NALTREXONE IN THE TREATMENT OF ALCOHOL DEPENDENCE

JOHN H. KRYSTAL, M.D., JOYCE A. CRAMER, B.S., WILLIAM F. KROL, PH.D., GAIL F. KIRK, M.S., AND ROBERT A. ROSENHECK, M.D., FOR THE VETERANS AFFAIRS NALTREXONE COOPERATIVE STUDY 425 GROUP

ABSTRACT

Background Although naltrexone, an opiate-receptor antagonist, has been approved by the Food and Drug Administration for the treatment of alcohol dependence, its efficacy is uncertain.

Methods We conducted a multicenter, double-blind, placebo-controlled evaluation of naltrexone as an adjunct to standardized psychosocial treatment. We randomly assigned 627 veterans (almost all men) with chronic, severe alcohol dependence to 12 months of naltrexone (50 mg once daily), 3 months of naltrexone followed by 9 months of placebo, or 12 months of placebo. All patients were offered individual counseling and programs to improve their compliance with study medication and were encouraged to attend Alcoholics Anonymous meetings.

Results There were 209 patients in each group; all had been sober for at least five days before randomization. At 13 weeks, we found no significant difference in the number of days to relapse between patients in the two naltrexone groups (mean, 72.3 days) and the placebo group (mean, 62.4 days; 95 percent confidence interval for the difference between groups, −3.0 to 22.8). At 52 weeks, there were no significant differences among the three groups in the percentage of days on which drinking occurred and the number of drinks per drinking day.

Conclusions Our findings do not support the use of naltrexone for the treatment of men with chronic, severe alcohol dependence. (N Engl J Med 2001;345: 1734-9.)

ALCOHOLISM is a devastating medical illness with a profound public health impact.[1] In 1995, because of its extensive record for safety when administered for other indications, the Food and Drug Administration (FDA) approved naltrexone, an opioid-receptor antagonist, for the treatment of ethanol dependence, in part on the basis of two well-designed single-site studies.[2-4] The initial studies suggested that naltrexone substantially increased sobriety and reduced ethanol consumption when combined with psychosocial treatment.

Naltrexone was incorporated into the treatment of alcoholism on the premise that stimulation of the μ opioid receptor contributed to the rewarding effects of alcohol.[5-7] Data from clinical trials suggested that naltrexone reduced the rewarding effects of alcohol and contributed to reduced alcohol craving and lower alcohol consumption.[8,9] Subsequent studies suggested that naltrexone was less effective for treating alcohol dependence and had more adverse effects than was initially suggested.[10-15] We conducted a multicenter, double-blind, placebo-controlled evaluation of the efficacy of naltrexone when administered for 3 or 12 months as an adjunct to standardized psychosocial treatment.

METHODS

Protocol

The Human Rights Committees of the Department of Veterans Affairs Cooperative Studies Program and the 15 participating Veterans Affairs medical centers approved this study. All patients provided written informed consent. An independent data and safety monitoring board monitored patient safety.

The three treatment groups were as follows: patients in the long-term naltrexone group were treated with naltrexone (ReVia, Dupont Pharma) for 12 months; patients in the short-term naltrexone group were treated with naltrexone for 3 months and then received placebo for 9 months; and patients in the placebo group received placebo for 12 months. During a six-month post-treatment follow-up, we assessed the durability of improvement after the period of randomized treatment. Patients were asked to continue through the 18-month follow-up even if they discontinued the study medication or counseling.

Patients were enrolled over a two-year period. Double-blind treatment was initiated within a day of randomization. Patients receiving naltrexone started with 25 mg once daily for 2 days, followed by 50 mg once daily for 3 or 12 months. The short-term naltrexone group was switched in a double-blind fashion to matching placebo when naltrexone was discontinued at the 13-week visit. Patients assigned to placebo received one placebo tablet daily for 12 months. Medication for all groups was discontinued after 12 months.

