ORIGINAL ARTICLE

A Double-blind, Placebo-Controlled Study of Oral Nalmefene for Alcohol Dependence

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Background: Nalmefene is a newer opioid antagonist that is structurally similar to naltrexone but with a number of potential pharmacological advantages for the treatment of alcohol dependence, including no dose-dependent association with toxic effects to the liver, greater oral bioavailability, longer duration of antagonist action, and more competitive binding with opioid receptor subtypes that are thought to reinforce drinking.

Methods: A double-blind, placebo-controlled trial was conducted to evaluate the safety and efficacy of 2 doses of oral nalmefene for alcohol dependence. The 105 outpatient volunteers were abstinent for a mean of 2 weeks prior to random assignment to the placebo or 20- or 80-mg/d dose nalmefene groups for 12 weeks. Cognitive behavioral therapy was provided weekly during treatment. Self-reported drinking or abstinence was confirmed by determinations of breath alcohol concentration and by collateral informant reports.

Results: Outcomes did not differ between the 20- and 80-mg dose nalmefene groups. Significantly fewer patients treated with nalmefene than patients given placebo relapsed to heavy drinking through 12 weeks of treatment ($P<.02$), with a significant treatment effect at the first weekly study visit ($P<.02$). The odds ratio of relapsing to heavy drinking was 2.4 times greater with placebo compared with nalmefene (95% confidence interval, 1.05-5.59). Patients treated with nalmefene also had fewer subsequent relapses ($P<.03$) than patients given placebo.

Conclusions: Treatment with nalmefene was effective in preventing relapse to heavy drinking relative to placebo in alcohol-dependent outpatients and was accompanied by acceptable side effects.

Arch Gen Psychiatry. 1999;56:719-724

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THE FIRST months following cessation of drinking represent the highest risk for relapse and offer the greatest opportunity for pharmacological intervention in outpatients with alcohol dependence.[1] Pharmacological treatment options for this indication have been limited. Aversive therapy with disulfiram (Antabuse) was the only pharmacological treatment for alcohol dependence available in the United States until recently, despite high rates of severe adverse drug reactions, drinking relapse, and medication noncompliance.[2] The drug 3-acetamido-1-pro-panesulfonic acid, calcium salt (acamprosate), is available internationally and is being studied in the United States as a nonaversive pharmacotherapy to maintain abstinence in recently detoxified alcoholics.[3] Naltrexone (ReVia), an opioid antagonist, was approved in 1994 as a nonaversive prescription drug for alcohol dependence on the basis of 2 small placebo-controlled trials (N = 186)[4,5] and a large open-label safety study (N = 570).[6] The results of recent naltrexone studies are more modest but reinforce earlier reports regarding reduced risk of relapse to heavy drinking among subjects who are highly compliant with treatment.[7-9] Use of naltrexone has certain limitations, eg, 15% of patients participating in the open-label safety study terminated treatment owing to adverse events, primarily intolerable nausea.[6] Additionally, naltrexone is associated with dose-dependent hepatotoxic side effects, which may make use problematic and contraindicated in alcoholic patients with liver disease.[10] Replicating naltrexone results with a structurally similar but better tolerated compound would validate opioid antagonist treatment of alcohol dependence and identify an alternative form of drug for patients with medical contraindications, adverse drug experiences, or nonresponse to naltrexone.

Nalmefene is a newer opioid antagonist that is structurally similar to naltrexone but with a number of potential pharmacological and clinical advantages for the treatment of alcohol dependence.[11] Like naltrexone, nalmefene is a pure opioid antagonist with no agonist activity and no abuse potential.[12] Nalmefene has been found to have no dose-dependent association with toxic side effects to the liver in more than 1300 patients studied for other indications, including patients with liver disorders (con-

