

EXHIBIT G

A Pilot Evaluation of the Safety and Tolerability of Repeat Dose Administration of Long-Acting Injectable Naltrexone (Vivitrex®) in Patients With Alcohol Dependence

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Background: Oral naltrexone is currently used as part of a treatment regimen for alcohol-dependent patients, but its clinical utility is hampered by poor patient adherence. A long-acting injectable naltrexone formulation (Vivitrex®) was designed to facilitate patient adherence by providing an extended duration of therapeutic naltrexone over 1 month, thereby eliminating the need for daily dosing.

Methods: A multicenter, randomized, double-blind, placebo-controlled pilot study was conducted to evaluate the safety and tolerability of intramuscular repeat dose administration of this extended-release naltrexone formulation in DSM-IV alcohol-dependent patients. Thirty patients were randomized to treatment with injectable naltrexone (400 mg; $n = 25$) or a matching placebo injection ($n = 5$) and were dosed once every 28 days over 4 months. Psychosocial treatment was offered to patients in both treatment groups. Outcome measures related to drinking activity and trough plasma concentrations of naltrexone and its primary metabolite, 6- β -naltrexol, were evaluated.

Results: Injectable naltrexone was generally safe and well tolerated. Reported adverse events were mild to moderate and resolved without intervention; only two patients discontinued due to adverse events. The most common adverse events (nausea and headache) occurred at a similar rate for patients in both treatment groups. Pharmacokinetic analysis confirmed that therapeutic levels of naltrexone were delivered throughout the four 1-month treatment cycles.

Conclusions: The results of this pilot study provide the basis and methods for a larger, more definitive trial to determine the utility of this long-acting injectable naltrexone formulation in the treatment of alcohol-dependent patients.

Key Words: Alcohol, Naltrexone, Treatment, Opioid, Humans.

TRADITIONALLY, THE TREATMENT of alcohol dependence has been based on various forms of counseling, including self-help groups, psychosocial approaches, and other relapse-prevention techniques. Although psychosocial and behavioral therapies help many alcohol-dependent persons to reduce alcohol consumption and maintain abstinence, 40–70% of patients who achieve abstinence from alcohol after detoxification or psychosocial

or behavioral treatment resume drinking within 1 year of such treatment (Swift, 1999).

Advances in neuroscience research and in our understanding of the pharmacology of alcohol during the past two decades have led to the development of medications to improve the efficacy of concurrent pharmacological and psychosocial approaches to treat alcohol dependence (Johnson and Ait-Daoud, 1999). Naltrexone, a μ -opioid receptor antagonist, was approved for the treatment of alcohol dependence in the United States in 1994. Perhaps, by modulation of central dopamine function through reduced endogenous opioid receptor activity (Johnson and Ait-Daoud, 2000), naltrexone might reduce alcohol-induced reward, including craving (O'Malley et al., 2002). In two pivotal randomized, double-blind, placebo-controlled studies of alcohol-dependent patients, daily naltrexone tablets combined with psychosocial therapy reduced 3-month relapse rates from 50% among placebo-treated patients to 25% among patients who received naltrexone (O'Malley et al., 1992; Volpicelli et al., 1992). Oral naltrexone also has been shown to reduce relapse to heavy

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drinking, to decrease the number of drinks consumed when relapse occurs, and to promote abstinence in alcohol-dependent patients (Anton et al., 1999; Kiefer et al., 2003; O'Brien et al., 1996; O'Malley et al., 1992; Volpicelli et al., 1992; cf. Kranzler et al., 2000; Krystal et al., 2001).

Poor adherence to therapy can limit naltrexone's effectiveness and broader clinical utility (Johnson and Ait-Daoud, 2000). Indeed, in a 3-month follow-up study, Volpicelli et al. (1997) found that only patients who took their oral daily dose of naltrexone on 90% of study days experienced an improvement in drinking outcomes, whereas among less compliant patients (who took the dose on less than 90% of study days), no significant differences between the naltrexone and placebo groups were found for any dependent drinking measure, and 50% of them changed their drinking behavior from abstinence to clinically significant drinking during the study. Similarly, in the large-scale UK collaborative study of Chick et al. (2000), only patients who took at least 80% of their naltrexone tablets experienced better drinking outcomes than those taking placebo over 12 months.