Enhancement of Compliance

Medication was provided in bottles with caps (MEMS, Aprex, Union City, Calif.) that recorded the date and time of each opening and showed the number of hours that had elapsed since the previous opening. All patients participated in a feedback program designed to enhance compliance with the once-daily medication regimen for 12 months.[16] The Medication Usage Skills for Effectiveness monthly feedback system has been demonstrated to enhance compliance among patients with psychiatric disorders by teaching daily cues (e.g., linking doses to a specific time, meal, or daily activity) and reviewing dosing calendars on a computer screen (with data downloaded from the patients' MEMS caps).[16,17] Plasma 6-beta-naltrexol was measured in some patients at 13 and 24 weeks.

Counseling

Patients received individual 12-step facilitation counseling[18] for 13 months and were encouraged to attend Alcoholics Anony-

From the Department of Veterans Affairs Alcohol Research Center, Veterans Affairs Connecticut Healthcare System, West Haven, Conn. (J.H.K., J.A.C., R.A.R.); the Department of Psychiatry, Yale University School of Medicine, New Haven, Conn. (J.H.K., J.A.C., R.A.R.); the Department of Veterans Affairs Cooperative Studies Program Coordinating Center, Perry Point, Md. (W.F.K., G.F.K.); and the Northeast Program Evaluation Center, Department of Veterans Affairs Connecticut Healthcare System, West Haven, Conn. (R.A.R.). Address reprint requests to Dr. Krystal at the Alcohol Research Center (G7E), the Department of Veterans Affairs Connecticut Healthcare System, 950 Campbell Ave., West Haven, CT 06516-2770, or at john.krystal@yale.edu.

mous meetings. Counseling was aimed at reinforcing abstinence, providing basic relapse-prevention information, promoting acceptance of drug therapy, and reducing attrition. Visits were once weekly for 16 weeks, every 2 weeks during weeks 17 to 36, and once monthly during weeks 37 to 56.

Screening and Eligibility Criteria

We screened veterans 18 years of age or older who had a recent history of drinking to intoxication (heavy drinking two times in at least 1 week in the 30 days before screening) and who had been given a diagnosis of alcohol dependence according to the criteria of the *Diagnostic and Statistical Manual of Mental Disorders,* fourth edition (DSM-IV).[19] All patients were outpatients who had been sober for five days before randomization. Specific exclusion criteria included previous use of naltrexone, liver disease, a psychiatric diagnosis other than alcoholism requiring current psychotropic medication, homelessness, other substance abuse or dependence (excluding nicotine or occasional marijuana use), any past illicit opiate use, and marijuana dependence. Patients who had pending legal charges with the potential for incarceration or who received a disability pension related to alcoholism were excluded, to avoid any secondary motive to sustain disability status or legally imposed treatment requirements.

Base-line and monthly assessments included a review of drinking,[20] medication use, and counseling progress. Compensation ($20) was provided for the time required to complete monthly ratings, including drinking calendars, whether the patient was taking a study medication, attended counseling sessions or Alcoholics Anonymous meetings, or had discontinued participation. Longer interviews at 6, 12, and 18 months were compensated at $50 per session.

Outcomes

Three variables were defined that would allow us to answer the primary questions of the study (at 3 and 12 months): time to relapse during the first 3 months (number of days from randomization until relapse, with relapse defined as the first day of heavy drinking [six or more drinks for men and four or more for women]); the percentage of drinking days over a 12-month period (the number of drinking days reported during that period divided by the number of days for which data were available); and number of drinks per drinking day over a 12-month period (the total number of drinks reported during the period divided by the number of days on which consumption of one or more drinks was reported).

Our objectives were to determine whether the short-term (3-month) use of naltrexone, as compared with placebo, decreased drinking (measured by the time to relapse) in alcohol-dependent patients and whether the long-term (12-month) use of naltrexone, as compared with placebo and short-term naltrexone, decreased drinking (measured by the percentage of drinking days and the number of drinks per drinking day).