SUBJECTS AND METHODS

SUBJECTS

This study was conducted at the Alcohol Disorders Research Clinic, Jackson Memorial Medical Center, University of Miami School of Medicine, Miami, Fla, and approved by the hospital's Institutional Review Board. Subjects were alcohol-dependent outpatients recruited primarily through advertisements and press releases. After an initial telephone interview, subjects attended an interview at which the study was explained, written informed consent was provided, and single-blind placebo medication was dispensed to be administered over a 2-week period while study eligibility criteria were assessed. Subjects underwent standardized ratings, physical examination, electrocardiography, and laboratory testing that included γ-glutamyltransferase (GGT) and a urine toxicology screening for drug abuse to determine study eligibility. Men and women were eligible for inclusion if they were between 18 and 65 years of age and met *DSM-III-R* criteria for current alcohol dependence.[25] Exclusion criteria included dependence on illicit drugs; current use of naltrexone, disulfiram, narcotic-containing medication, or psychotropic medications; notable medical or psychiatric disorders, including mood and anxiety disorders; considerable hepatocellular injury, including cirrhosis of the liver or liver function test levels higher than 2 times normal; pregnancy, lactation, or refusal to use reliable birth control by women with reproductive potential; and inability to understand or comply with the provisions of the protocol. A total of 162 outpatient volunteers were evaluated, of whom 105 met study criteria and were randomized. Of the 162 patients initially interviewed, 15 declined participation owing to lack of interest, and 28 met study exclusion criteria, primarily related to abnormal laboratory values (n = 13) or current dependence on illicit drugs (n = 8). Candidates who did not meet admission criteria were referred for alternative treatment.

TREATMENT

Eligible subjects were randomly assigned to treatment with oral nalmefene at a dose of 20 mg/d (10 mg twice a day) or 80 mg/d (40 mg twice a day), or placebo (Ivax Corporation). The oral formulation in tablet form supplied by the manufacturer for this study is not yet available commercially, although nalmefene is available in an injectable form (Revex) to treat opiate overdose. Decisions about oral dosing were made to bracket the 40-mg (20 mg twice a day) dose found to be therapeutically active in our pilot study.[11] All patients received the same number of identical tablets. Medication was packaged to provide a standardized 1-week dose titration that began with 0.5 mg.

Compliance with study medication was monitored with the Medication Management System, which uses medication caps containing microelectronics to record each time and date the bottle is opened and closed, thus providing immediate estimates of compliance.[26,27] Additionally, a tablet count of returned medication was made at each study visit. Patients were provided with ongoing feedback about their compliance, and those who failed to take study medication as prescribed were provided with compliance counseling. All patients received individual, manual-guided, cognitive behavioral therapy (CBT), as used in Project MATCH.[28,29] The 45-minute CBT sessions were administered by a study psychiatrist (F.R.S., L.D.W., and E.C.R.) or social worker (Gloria Goldberg-Nelson, MSW). The aim of CBT is to facilitate abstinence by increasing patients' ability to avoid or cope with high-risk situations for drinking. Subjects were not excluded from attending self-help groups or receiving other forms of therapy outside of the study. Subjects returned weekly during the 12-week double-blind treatment phase to receive CBT, complete study assessments, return unused study medication, and have medication dispensed.

ASSESSMENTS

Study assessments were conducted by master's level research associates. Baseline severity of alcoholism was assessed with the alcohol dependence scale,[30] a 25-item instrument, with higher alcohol dependence scale scores associated with greater severity of alcohol dependence (score range, 0-47). Quantity and frequency drinking data from 90 days prior to screening and during the 12-week double-blind phase were collected using a computerized version of the Timeline Follow Back Interview (Timeline Follow Back Addiction Research Foundation, Toronto, Ontario).[31] The timeline method quantifies ethanol

fidential communication supplied by Ivax Corporation, Miami, Fla, March 1992). It has a longer half-life in plasma (8-10 hours), with greater biosystemic availability (40%-50%), and may give a more sustained opioid antagonist effect than naltrexone.[13-18] Additionally, non-μ receptors (Δ and κ) are thought to reinforce alcohol consumption, and nalmefene binds more competitively with μ, Δ, and κ receptors than naltrexone and may thereby prove superior for diminishing the reinforcing effects of drinking.[19-23] A μ-selective opioid antagonist such as naltrexone may affect Δ and κ receptors when used in high doses,[24] but a universal opioid antagonist such as nalmefene may obviate the need for such high doses with associated side effects, such as intolerable nausea, that reduce retention in treatment. A 3-month double-blind, placebo-controlled pilot study in outpatient volunteers with alcohol dependence found significantly fewer relapses to heavy drinking when treated with 40-mg doses of nalmefene (2 of 7) relative to 10- (6 of 6) or 0-mg (4 of 6) doses, thereby serving as the basis for this larger-scale trial.[11]

