrich.
Critical revision of the manuscript for important intellectual content: Garbutt, Kranzler, O'Malley, Gastfriend, Pettinati, Silverman, Loewy, Ehrich.
Statistical analysis: Loewy, Ehrich.
Obtained funding: Silverman, Ehrich.
Administrative, technical, or material support: Silverman, Loewy.
Study supervision: Garbutt, Kranzler, O'Malley, Gastfriend, Pectinati.
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Role of the Sponsor: Data were collected and monitored by Alkermes and Pharmaceutical Product Development Inc, a contract research organization. Data were managed and analyzed by Alkermes clinical and regulatory personnel and were interpreted by authors on the study with input from Alkermes clinical and statistical staff. The majority of the first draft was prepared by the lead author. The draft was reviewed by all authors over 2 meetings and at least 6 teleconferences, at which time the selection of data and their interpretation were determined by consensus.
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Vivitrex Study Group/Principal Investigators: Robert Anthenelli, MD, Cincinnati, Ohio; Louise Beckett, MD, Oklahoma City, Okla; Michael Bohn, MD, Middleton, Wis; Paul Casadonte, MD, New York, NY; Domenic Ciraulo, MD, Boston, Mass; James Garbutt, MD, Chapel Hill, NC; David Gastfriend, MD, Boston, Mass; Lawrence Ginsberg, MD, Houston, Tex; Hisham Hafez, MD, Nashua, NH; Bankole Johnson, MD, San Antonio, Tex; Philip Kanof, MD, PhD, Tucson, Ariz; Henry Kranzler, MD, Farmington, Conn; Sandra Lapham, MD, Albuquerque, NM; Peter Martin, MD, Nashville, Tenn; Barbara Mason, PhD, Miami, Fla; Mary McCaul, PhD, Baltimore, Md; Denis Mee-Lee, MD, Honolulu, Hawaii; Stephanie O'Malley, PhD, New Haven, Conn; Helen Pettinati, PhD, Philadelphia, Pa; Robert Riesenberg, Atlanta, Ga; Ihsan Salloum, MD, Pittsburgh, Pa; Jeffery Wilkins, MD, Los Angeles, Calif; Mark Willenbring, MD, Minneapolis, Minn; Allen Zweben, PhD, Milwaukee, Wis.
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opioids in combination. Tramadol has consistently occupied a high standing in these reports.

Numerator/denominator mismatching that leads to an underestimation of abuse liability is found in the data cited from the study by Knisely et al,[2] in which the number of known cases of tramadol abuse (N=15) was divided by a population (N=1601) consisting mostly (>90%) of individuals who showed no evidence of tramadol exposure. They therefore calculated an abuse incidence in a mixed population, not an abuse potential in people exposed to tramadol. It is not possible for a drug to have abuse liability in a person who has not taken that drug. For example, if only 5 people in a population of 1000 take a drug and all become addicted, the abuse liability is 100%, not 0.5%. The actual abuse potential in the study by Knisely et al should be reported as 10% (ie, 15 cases of abuse divided by 155 physicians known to have taken tramadol).

Gregory E. Skipper, MD
gregskipper@usa.net
Alabama Physician Health Program
Montgomery

David A. Brase, PhD
Rockville, Md

1. Litovitz TL, Klein-Schwartz W, Rodgers GC, et al. 2001 Annual Report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. *Am J Emerg Med*. 2002;20:391-452.
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Szasz Under Fire

To the Editor: In reading Dr Henderson's review of the book *Szasz Under Fire: The Psychiatric Abolitionist Faces His Critics*,[1] it was difficult to determine why Henderson seems surprised that Dr Szasz and his critics continue to disagree. In Thomas Kuhn's terms,[2] Szasz and psychiatrists have incommensurate paradigms. The essays in this book were well-chosen and illuminated the continuing refusal of psychiatry to understand the completeness of Szasz's rejection of what he has called "the therapeutic state."

I am most disturbed by Henderson's suggestion that Szasz is anti-Semitic, particularly by quoting Karl Popper and not Szasz himself. And Henderson's statement that the book lacks a human rights perspective indicates that he has apparently not read Szasz's work where he clearly rejects, for example, a "mental patient's bill of rights" because it claims to give the mental patient all kinds of fake freedoms but not the real freedom that matters most: freedom from being labeled and treated as a mental patient.

Keith Hoeller, PhD
Editor, *Review of Existential Psychology & Psychiatry*
RKHoeller@aol.com
Seattle, Wash

1. Henderson SW, reviewer. *JAMA*. 2005;293:240-241. Review of: *Szasz Under Fire: The Psychiatric Abolitionist Faces His Critics*.
2. Kuhn TS. *The Structure of Scientific Revolutions*. 2nd ed. Chicago, Ill: University of Chicago Press; 1970.