Statistical Analysis

Data were held and analyzed by the Veterans Affairs Cooperative Studies Program. A two-sided level of significance of 0.0167 for each comparison among groups was needed to produce an overall P value of 0.05 after Bonferroni correction. The sample size of 200 yielded sufficient power for the comparison of the three-month curves for time to the first episode of heavy drinking.

The primary analysis was based on the intention to treat. Secondary analyses were planned on the basis of actual treatment or to include only patients who complied with the treatment regimen. The Kaplan–Meier product-limit estimator was used to estimate the time to the three-month outcomes.[21] Differences in the proportion of drinking days and numbers of drinks per drinking day were analyzed by the chi-square test and t-test. Analyses of drinking days included only days for which data were available and on which the patient was able to drink (e.g., not incarcerated or hospitalized). Secondary analyses were performed by analysis of covariance and an accelerated failure-time model with the SAS procedure Lifereg.[22] Compliance with medication was defined by the percentage of days on which the medication bottle was opened during the period; the covariates for counseling and Alcoholics Anonymous were the numbers of sessions attended during the period.

RESULTS

The study was conducted from April 1997 to October 2000. We screened 3372 alcohol-dependent veterans to assign 627 patients to three groups of 209 patients each (with 30 to 50 patients per site). Base-line characteristics of the patients are shown in Table 1, and

TABLE 1. BASE-LINE CHARACTERISTICS OF THE 627 PATIENTS.*

CHARACTERISTIC	LONG-TERM NALTREXONE (N=209)	SHORT-TERM NALTREXONE (N=209)	PLACEBO (N=209)
Age (yr)	49.3±10	48.5±10	49.5±10
Male sex (%)	97.1	97.6	99.5
Race or ethnic group (%)			
White	61.2	68.4	60.3
Black	31.1	25.8	31.6
Hispanic	5.7	4.8	5.7
Other	2.0	1.0	2.4
Marital status (%)†			
Single	15.8	18.2	18.2
Married or living with partner	33.5	36.9	33.0
Divorced, separated, or widowed	50.7	45.0	48.3
Education (yr)	13.2±2	13.3±2	13.2±2
Disability not related to alcoholism (%)			
Military — psychiatric	2.9	0.5	1.9
Military — medical	14.8	17.7	15.4
Nonmilitary	14.8	18.2	13.4
Psychoactive substance use disorder (lifetime %)			
Cannabis	15.3	19.6	21.1
Cocaine	8.1	11.0	5.7
DSM-IV diagnosis (lifetime %)‡			
Major depression	15.8	11.5	14.4
Social phobia	6.7	6.7	9.6
Generalized anxiety disorder	6.2	3.3	5.7
Post-traumatic stress disorder	15.3	12.4	13.4
Antisocial personality disorder	8.1	7.7	8.6
Current smoker (%)	74.6	68.9	71.8
Age when began getting intoxicated regularly (yr)	23.0±9	22.9±10	22.7±9
Age when first had difficulty stopping before intoxication (yr)	30.3±11	30.5±12	30.0±11
History of alcoholism in first-degree relatives (%)	83.7§	89.0§	80.4§
Liver enzymes (mU/ml)			
Aspartate aminotransferase	39.7±29	41.4±29	39.0±31
Alanine aminotransferase	40.9±28	41.8±29	39.8±32
γ-Glutamyltransferase	107.1±134	97.1±123	95.9±123
Drinking days in previous 90 days (%)	65.9±30	68.3±29	65.6±29
No. of drinks per drinking day in previous 90 days	13.1±8	14.1±9	13.0±7

*Plus–minus values are means ±SD.

†Data were missing for one patient.