RESULTS

SUBJECTS

There were no significant differences among the 20- and 80-mg dose nalmefene groups on baseline characteristics, study outcomes, treatment completion, medication compliance, or adverse drug experiences. Therefore, data from the nalmefene groups were combined, and the results presented are nalmefene and placebo group comparisons. The baseline demographics and clinical characteristics of subjects did not differ between the placebo and nalmefene groups (**Table 1**).

consumption using a standard drink formula that equates one 12-oz beer, one 5-oz glass of wine, and one 1½-oz shot of distilled spirits. These self-reported drinking data were verified by monthly reports from a collateral informant designated at baseline by the patient, and by weekly measurements of breath alcohol concentrations. In the rare case of an unresolved discrepancy between data sources, the most negative report was assumed accurate. Monthly GGT values were used to evaluate any hepatotoxic effects of nalmefene. Two assessments of craving were made on an exploratory basis at every study visit to assess any relationship between nalmefene and decreased craving severity. Subjects were asked to use an 11-point visual craving scale (0 = no desire, 10 = extreme desire) to answer the question, "Over the past week, what has your desire or craving for an alcoholic beverage been at the time of day that you usually drink?" Subjects also completed the obsessive compulsive drinking scale (OCDS),[32] a 14-item self-report of craving, with total scores ranging from 0 to 56. The OCDS includes a 6-item obsessive subscale to assess intensity and intrusiveness of thoughts about drinking (obsessive subscale range, 0-24), and an 8-item compulsive subscale to assess compulsive behaviors toward drinking (compulsive subscale range, 0-32).

OUTCOME DEFINITIONS

Outcome variables included the rate of relapse to heavy drinking (defined as 6 or more drinks consumed per day for men and 4 or more drinks per day for women), percentage of days abstinent, and change from baseline in the number of standard drinks consumed per drinking day over the 12-week period of double-blind treatment. The definition of relapse, the choice of percentage of days abstinent as an indicator of drinking frequency, and the number of drinks consumed per drinking day as a measure of the intensity of drinking on the occasions when drinking occurs were based on the primary outcome variables of Project MATCH.[29] A lower drink cut off for women in the definition of relapse reflects the finding that women achieve higher blood alcohol concentrations than men after consuming similar amounts of ethanol and are more vulnerable to alcoholic liver disease.[33] It was hypothesized a priori that patients treated with nalmefene would show significantly greater treatment effects on outcome variables than patients given placebo, and that outcomes would not differ between high- and low-dose nalmefene groups, given the threshold and ceiling effects previously reported for nalmefene treatment.[11,34,35]

STATISTICAL ANALYSES

The baseline characteristics of the nalmefene vs placebo groups were analyzed using *t* tests for continuous variables and the χ^2 test for categorical variables. Tests of group differences on outcome variables were conducted using an intention-to-treat analysis plan that included all randomized subjects. Additionally, group differences on outcome variables were analyzed within subgroups of subjects who completed the 12-week trial and nonabstinent subjects. Tests of a priori hypotheses were directional (1 tailed); all other comparisons, including tests of baseline differences and adverse drug experiences, were 2 tailed. An α level of .05 was used to determine statistical significance. Outcomes were compared for the 20- and 80-mg dose nalmefene groups, and if no difference was obtained, the data from the nalmefene groups were combined to maximize power and evaluate drug and placebo differences. Rates of nonrelapse to heavy drinking were tested using survival methods (Kaplan-Meier method estimates). The odds ratio of relapsing was calculated as the incidence of relapse to heavy drinking among subjects given placebo divided by the corresponding rate among subjects treated with nalmefene. Differences in the rate of relapse and the rate of abstinent days over the double-blind period and the rate of study completion were tested using contingency table analyses and χ^2 tests. Analyses of group differences in the number of days in treatment, the mean percentage of medication compliance by Medication Management System and returned pill counts, visual craving scale scores, OCDS scores, and GGT values were examined by *t* test. Significance levels for group comparisons of mean number of drinks consumed per drinking day, time to relapse, number of relapses, and duration of relapse were calculated using Mann-Whitney *U* tests. Fisher exact test probabilities were calculated for frequency analyses of adverse drug experiences.