Vivitrex® (naltrexone for injectable suspension; Alkermes, Inc., Cambridge, MA), a long-acting formulation of naltrexone, was designed to facilitate adherence to treatment by providing therapeutic levels of naltrexone over 1 month through an intramuscular (im) injection of drug-encapsulated microspheres, thus eliminating the need for daily oral dosing. Monthly extended-release im naltrexone administration also might lessen the daily peak-to-trough levels that are apparent with oral dosing. Compared with oral dosing, the relatively lower naltrexone plasma levels from im administration would be expected to result in reduced levels of 6- β -naltrexol (naltrexone's primary metabolite). Increased 6- β -naltrexol levels have been associated with greater frequency and severity of naltrexone-associated adverse events (King et al., 1997). Thus, this injectable naltrexone formulation might reduce the limitations of oral naltrexone while retaining the potential to effectively treat alcohol dependence.

The formulation's extended-release drug delivery technology (Medisorb®; Alkermes, Inc., Cambridge, MA) uses injectable, biodegradable, polymeric microspheres as the delivery medium. The microspheres (approximately 100 μ m in diameter) are composed of naltrexone incorporated into a matrix of polylactide-co-glycolide (PLG). PLG is a common biodegradable medical polymer with a history of safe human use in sutures, bone plates, abdominal mesh, and extended-release pharmaceuticals. Once injected into the body, the PLG slowly hydrolyzes into lactic and glycolic acids, which are naturally occurring metabolic intermediates. Lactic and glycolic acids are further metabolized into carbon dioxide and water. The ratio of lactide to glycolide in the polymer, the polymer molecular weight, and other manufacturing conditions can influence the rate of release. As the polymer degrades, by a combination of diffusion and

erosion, naltrexone is released continuously from the microspheres.

This pilot study was designed to assess the safety and tolerability of repeat-dose im naltrexone over 4 months in DSM-IV–diagnosed alcohol-dependent patients. Outcome measures related to safety, tolerability, drinking activity, and trough plasma concentrations of naltrexone and 6- β -naltrexol after repeat dosing were evaluated.

METHODS

Patient Enrollment and Assessment

The study population consisted of men and nonpregnant women 18 years or older who met DSM-IV criteria for alcohol dependence. We included patients who were physically healthy, as evidenced by nonpathologic biochemical and hematological tests, and with hepatic enzymes (except γ -glutamyl transferase; GGT) no greater than 3 times the upper limit of normal. Eligible patients also had to refrain from drinking for at least 5 days before study enrollment. We excluded patients with clinically significant medical conditions requiring immediate treatment to avoid deterioration (including hyperbilirubinemia), as well as other axis I diagnoses, including narcotic or benzodiazepine dependence (but not nicotine dependence). Also excluded were patients treated with naltrexone 10 days or less before screening and those intolerant to naltrexone; users of opiates within 2 weeks of screening; and those receiving pharmacological treatment for alcohol dependence (e.g., disulfiram, acamprosate, or ondansetron). Pregnant or breast-feeding women were not studied. Included women of childbearing potential were required to use an acceptable method of contraception: hormonal contraception, surgical sterilization, or condom plus barrier.

The study protocol was approved by each study site's governing institutional review board/independent ethics committee. All participants provided written, informed consent before enrollment.

Study Design and Procedure

A 4-month double-blind, placebo-controlled, randomized study was performed at two sites in the United States and two sites in Europe. Eligible patients were randomized in a 5:1 ratio to either injectable im naltrexone (400 mg) or im placebo (i.e., a matching volume of microspheres without naltrexone). Injections were administered im every month for 4 months—a total of four injections. All patients received psychosocial support.

Potential patients who had provided informed consent were screened 7 days or less before the administration of study drug (day 0). At screening, we determined patient eligibility, collected demographic and medical information, assessed DSM-IV criteria to diagnose alcohol dependence, measured alcohol dependence severity by using the Alcohol Dependence Scale (Skinner and Horn, 1984), recorded baseline alcohol drinking behavior, and performed routine safety and laboratory evaluations.

On day 0, enrolled patients were administered the first dose of study drug. Subsequent doses were administered on days 28, 56, and 84. The im injections (up to 4 ml) were administered as a gluteal injection, and injection sites were alternated between the left and right gluteal muscles with each subsequent dose. The injections were administered to each patient by a nurse or physician. Follow-up visits were scheduled at weeks 2, 3, 4, 6, 8, and 12 after the initial dose of study medication. Additionally, patients were evaluated 30 days and 60 days (± 2 days) after the last injection or early termination. Blood samples were collected for hematology, chemistry, and urinalysis, and trough plasma naltrexone and 6- β -naltrexol concentrations were determined before dosing on days 0, 28, 56, and 84. Safety and kinetic assessments were performed at the two follow-up visits, approximately 1 and 2 months after the final dose of study medication.