‡DSM-IV denotes *Diagnostic and Statistical Manual of Mental Disorders,* fourth edition.[19]

§P=0.05 by the chi-square test for the comparison among the three groups.

adverse events during treatment in Table 2. There were no significant differences among the groups in any base-line measures (except family history of alcoholism) or follow-up measures of compliance with the protocol (Table 3), including attendance at monthly follow-up visits, duration of compliance with the medication, percentage of days on which medication was taken, attendance at counseling sessions or Alcoholics Anonymous meetings, and adverse events. Overall, 73 percent of the patients completed the trial. The reasons for not completing the trial did not differ significantly among treatment groups: 95 patients were lost to follow-up, 21 withdrew, 14 moved or were unable to return, 12 died, and 28 discontinued participation for other reasons.

MEMS monitors showed that 89 percent of the patients took at least some medication for 52 weeks. Plasma 6-beta-naltrexol levels in blood samples obtained from 189 patients at week 13 and 69 patients at week 24 were consistent with MEMS data; they showed that 84 percent of the patients were taking the medication. Complete drinking data were collected from 78 percent of the patients for the first 13 weeks and 52 percent of the patients for 52 weeks. Full or partial 52-week data on drinking were available for 93 percent of the patients.

In the first 13 weeks, we obtained data from 378 patients who received naltrexone and 187 patients who received placebo. We found no significant differences in the primary end point of time to relapse. The median time to relapse overall was 135 days. There were also no significant differences between the naltrexone groups and the placebo group in terms of the relapse rate, percentage of drinking days, or number of drinks per drinking day (Table 4). At 52 weeks, there were no significant differences among the three groups in the percentage of drinking days or the number of drinks per drinking day (Table 4).

Patients who were more compliant with medication and those who attended more counseling or Alcoholics Anonymous sessions had better outcomes, whether they took naltrexone or placebo (Table 5). Analyses of covariance, with one covariate taken at a time, showed that compliance with medication, counseling, and attendance at Alcoholics Anonymous meetings had strong effects on the number of days to relapse that were independent of treatment assignment. Analyses of covariance for the percentage of drinking days, taking one covariate at a time, showed that compliance with medication, counseling, and attendance at Alcoholics Anonymous also had strong effects that were independent of treatment assignment. None of the covariates alone had a significant effect on the number of drinks per drinking day (Table 5). Analyses of the multiple-covariate models found that attendance at counseling sessions and Alcoholics Anonymous meetings had the greatest effect on the percentage of drinking days and that compliance with medication had the greatest effect on the number of drinks per drinking day (Table 5).

In post hoc analyses, we examined possible interactions of the primary outcomes with treatment site, disability, psychiatric diagnoses, family history, motivation,[23] craving,[24] dependence,[25] and age at onset of drinking. No interactions were found (data not shown).

TABLE 2. ADVERSE EVENTS REPORTED MORE COMMONLY IN THE NALTREXONE GROUP THAN IN THE PLACEBO GROUP.*

ADVERSE EVENT	NALTREXONE (N=418)	PLACEBO (N=209)
	no. (%)	
Pain	91 (22)	39 (19)
Flu-like symptoms	74 (18)	36 (17)
Headache	53 (13)	24 (11)
Back pain	49 (12)	24 (11)
Injury	39 (9)	17 (8)
Nausea	32 (8)	9 (4)
Asthenia	31 (7)	8 (4)
Dizziness	30 (7)	10 (5)
Somnolence	21 (5)	5 (2)

*There were no significant differences between groups.

DISCUSSION

In this large, multisite study, in which we used the same alcoholism outcome measures that were employed in earlier single-site studies, we did not detect an effect of naltrexone. Relative to placebo, naltrexone did not prevent or delay relapse to heavy drinking, reduce the number of drinking days, or decrease the amount of alcohol consumed during episodes of drinking. Major outcomes were not influenced by the duration of naltrexone administration, the degree of compliance with study medication, participation in counseling sessions, or attendance at Alcoholics Anonymous meetings. Our data do not support the treatment of alcohol dependence with naltrexone combined with a psychosocial treatment program in men with chronic, severe alcohol dependence.