In Reply: First and foremost, I have no reason to believe that Dr Szasz is anti-Semitic and every reason to believe that Karl Popper was not, and I regret any implication to the contrary. Rather, I was concerned that Popper's letter, otherwise uncontextualized in the vituperative milieu of this book, could be read as an allusion to the anti-Semitism that has occasionally but notoriously lurked in criticisms of psychiatry, from both within and without.[1]

I was not surprised that there is disagreement between Szasz and his critics (a lack of which would have made for dull reading, and this book is certainly not dull). I was, however, startled by the vehemence of the invective and the degree to which many, but not all, of the parties refused this opportunity to think through and beyond various points of impasse. After all, the "continuing refusal of psychiatry to understand the completeness of Szasz's rejection of . . . 'the therapeutic state'" is simply matched by Szasz's refusal to understand the rejection of his positions. Some differences cannot be reconciled, but I question whether Szasz and psychiatrists have entirely incommensurate paradigms, particularly since Szasz has practiced and taught as a psychiatrist, not without commendation.[2]

Because human rights are important to Szasz's thinking and libertarian philosophies, I had noted that this book would have benefited from an expert in that field, just as the editor sought out experts in other areas pertinent to Szasz's thinking. That Szasz might reject aspects of this perspective would be all the more reason to include such a voice.

Schuyler W. Henderson, MD
HendersS@childpsych.columbia.edu
Columbia University
New York, NY

1. Frosh S. Freud, psychoanalysis and anti-semitism. *Psychoanal Rev*. 2004;91:309-330.
2. Dewan M Presentation at: Liberty and/or Psychiatry? 40 Years After *The Myth of Mental Illness*: A Symposium in Honor of Thomas Szasz on his 80th Birthday; April 15, 2000; Syracuse: State University of New York. Available at: http://www.szasz.com/Dewan.htm. Accessed March 9, 2005.

CORRECTION

Incorrect data: In the Original Contribution entitled "Efficacy and Tolerability of Long-Acting Injectable Naltrexone for Alcohol Dependence: A Randomized Controlled Trial" published in the April 6, 2005, issue of *JAMA* (2005;293:1617-1625), incorrect data were reported in the abstract and in Table 3. On page 1617 in the "Results" section of the abstract, "Compared with placebo, 380 mg of long-acting naltrexone resulted in a 25% decrease in the event rate of heavy drinking days" should have been reported as "(P=.02)" instead of "(P=.03)" and on page 1622 in the "Heavy drinking" row in the "Naltrexone 380 mg vs Placebo" columns of Table 3, the P value should have been reported as ".02" instead of ".03."

ponin level was normal. Electrocardiogram, echocardiogram, chest radiograph, and head and chest computed axial tomographic scan were normal. Carotid scanning was not performed. There was no arrhythmia during 24 hours of cardiac monitoring. During 2 years of follow-up there were no further episodes of syncope or near syncope or any symptoms suggesting neurological or cardiac disease.

Comment. This episode most likely represents a Valsalva-type/vagally mediated syncopal attack caused by the sustained episode of laughing. Other causes of vagal syncope are not likely because of the presence of mild temperature and the lack of prior or subsequent episodes despite standing throughout the day. Immediate return to an asymptomatic state, with a normal blood glucose level in the emergency department, similarly makes hypoglycemia an unlikely explanation. Elevated creatine kinase level with normal troponin level is consistent with muscle contusion during the fall. Absence of other symptoms with the episode, combined with the negative diagnostic test results and lack of subsequent development of overt disease over 2 years, make an underlying cardiac or neurological condition unlikely.

The only previous report of laugh-induced syncope[1] occurred in a 62-year-old man who had 3 episodes of syncope while laughing during watching "Seinfeld" on television. That patient also smoked, had hypertension and hypercholesterolemia, and had a history of coronary artery bypass graft surgery. He had widespread coronary and peripheral arterial narrowing (including carotid occlusion), with 90% occlusion in the brachiocephalic trunk. This lesion was believed to be the principal cause of the syncope because there was no recurrence after it was opened by angioplasty.

In contrast, our patient appears to represent the first reported case in an otherwise normal, healthy person. Laughing predisposes the patient to increased intrathoracic venous pressure, which is considered the underlying mechanism for syncope from such well-recognized causes as coughing, sneezing, the Valsalva maneuver, and weight lifting. These events are usually associated with acute vasodilatation of the vascular bed, reduced cardiac output, and relative bradycardia,[2,3] producing transient reduction of cerebral circulation.

The physiological as well as the acoustic similarities between coughing and laughing episodes are great. Both share a sustained state of repetitive bursts of progressive, forced expiration. They constitute a staccato pattern rather than the continuous Valsalva-like state produced by forced voiding, defecating, sneezing, swallowing, and blowing against obstruction. An extensive review of syncope[4] describes 15 variations of vasovagal syncope concluding with weight lifting and trumpet playing, but not including laughing.

Laughter has frequently been proposed to be the best medicine. However, as with any intervention, an excessive dose may result in adverse events.

Dennis Bloomfield, MD
DbloomfieldMD@aol.com
Saad Jazrawi, MD
St Vincent Catholic Medical Centers
Staten Island, NY

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CORRECTION

Additional Financial Disclosure: Stephanie O'Malley, PhD, a coauthor of the Original Communication entitled "Efficacy and Tolerability of Long-Acting Injectable Naltrexone for Alcohol Dependence: A Randomized Controlled Trial" published in the April 6, 2005, issue of *JAMA* (2005;293:1617-1625) has reported an additional financial disclosure. Dr O'Malley is an inventor on a patent held by Yale University entitled "Smoking Cessation Treatments Using Naltrexone and Related Compounds."