Blood samples obtained for drug concentration measurements were collected in 10-ml polypropylene EDTA blood tubes, which were centrifuged at 2 to 8°C at 2000 × g for 4 min. At least 4 ml of plasma was transferred into two separate tubes, which were frozen at -20°C. After the addition of naloxone as the internal standard, plasma samples were mixed with ethyl acetate and hexane under alkaline conditions and then centrifuged. The organic phase was removed and evaporated, and then the mobile phase was added to reconstitute the sample. An aliquot of the reconstituted extract was then injected onto an Applied Biosystems/MDS SCIEX API 3000™ LC-MS-MS System (Foster City, CA) equipped with a high-performance liquid chromatography column to determine plasma concentrations of naltrexone and 6-β-naltrexol.

Alcohol consumption was measured by using the timeline follow-back (TLFB) method (Sobell and Sobell, 1992). Drinking history for the month before screening was recorded at the screening visit and after each month's medication dose. GGT was used as a biochemical marker of heavy drinking (Conigrave et al., 2002; Johnson et al., 2003).

Participants received psychosocial support at each monthly study visit. For the two European centers, psychosocial support reflected common best practice. At a minimum, this included a biopsychosocial evaluation and feedback to the patient, education, motivation, strategies for change, and monitoring. For two centers in the United States, patients received standardized biopsychosocial support with the BRENDA model (Volpicelli et al., 2001). BRENDA is a psychosocial intervention that focuses on motivating patients to change and on adhering to treatment (Kaempf et al., 1999; Pettinati et al., 2000). The core components of BRENDA include biopsychosocial assessment, reporting the assessment to the patient, an empathetic approach, identified and stated patient needs, direct advice to stop or decrease alcohol consumption and comply with treatment and assessment of the patient's reaction to the advice.

Outcome Measures

Criteria for evaluating safety included the incidence of adverse events, injection site assessment findings, laboratory test results (blood chemistry, hematology, and urinalysis), and physical examination findings. Pharmacokinetic parameters included repeated predosing plasma naltrexone and 6-β-naltrexol trough levels.

Alcohol consumption was recorded and analyzed to assess data collection methods. Outcome measures collected by the timeline follow-back (TLFB) method included the following:

1. Percentage of heavy drinking days, where heavy drinking was defined as five or more drinks per day for men or four or more drinks per day for women.
2. Percentage of days abstinent from alcohol.
3. Number of drinks per drinking day.

Change in GGT levels during the study was used as a biochemical marker of heavy alcohol consumption.

Statistical Methods

Because this was a pilot study, the a priori analyses for this clinical trial were descriptive, and summary statistics were derived for all variables. No inferential statistical tests were performed. The purpose of the placebo group was to blind both investigators and patients to treatment, thus allowing unbiased evaluation of the causality and severity of adverse events. All randomized patients who received at least one treatment were included in the safety analysis. Activities events were coded and tabulated by Medical Dictionary for Regulatory Activities preferred body system terms. The incidence of adverse events by treatment group was summarized.

RESULTS

Study Population

Thirty patients were enrolled in this trial and were randomized according to the planned 5:1 (active:placebo) ratio; 25 patients were randomized to treatment with injectable naltrexone, and 5 were randomized to placebo treatment. Patient demographics and baseline characteristics are summarized in Table 1. The mean age of the study patients was 42.6 years, and 73.3% of patients were men. All five patients assigned to the placebo treatment group were men, whereas all eight women were in the injectable naltrexone treatment group. Apart from gender distribution, patient demographics were similar between treatment groups.

Alcohol problem severity was moderate (mean Alcohol Dependence Scale score, 17.8) for the cohort but was slightly higher among placebo versus injectable naltrexone recipients—23.8 vs. 16.6, respectively. The most common treatment goal was total abstinence, reported by 17 patients (56.7%). Seven patients (23.3%) had a goal of occasional use; five patients (16.7%) had a goal of regular but controlled use, and one patient (3.3%) had a goal of total abstinence with a possible relapse. In the month before screening, patients consumed an average of 7.9 drinks per drinking day, with a mean of 60.8% drinking days and 47.5 heavy-drinking days (Table 2).