Naltrexone is the second medication approved by the FDA for the treatment of alcoholism for which a finding of efficacy has not been replicated in a multicenter, placebo-controlled study. Disulfiram was the other.[26] Previous small, single-site studies compared the short-term effects (over 12 weeks) of naltrexone and placebo.[2,3,11,15] In a systematic review of previous studies, Garbutt et al. concluded that "naltrexone reduces the risk of relapse to heavy drinking and frequency of drinking compared with placebo but does not substantially enhance abstinence, i.e., avoidance

TABLE 3. COMPLIANCE WITH THE PROTOCOL.*

MEASURE	LONG- AND SHORT-TERM NALTREXONE (N=418)†	PLACEBO (N=209)
At 13 weeks		
Mean no. of days taking medication	73	70
Compliance — %	72±31	70±31
Average rate of attendance at monthly follow-up visits — %	63	60
Drinking calendars at week 13 — no. (%)		
Complete data for patient	321 (77)	166 (79)
Complete or partial data for patient	378 (90)	187 (89)

	LONG-TERM NALTREXONE (N=209)	SHORT-TERM NALTREXONE (N=209)	PLACEBO (N=209)
At 52 weeks			
Mean no. of days taking medication	163	160	155
Compliance — %	44±34	43±33	42±33
Average rate of attendance at monthly follow-up visits — %	61	61	57
Drinking calendars at week 52 — no. (%)			
Complete data for patient	115 (55)	103 (49)	107 (51)
Complete or partial data for patient	190 (91)	196 (94)	195 (93)

*Plus–minus values are means ±SD.

†These groups were the same for the first 13 weeks.

TABLE 4. OUTCOMES OF TREATMENT.*

OUTCOME	LONG- AND SHORT-TERM NALTREXONE (N=378)	PLACEBO (N=187)	DIFFERENCE BETWEEN GROUPS (95% CI)
At 13 weeks			
Rate of relapse (%)	37.8	44.4	−6.6 (−19.9 to 6.7)
No. of days to relapse (primary end point)†	72.3±36	62.4±34	9.9 (−3.0 to 22.8)
Drinking days (%)	11.3±21	14.0±23	−2.7 (−6.5 to 1.1)
No. of drinks/drinking day‡	9.2±8	9.0±6	0.2 (−1.5 to 1.9)

	LONG-TERM NALTREXONE (LT) (N=190)	SHORT-TERM NALTREXONE (ST) (N=196)	PLACEBO (PL) (N=195)	COMPARISON GROUPS	DIFFERENCE BETWEEN GROUPS (95% CI)
At 52 weeks					
Drinking days (%)	15.1±23	19.4±26	18.0±25	LT–ST	−4.3 (−9.2 to 0.6)
				LT–PL	−2.9 (−7.7 to 1.9)
				ST–PL	1.4 (−3.6 to 6.5)
No. of drinks/drinking day§	9.6±10	10.5±8	9.3±7	LT–ST	−0.9 (−3.0 to 1.3)
				LT–PL	0.3 (−1.8 to 2.4)
				ST–PL	1.2 (−0.5 to 2.9)

*Analyses included all patients with complete or partial data. Plus–minus values are means ±SD. CI denotes confidence interval.

†The median number of days to relapse was 176 for the group assigned to long-term naltrexone, 115 for the group assigned to short-term naltrexone, and 104 for the group assigned to placebo (135 overall).

‡The sample size for the number of drinks per drinking day at 13 weeks was 198 for patients in the naltrexone group and 110 for patients in the placebo group.

§The sample size for the number of drinks per drinking day at 52 weeks was 128 for the group assigned to long-term naltrexone, 142 for the group assigned to short-term naltrexone, and 142 for the group assigned to placebo.

TABLE 5. SECONDARY ANALYSES OF PRIMARY END POINTS.