TREATMENT

The rate of completion of the study did not differ across treatment groups and was 65.7% (23) for the placebo group and 64.3% (45) for the nalmefene groups ($\chi^2_1 = 0.02$, $P = .89$). Similarly, the number of days that patients were in double-blind treatment did not differ across treatment groups (mean ± SD days, 68.5 ± 28.5 in the placebo group, 66.6 ± 31.3 in the nalmefene groups, $t_{103} = 0.31$, $P = .76$). A total of 37 subjects did not complete the 12-week double-blind treatment phase. Of these subjects, 14 required more intensive alcoholism treatment; 4 were discontinued for having 2 consecutive urine screenings positive for illicit drugs; 3 stopped participating because of an adverse event; 3, because of schedule conflicts due to a new job; 2, because of protocol violations; and 1, for meeting study criteria for poor compliance (failure to take at least 75% of the study medication for 2 consecutive study visits). The remaining 10 subjects withdrew their consent for various personal reasons (moved away or did not want blood drawn). Reasons for not completing the study did not differ significantly across treatment groups.

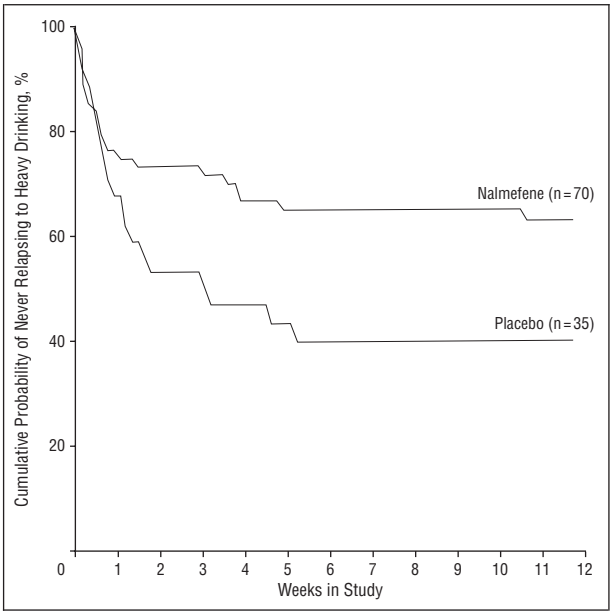
Measures of medication compliance did not differ across treatment groups, with an overall mean rate of compliance of 86.1% based on Medication Management System recordings and a mean of 89.9% based on returned pill counts. Only 1 patient, assigned to the placebo arm, met study criteria for poor medication compliance and was discontinued from the study.

Patients and therapists were asked to guess the identity of the double-blind treatment at the completion of the study to test the integrity of the double-blind element. There was no significant association between patient or therapist guesses and the identity of the assigned medication.