Table 1. Patient Demographics and Baseline Characteristics

Variable	All subjects	Treatment group	
		Injectable naltrexone (Vivitrex®)	Placebo
No. subjects dosed	30	25	5
Gender, n (%)			
Male	22 (73.3)	17 (68.0)	5 (100)
Female	8 (26.7)	8 (32.0)	0
Age (years)			
Mean (SD)	42.6 (9.2)	42.1 (9.4)	45.2 (8.2)
Range	26–58	26–58	32–54
Race, n (%)			
Black	2 (6.7)	2 (8.0)	0
Caucasian	19 (63.3)	15 (60.0)	4 (80.0)
Other	5 (16.7)	4 (16.0)	1 (20.0)
Not collected	4 (13.3)	4 (16.0)	0
Weight (kg)			
Mean (SD)	82.4 (15.4)	83.8 (16.1)	75.6 (9.8)
Range	50–115	50–115	63–86
ADS score			
Mean (SD)	17.8 (8.8)	16.6 (8.2)	23.8 (10.0)
Range	4–39	4–39	13–36
Treatment goal, n (%)			
Total abstinence	17 (56.7)	14 (56.0)	3 (60.0)
Total abstinence with possible relapse	1 (3.3)	1 (4.0)	0
Occasional use	7 (23.3)	5 (20.0)	2 (40.0)
Temporary abstinence	0	0	0
Regular but controlled use	5 (16.7)	5 (20.0)	0
No goal	0	0	0

ADS, Alcohol Dependence Scale.

Table 2. Prestudy and On-Study Drinking Behavior

Variable	All subjects	Treatment group	
		Injectable naltrexone (Vivitrex®) (n = 25)	Placebo (n = 5)
Prestudy ^a			
Days abstinent (%)	39.2 (33.8)	39.2 (34.2)	39.3 (35.4)
Drinks per drinking day	7.9 (4.0)	7.4 (3.9)	10.3 (4.3)
Heavy-drinking days (%)	47.5 (35.0)	45.3 (35.2)	58.6 (35.8)
Predose GGT (units/liter)		81.1 (127.0)	33.8 (19.1)
On-study			
Days on study after dosing		125.9 (30.1)	120.0 (49.3)
Days abstinent (%)		69.4 (33.7)	62.6 (51.4)
Drinks per drinking day		3.8 (1.8)	6.0 (0.8)
No. of heavy-drinking days		15.4 (24.9)	23.4 (44.4)
Heavy-drinking days (%)		11.7 (17.8)	25.3 (35.0)
Postdose GGT (units/liter)		48.5 (62.6)	30.8 (16.5)

Values are mean (SD); GGT, γ -glutamyl transferase.

^a Self-reported drinking behavior within 28 days before screening.

Table 3. Patient Disposition

Variable	All subjects	Treatment group	
		Injectable naltrexone (Vivitrex®)	Placebo
No. randomized	30	25	5
No. dosed	30	25	5
Total no. doses received, n (%)			
1	2 (7%)	1 (4%)	1 (20%)
2	3 (10%)	3 (12%)	0
3	1 (3%)	1 (4%)	0
4	24 (80%)	20 (80%)	4 (80%)
Completed, n (%)	21 (70%)	17 (68%)	4 (80%)
Discontinued, n (%)			
Adverse event	2 (7%)	2 (8%)	0
Subject noncompliance	1 (3%)	1 (4%)	0
Subject withdrew consent	2 (7%)	1 (4%)	1 (20%)
Lost to follow-up	4 (13%)	4 (16%)	0

All percentages are based on the number of subjects dosed.

Patient Disposition

Twenty-four subjects (20 injectable naltrexone-treated patients and 4 placebo-treated patients) received all 4 doses of study medication; of these, 21 patients (17 injectable naltrexone; 4 placebo) successfully completed the study. Of the nine patients who discontinued prematurely, eight had received injectable naltrexone, and one had received placebo. Table 3 summarizes patient disposition and reasons for discontinuation by treatment group. All 30 randomized patients received at least 1 cycle of treatment.