END POINT	MULTIPLE-COVARIATES MODEL*		
	TREATMENT P VALUE	COVARIATE	COVARIATE P VALUE
Days to relapse at 13 wk (n=565)†	0.16	Medication compliance	0.13
		Attendance at counseling sessions	0.007
		Attendance at Alcoholics Anonymous meetings	0.23
Percentage of drinking days at 52 wk (n=503)‡	0.31	Medication compliance	0.47
		Attendance at counseling sessions	<0.001
		Attendance at Alcoholics Anonymous meetings	0.001
Drinks per drinking day at 52 wk (n=387)‡	0.45	Medication compliance	0.03
		Attendance at counseling sessions	0.62
		Attendance at Alcoholics Anonymous meetings	0.20

*Analyses of covariance including three covariates were performed. None of the three end points were significantly affected by treatment, after adjustment for the three covariates. Some of the individual covariates were related to the end points after adjustment for the other two covariates.

†Analyses of accelerated failure-time model were performed with the SAS procedure Lifereg[22] to compare combined long-term and short-term naltrexone with placebo.

‡Long-term naltrexone, short-term naltrexone, and placebo were compared.

of any alcohol consumption."[27] In contrast, we and others[12,14] have found no significant differences in favor of short- or long-term naltrexone treatment. Our study was larger than other studies and had longer patient follow-up. Patients who interrupted their treatment were not dropped from the study and could return to treatment, as happens in clinical practice. Although the eligibility criteria stipulated a minimal drinking level, patients with high and low drinking rates at base line were enrolled equally in all treatment groups.

With respect to the level of training of counselors and the frequency of clinical contact, the counseling we provided was typical of treatment available within Veterans Affairs medical centers and was similar to that provided in previous studies. Consistently with previous studies, we found evidence that patients who were more compliant with prescribed medication, attended more counseling sessions, and participated in more Alcoholics Anonymous meetings had better treatment outcomes.[28-30] However, these associations cannot be interpreted as causal, because abstinent patients might have been more likely to take medication, to attend counseling sessions, and to participate in Alcoholics Anonymous meetings. Our results were more consistent with those of two Veterans Affairs studies evaluating treatment for alcoholism, in which good compliance was associated with less drinking in the disulfiram, lithium, and placebo groups.[29,30]

Some limitations of our study should be noted. We studied a severely affected population typical of male Veterans Affairs patients: that is, older, heavier drinkers, with long duration of alcoholism. Inclusion of patients with mild alcohol dependence would increase variability in outcomes and require a larger sample to find differences. We cannot rule out the possibility that a different dose of naltrexone or the use of adjunctive medications along with naltrexone might have been effective in our patients. The results might not be generalizable to patients with less chronic and severe alcohol dependence, non–Veterans Affairs settings, or women.

In summary, in a large study, we found no evidence that naltrexone combined with psychosocial therapy was an effective treatment for alcohol dependence. Our data raise doubts about the current use of naltrexone for patients with chronic, severe alcohol dependence. Our findings do not rule out the possibility that naltrexone in combination with other medications or with other types of psychosocial interventions, or in other patient groups, may have a role in the treatment of alcoholism.

Supported by the Cooperative Studies Program of the Department of Veterans Affairs Office of Research and Development. Naltrexone and matching placebo were donated by Dupont Pharmaceuticals, which also analyzed blood naltrexone levels.

We are indebted to the members of the Data Monitoring Committee (K. Dickerson, Providence, R.I.; J. Fertig, Bethesda, Md.; M. Fisher, Madison, Wis.; H. Goldman, Baltimore; R. Meyer, Washington, D.C.; M. Shuckit, San Diego, Calif.) and the Planning Committee (R. Anton, Charleston, S.C.; S. O'Malley and B. Rounsaville, New Haven, Conn.; C. O'Brien and J. Volpicelli, Philadelphia).