Table 1. Demographic and Clinical Characteristics of the Treatment Groups at Baseline*

Characteristics	Placebo Group (n = 35)	Nalmefene Groups† (n = 70)
Demographic		
Sex, male	62.9	68.6
White	82.9	81.4
Married	31.4	40.6
Paid employment	77.1	66.2
Education, ≥12 y	90.0	86.6
Age, y	41.7 ± 9.9	41.9 ± 8.2
Clinical		
Age at alcoholism onset, y	25.6 ± 10.9	25.0 ± 11.0
Parental history of alcoholism	71.4	64.3
Alcohol dependence scale (0-47)	18.2 ± 8.0	16.2 ± 7.9
Drinks consumed per drinking day in last 3 mo	7.8 ± 4.3	8.1 ± 4.5
Abstinent days in last 3 mo	42.4	33.6
Abstinent days prior to randomization	16.0 ± 19.7	13.0 ± 17.4
γ-Glutamyltransferase (normal range, 0-65), U/L	35.6 ± 33.6	39.5 ± 28.9
Visual craving scale (0-10)	6.4 ± 2.6	6.5 ± 2.9
Obsessive compulsive drinking scale total score (0-56)	16.6 ± 5.6	16.4 ± 5.6

*Values are given as mean ± SD or percentage.
†There were no statistically significant differences between groups.



Rates of never relapsing to heavy drinking from randomization (week 0) through the end of double-blind treatment (week 12).

PRIMARY OUTCOME VARIABLES

Drinking outcome data were available for all 105 randomized subjects. Kaplan-Meier survival curves demonstrate a significant difference in favor of treatment with nalmefene over placebo in the rate of never relapsing to heavy drinking (**Figure**, Wilcoxon [Gehan] test statistic$_1$, 2.84, $P = .046$). A significant treatment effect was detected at the first weekly study visit in the percentage of patients reporting any heavy drinking days during the first week of double-blind treatment (15.7% [11/70] in the nalmefene groups and 34.3% [12/35] in the placebo group, $\chi^2_1 = 4.70$, $P<.02$). Overall, significantly fewer patients treated with nalmefene than those given placebo reported any relapse to heavy drinking over the 12-week double-blind treatment period (**Table 2**). The odds ratio of relapsing to heavy drinking was 2.4 times greater for those given placebo than for those given nalmefene (95% confidence interval, 1.05-5.59). Supportive analyses related to relapse found that patients treated with nalmefene also had significantly fewer heavy drinking episodes than those given placebo (Table 2). Final GGT values greater than the upper limit of normal values correlated significantly with each outcome variable given in Table 2, thus providing additional objective validation of these self-reported drinking behaviors.

A subgroup analysis of patients who sampled alcohol (had at least 1 drink while in the study [n = 71]) likewise found significantly fewer patients treated with nalmefene (56.5% [26/46]) than were given placebo (80.0% [20/25]) reporting any episodes of heavy drinking over the 12-week study period ($\chi^2_1 = 3.91$, $P<.03$). That subgroup of patients (n = 68) who completed the 12-week double-blind phase also demonstrated a lower rate of relapse to heavy drinking while being treated with nalmefene (37.8% [17/45]) than did those given placebo (60.9% [14/23], $\chi^2_1 = 3.27$, $P<.04$).

Treatment groups did not differ in the percentage of abstinent days during the study, with both groups showing significant increases in the percentage of days abstinent during the 12-week double-blind treatment in comparison with the 12-week pretreatment interval (+39% in the placebo group, $P<.001$, and +46% in the nalmefene groups, $P<.001$). Similarly, although group differences did not achieve statistical significance in the mean number of drinks consumed per drinking day during the 12-week double-blind treatment ($P = .06$), both groups showed significant reductions relative to the 12-week pretreatment interval (–2.6 ± 3.0 in the placebo group, $P<.001$, and –3.2 ± 3.9 in the nalmefene groups, $P<.001$). There was no evidence of an interaction between sex and treatment on any outcome variable.

EXPLORATORY OUTCOME VARIABLES

There was no difference in self-report measures of craving severity between nalmefene and placebo groups during double-blind treatment. However, the sample as a whole showed significant decreases in self-reported craving severity from baseline to end of study on the visual craving scale (mean ± SD change, –3.9 ± 4.0, $t = 8.94$, $P<.001$), the total score on the OCDS (mean ± SD change, –8.9 ± 6.2, $t = 13.05$, $P<.001$), the OCDS compulsive subscale score (mean ± SD change, –6.4 ± 4.2, $t = 12.77$, $P<.001$), and the OCDS obsessive subscale score (mean ± SD change, –2.5 ± 3.1, $t = 7.37$, $P<.001$).