Evaluation of Outcomes Related to Drinking Behavior

Double-blind drinking behavior is summarized by treatment group in Table 2. Compared with their prestudy drinking behavior, patients treated with injectable naltrexone plus psychosocial therapy experienced an increase in the mean percentage of days abstinent from alcohol (69.4

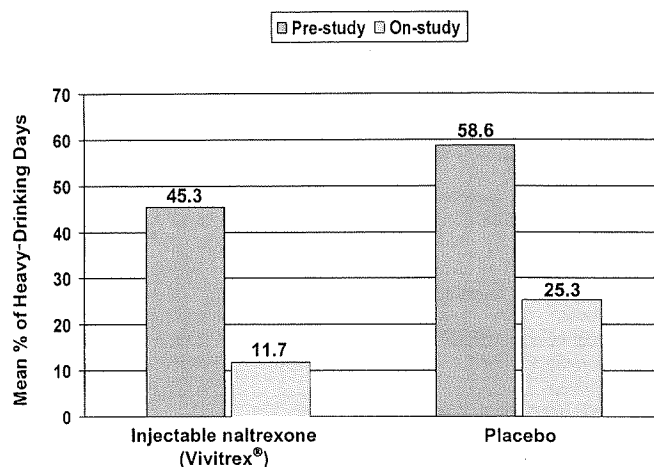


Fig. 1. Mean percentage of heavy-drinking days, pre-study and during the treatment period.

vs. 39.2% before the study) and a reduction in both the number of drinks per drinking day (3.8 vs. 7.4 before the study) and the percentage of heavy-drinking days (11.7 vs. 45.3% before the study). Improvements in outcomes related to drinking behavior were also demonstrated by patients receiving placebo injection plus psychosocial therapy; however, changes were not as pronounced. For example, the mean percentage of heavy drinking days was reduced to 25.3% for placebo-treated patients, compared with 11.7% for patients receiving injectable naltrexone (Fig. 1).

Patients treated with injectable naltrexone experienced a mean reduction of -32.6 units/liter (SD, 70.1 units/liter) in serum GGT activity from predose levels. Patients treated with placebo had a mean reduction of -3.0 units/liter (SD, 4.0 units/liter).

Clinical Laboratory Evaluation

No clinically significant changes from baseline levels were observed. Analysis of individual hematology and urinalysis values revealed no significant changes from baseline for any parameter for patients in either treatment group.

Before the second injection, the mean trough plasma naltrexone concentration was 1.23 ng/ml (SD, 0.83 ng/ml), and this remained relatively constant for the remainder of the study; the average mean trough naltrexone level was 1.33 ng/ml (SD, 1.74 ng/ml). Trough 6- β -naltrexol concentrations were slightly higher than those observed for naltrexone. The mean concentration before the second injection was 2.91 ng/ml (SD, 2.17 ng/ml), and this did not increase significantly with subsequent doses; the average mean trough 6- β -naltrexol concentration was 3.03 ng/ml (SD, 3.29 ng/ml).

Safety Evaluation

Twenty-three (92%) of the 25 patients in the injectable naltrexone group and 4 (80%) of the 5 subjects in the

Table 4. Most Common Adverse Events by Treatment Group^a

System organ class preferred term (MedDRA)	Treatment group	
	Injectable naltrexone (Vivitrex®) (n = 25)	Placebo (n = 5)
No. (%) with AE	23 (92)	4 (80)
Nervous-system disorders		
Headache NOS	8 (32)	1 (20)
Dizziness	4 (16)	1 (20)
Somnolence	3 (12)	0
Gastrointestinal disorders		
Nausea	8 (32)	1 (20)
Abdominal pain NOS	6 (24)	0
Dry mouth	4 (16)	1 (20)
Vomiting	3 (12)	0
General disorders and administration-site conditions		
Injection site pain	4 (16)	0
Fatigue	3 (12)	0
Metabolism and nutrition disorders		
Appetite decreased NOS	3 (12)	1 (20)

MedDRA, Medical Dictionary for Regulatory Activities; AE, adverse event; NOS, not otherwise specified.

^a Occurring in $\geq 10\%$ of patients on study.

placebo group reported at least 1 adverse event during the course of the study. The most frequent adverse events (occurring in $\geq 10\%$ of patients in the study) are shown by treatment group and body system in Table 4. Headache and nausea were the most common adverse events among patients in both treatment groups.