APPENDIX

In addition to the authors, the members of the Department of Veterans Affairs Cooperative Study 425 Group were as follows: K. Drexler, F. Mohammad, L. Siklosky, K. Walker, C. Arnold-Hunter, and R. Head, Atlanta; J. Hermos, H. Behr, B. Kinne, D. Savage, and J. Wickis, Boston; L. Rugle, O. Kausch, H. Zegarna, K. Conti, H. Adkins, G. Harris, and C. Cartier, Cleveland; B. Adinoff, L. Burney, J. Fields, B. Hudson, J. Corder, and A. Quintero, Dallas; J. Grabowski, R. Wancha, Y. Ruiz, S. Chermack, S. Fleming, K. Gamel, and B. Sullivan, Detroit; L. Madlock, R. Murray, J. Williams, R. Lewandowski, and T. Owens, Memphis, Tenn.; M. FeBornstein, J. Pena, B. Cotton-Brown, M. Cowie, A. Connelly, W. Hill, A. Holmes, and J. Fiery, New Orleans; P. Casadonte, S. Kushner, S. Johnson, J. Siegris, N. Lynch, E. Richardson, and A. Butcher, New York; S. Nixon, C. Shaw, R. Joswick, D. Bertoch, and H. Engebretson, Oklahoma City; L. Haynes-Tucker, L. Moffet, J. Weintraub, R. Lutz, S. Clinton, F. Pohlman, R. Royal, and S. Harris, Menlo Park, Calif.; I. Maany, J. DeStefano, M. Andem, C. Hackett, J. McNeely, S. Dyanick, D. Torpey, S. Poole, E. Moeller, and A. Scheamania, Philadelphia; G. Kaplan, H. MacAskill, P. Charnley, and C. Williams, Providence, R.I.; C. Stock, P. Stevenson, S. Plumb, M. Dean, and J. Hunter, Salt Lake City; P. Banys, I. Rhew, S. Staccone, J. Kelly, and S. Shives, San Francisco; A. Saxon, M. Willey-Allen, J. Williams, K. Lunna, V. Ruscigno, S. Brown, and K. Shaffer, Seattle; J. Collins, S. Kilby, T. Burke, L. Linzy, C. Dalzell, M. Rhoads, J. Kelly, N. Banks, J. Arflin, and D. Briones, Perry Point, Md.; and M. Miller and C. Messick, Albuquerque, N.M.

REFERENCES

1. Swift RM. Medications and alcohol craving. Alcohol Res Health 1999; 23:207-13.

2. Volpicelli JR, Alterman AI, Hayashida M, O'Brien CP. Naltrexone in the treatment of alcohol dependence. Arch Gen Psychiatry 1992;49:876-80.

3. O'Malley SS, Jaffe A, Chang G, Schottenfeld RS, Meyer RE, Rounsaville B. Naltrexone and coping skills therapy for alcohol dependence: a controlled study. Arch Gen Psychiatry 1992;49:881-7.

4. O'Malley SS, Croop RS, Wroblewski JM, Labriola DF, Volpicelli JR. Naltrexone in the treatment of alcohol dependence: a combined analysis of two trials. Psychiatr Ann 1995;25:681-8.
5. Gianoulakis C. Implications of endogenous opioids and dopamine in alcoholism: human and basic science studies. Alcohol Alcohol Suppl 1996;1: 33-42.
6. Herz A. Endogenous opioid systems and alcohol addiction. Psychopharmacology 1997;129:99-111.
7. Swift RM, Whelihan W, Kuznetsov O, Buongiorno G, Hsuing H. Naltrexone-induced alterations in human ethanol intoxication. Am J Psychiatry 1994;151:1463-7.
8. Volpicelli JR, Watson NT, King AC, Sherman CE, O'Brien CP. Effect of naltrexone on alcohol "high" in alcoholics. Am J Psychiatry 1995;152: 613-5.
9. O'Malley SS, Jaffe AJ, Rode S, Rounsaville BJ. Experience of a "slip" among alcoholics treated with naltrexone or placebo. Am J Psychiatry 1996;153:281-3.
10. Monti PM, Rohsenow DJ, Hutchison KE, et al. Naltrexone's effect on cue-elicited craving among alcoholics in treatment. Alcohol Clin Exp Res 1999;23:1386-94.
11. Volpicelli JR, Rhines KC, Rhines JS, Volpicelli LA, Alterman AI, O'Brien CP. Naltrexone and alcohol dependence: role of subject compliance. Arch Gen Psychiatry 1997;54:737-42.
12. Kranzler HR, Modesto-Lowe V, Van Kirk J. Naltrexone vs. nefazodone for treatment of alcohol dependence: a placebo-controlled trial. Neuropsychopharmacology 2000;22:493-503.
13. Croop RS, Chick J. American and European clinical trial of naltrexone: international update: new findings on promising medications. Alcohol Clin Exp Res 1996;20:Suppl 8:216A-218A.
14. Chick J, Anton R, Checinski K, et al. A multicentre, randomized, double-blind, placebo-controlled trial of naltrexone in the treatment of alcohol dependence or abuse. Alcohol Alcohol 2000;35:587-93.
15. Anton RF, Moak DH, Waid LR, Latham PK, Malcolm RJ, Dias JK. Naltrexone and cognitive behavioral therapy for the treatment of outpatient alcoholics: results of a placebo-controlled trial. Am J Psychiatry 1999; 156:1758-64.
16. Cramer JA. Enhancing patient compliance in the elderly: role of packaging aids and monitoring. Drugs Aging 1998;12:7-15.
17. Cramer JA, Rosenheck R. Enhancing medication compliance for people with serious mental illness. J Nerv Ment Dis 1999;187:53-5.
18. Project MATCH (Matching Alcoholism Treatment to Client Heterogeneity): rationale and methods for a multisite clinical trial matching patients to alcoholism treatment. Alcohol Clin Exp Res 1993;17:1130-45.
19. Diagnostic and statistical manual of mental disorders, 4th ed.: DSM-IV. Washington, D.C.: American Psychiatric Association, 1994.
20. Sobell LC, Sobell MB, Leo GI, Cancilla A. Reliability of a timeline method: assessing normal drinkers' reports of recent drinking and a comparative evaluation across several populations. Br J Addict 1988;83:393-402.
21. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457-81.
22. Kalbfleisch JD, Prentice RL. The statistical analysis of failure time data. New York: John Wiley, 1980.
23. DiClemente CC, Hughes SO. Stages of change profiles in outpatient alcoholism treatment. J Subst Abuse 1990;2:217-35.
24. Anton RF, Moak DH, Latham P. The Obsessive Compulsive Drinking Scale: a self-rated instrument for the quantification of thoughts about alcohol and drinking behavior. Alcohol Clin Exp Res 1995;19:92-9.
25. Skinner HA, Allen BA. Alcohol dependence syndrome: measurement and validation. J Abnorm Psychol 1982;91:199-209.
26. Fuller RK, Branchey L, Brightwell DR, et al. Disulfiram treatment of alcoholism: a Veterans Administration cooperative study. JAMA 1986;256: 1449-55.
27. Garbutt JC, West SL, Carey TS, Lohr KN, Crews FT. Pharmacological treatment of alcohol dependence: a review of the evidence. JAMA 1999; 281:1318-25.
28. Fuller R, Roth H, Long S. Compliance with disulfiram treatment of alcoholism. J Chronic Dis 1983;36:161-70.
29. Collins JF, Dorus W. Patient selection bias in analyses using only compliant patients. In: Cramer JA, Spilker B, eds. Patient compliance in medical practice and clinical trials. New York: Raven Press, 1991:335-48.
30. Fawcett J, Clark DC, Aagesen CA, et al. A double-blind, placebo-controlled trial of lithium carbonate therapy for alcoholism. Arch Gen Psychiatry 1987;44:248-56.

IMAGES IN CLINICAL MEDICINE

The *Journal* welcomes consideration of new submissions for Images in Clinical Medicine. Instructions for authors and procedures for submissions can be found on the *Journal*'s Web site at www.nejm.org. At the discretion of the editor, images that are accepted for publication may appear in the print version of the *Journal,* the electronic version, or both.