Data indicate that injectable naltrexone was generally well tolerated. No serious adverse events occurred. The vast majority of adverse events were judged to be mild or moderate in severity. One severe event of hepatomegaly, determined to be unrelated to the use of study medication, was reported by one patient in the injectable naltrexone treatment group.

Two patients in the injectable naltrexone treatment group discontinued participation in the study due to adverse events (injection site induration and angioedema). Both events were moderate in severity and occurred after the second dose of injectable naltrexone.

DISCUSSION

Several clinical studies have shown that naltrexone, with daily oral administration, reduces drinking in alcohol-dependent patients. Nevertheless, a major obstacle to naltrexone's effectiveness in general clinical practice is that tolerance to its adverse events is only moderate. The primary objective of this pilot study was to assess the safety and tolerability of repeat-dose im administration of an extended-release injectable formulation of naltrexone in alcohol-dependent patients. Developed to facilitate adherence by eliminating the need for daily self-dosing by the patient, the extended-release injectable formulation was designed to deliver therapeutic levels of naltrexone over 1 month while eliminating first-pass metabolism and reduc-

ing the repetitive peak-to-trough plasma naltrexone levels associated with daily oral naltrexone administration.

The primary finding was that injectable naltrexone was generally safe and well tolerated when administered im to alcohol-dependent patients once a month during the 4-month treatment period. No serious adverse events occurred, and only two patients discontinued the study because of adverse events. Similar to the results of a previous study of this injectable naltrexone formulation in healthy volunteers (Osborn et al., 2000), the incidence of adverse events was generally similar to that observed with placebo. The most common adverse events (nausea and headache) had a similar rate of occurrence for patients in both treatment groups.

Pharmacokinetic analyses demonstrated that therapeutic levels of naltrexone were delivered by the extended-release injectable formulation throughout each 1-month treatment cycle. Plasma concentrations of 6- β -naltrexol (naltrexone's major metabolite) were slightly higher than those of plasma naltrexone but were substantially lower than those seen after oral administration, as reported in previous published studies (King et al., 1997).

Adherence to treatment in this study was generally high, and a similar percentage of patients in both treatment groups received all four cycles of treatment. In one previous clinical trial of patients treated with oral naltrexone, more than 40% of patients did not adhere to the daily oral regimen; their outcomes were similar to those of placebo-treated patients (Chick et al., 2000). Use of extended-release injectable naltrexone may, therefore, afford an opportunity to achieve high adherence rates when treating alcohol-dependent patients.

Because this was a pilot study, it was not designed to include a formal evaluation of efficacy, nor was it powered to demonstrate a treatment effect. Nevertheless, analysis of on-study drinking behavior revealed that patients treated with injectable naltrexone experienced relative improvements in the percentage of days abstinent, the number of drinks per drinking day, and the number and percentage of heavy-drinking days compared with their prestudy drinking behavior. The variability of drinking outcomes observed was generally comparable to results of previous clinical trials, and data indicated that drinking outcomes were influenced by key baseline variables before dosing (e.g., differences in outcomes related to drinking behavior may reflect differences in baseline drinking behavior between treatment groups). Nevertheless, the approximately 50% greater reduction in the mean percentage of heavy-drinking days for patients in the injectable naltrexone-treated group, as reported by the TLFB method, is suggestive of a treatment effect.

In summary, the results of this pilot study evaluating the safety and tolerability of repeated administration of the long-acting injectable formulation of naltrexone are encouraging. The high levels of patient adherence essential for demonstrating naltrexone's efficacy might be enhanced

by this once-a-month injectable formulation. Large-scale placebo-controlled treatment studies are now needed to determine whether this injectable naltrexone formulation is more effective than placebo at improving the drinking outcomes of alcohol-dependent patients.

REFERENCES

- Anton RF, Moak DH, Waid LR, Latham PK, Malcolm RJ, Dias JK (1999) Naltrexone and cognitive behavioral therapy for the treatment of outpatient alcoholics: results of a placebo-controlled trial. *Am J Psychiatry* 156:1758–1764.
- Chick J, Anton R, Checinski K, Croop R, Drummond DC, Farmer R, et al. (2000) A multicentre, randomized, double-blind, placebo-controlled trial of naltrexone in the treatment of alcohol dependence or abuse. *Alcohol Alcohol* 35:587–593.
- Conigrave KM, Degenhardt LJ, Whitfield JB, Saunders JB, Helander A, Tabakoff B (2002) CDT, GGT, and AST as markers of alcohol use: the WHO/ISBRA collaborative project, WHO/ISBRA Study Group. *Alcohol Clin Exp Res* 26:332–339.
- Johnson BA, Ait-Daoud N (1999) Medications to treat alcoholism. *Alcohol Res Health* 23:99–106.
- Johnson BA, Ait-Daoud N (2000) Neuropharmacological treatments for alcoholism: scientific basis and clinical findings. *Psychopharmacology* 149:327–344.
- Johnson BA, Ait-Daoud N, Bowden CL, DiClemente CC, Roache JD, Lawson K, Javors MA, Ma JZ (2003) Oral topiramate for treatment of alcohol dependence: a randomised controlled trial. *Lancet* 361:1677–1685.
- Kaempf G, O'Donnell C, Oslin DW (1999) The BRENDA model: a psychosocial addiction model to identify and treat alcohol disorders in elders. *Geriatr Nurs* 20:302–304.
- Kiefer F, Jahn H, Tarnaske T, Helwig H, Briken P, Holzbach R, et al. (2003) Comparing and combining naltrexone and acamprosate in relapse prevention of alcoholism: a double-blind, placebo-controlled study. *Arch Gen Psychiatry* 60:92–99.
- King AC, Volpicelli JR, Gunduz M, O'Brien CP, Kreek MJ (1997) Naltrexone biotransformation and incidence of subjective side effects: a preliminary study. *Alcohol Clin Exp Res* 21:906–909.
- Kranzler HR, Modesto-Lowe V, Van Kirk J (2000) Naltrexone vs. naltrexone for treatment of alcohol dependence. A placebo-controlled trial. *Neuropsychopharmacology* 22:493–503.
- Krystal JH, Cramer JA, Krol WF, Kirk GF, Rosenheck RA (2001) Naltrexone in the treatment of alcohol dependence, Veterans Affairs Naltrexone Cooperative Study 425 Group. *N Engl J Med* 345:1734–1739.
- O'Brien CP, Volpicelli LA, Volpicelli JR (1996) Naltrexone in the treatment of alcoholism: a clinical review. *Alcohol* 13:35–39.
- O'Malley SS, Jaffe AJ, Chang G, Schottenfeld RS, Meyer RE, Rounsaville B (1992) Naltrexone and coping skills therapy for alcohol dependence: a controlled study. *Arch Gen Psychiatry* 49:881–887.
- O'Malley SS, Krishnan-Sarin S, Farren C, Sinha R, Kreek J (2002) Naltrexone decreases craving and alcohol self-administration in alcohol-dependent subjects and activates the hypothalamo-pituitary-adrenocortical axis. *Psychopharmacology* 160:19–29.
- Osborn C, Benziger D, Henderson J, Ehrlich E, Mant T, Bartus R (2000) Sustained, 30-day therapeutic levels of naltrexone in a phase I clinical study. Presentation at the American College of Neuropsychopharmacology 39th Annual Meeting, San Juan, Puerto Rico.
- Pettinati HM, Volpicelli JR, Pierce JD Jr, O'Brien CP (2000) Improving naltrexone response: an intervention for medical practitioners to enhance medication compliance in alcohol dependent patients. *J Addict Dis* 19:71–83.
- Skinner HA, Horn JL (1984) *Alcohol Dependence Scale: User's Guide*. Addiction Research Foundation, Toronto.
- Sobell LC, Sobell MB (1992) Timeline follow-back: a technique for assessing self-reported alcohol consumption, in *Measuring Alcohol Consumption: Psychosocial and Biochemical Methods* (Litten RZ, Allen JP eds), pp 41–72. Humana Press, Totowa, NJ.
- Swift RM (1999) Drug therapy for alcohol dependence. *N Engl J Med* 340:1482–1490.
- Volpicelli JR, Alterman AI, Hayashida M, O'Brien CP (1992) Naltrexone in the treatment of alcohol dependence. *Arch Gen Psychiatry* 49:876–880.
- Volpicelli JR, Pettinati HM, McLellan AT, O'Brien CP (2001) *Combining Medication and Psychosocial Treatments for Addictions: The BRENDA Approach*. Guilford Press, New York.
- Volpicelli JR, Rhines KC, Rhines JS, Volpicelli LA, Alterman AI, O'Brien CP (1997) Naltrexone and alcohol dependence. Role of subject compliance. *Arch Gen Psychiatry* 54:737–742.