SAFETY AND TOLERABILITY

A total of 3 subjects stopped treatment prematurely because of adverse events. All 3 subjects who stopped participating owing to an adverse event were taking 80 mg of nalmefene; 1 complained of fatigue and tachycardia, 1 of a rash, and 1 of itching, abdominal bloating, heartburn, and

Table 2. Between-Group Comparisons of Treatment Outcome*

	Placebo Group (n = 35)	Nalmefene Groups (n = 70)	Test Statistic†	P
Patients relapsing‡	58.8	37.1	$\chi^2 = 4.36$	.02
No. of relapses	1.9 ± 2.5	1.5 ± 3.8	$U = 959.7$	.02
Duration of relapse, d	1.5 ± 3.3	0.9 ± 1.8	$U = 1022.0$	.06
No. of days to first relapse	33.5 ± 34.2	46.3 ± 37.5	$U = 1045.5$	.11
No. of drinks consumed per drinking day	5.3 ± 4.6	4.1 ± 3.3	$U = 427.0$	.06
Days abstinent	83.0	80.3	$U = 1182.5$	.48

*Values are given as mean ± SD or percentage.
†U indicates the Mann-Whitney U test.
‡Relapse is defined as drinking 6 or more standard drinks (men) or 4 or more standard drinks (women) per occasion.

mild depression. Adverse drug experiences were typically not associated with onset of treatment. No medically serious adverse drug experiences were reported. Patients treated with nalmefene reported significantly more experiences of nausea than those given placebo (**Table 3**), but no patients skipped medication or discontinued treatment because of nausea. Final GGT values decreased significantly from baseline in the sample as a whole, with no significant differences across treatment groups (mean ± SD change in GGT −11.1 ± 26.8, $t = 3.55$, $P = .001$).

Table 3. Percentage of Subjects Reporting Moderate to Severe Adverse Drug Experiences*

Adverse Drug Experiences	Placebo Group (n = 35)	Nalmefene Groups (n = 70)	P†
Headache	20.0	17.1	.79
Insomnia	5.7	14.3	.17
Fatigue	5.7	10.0	.71
Nausea	0	12.9	.03

*Moderate to severe adverse drug experiences that were reported 1 or more times by at least 10% of subjects in any group are listed in decreasing order according to overall frequency. No significant differences were found between nalmefene and placebo groups for adverse drug experiences reported by less than 10% of subjects in all groups. The percentage of patients complaining of any adverse drug reaction did not differ significantly between the 20- and 80-mg nalmefene-treated groups.
†By Fisher exact test.

COMMENT

We found that nalmefene was effective in preventing relapse to heavy drinking or in reducing the number of subsequent episodes of heavy drinking in those patients who did relapse. There was no evidence of hepatotoxic side effects or medically serious adverse drug experiences. High rates of medication compliance and treatment completion suggest that nalmefene is acceptable to patients with alcohol dependence. However, patients who enroll in a clinical trial may be more motivated and not representative of the general population of alcoholics. Treatment effects were evident at the first weekly study visit after initiation of treatment. Although 80% (20/25) of those subjects given placebo who "slipped" by sampling alcohol then went on to an episode of heavy drinking, a significantly smaller percentage of patients treated with nalmefene followed this course.

The heavy alcohol consumption that typifies alcohol dependence and increases the risk of mortality and morbidity may be explained by animal models of addiction that demonstrate that extended exposure to a drug can lead to a gradual upward shift in the dose-response function; such an increase requires heavier consumption in order to achieve and maintain a desirable level of intoxication.[36] Other animal models have shown that administration of a small dose of an opioid agonist increases motivation to consume more drug.[37,38] The small dose may serve as a priming dose for higher levels of consumption in order to reinstate or increase opioid activity. Opioid antagonists, like nalmefene, bind competitively with opioid receptor sites and displace opioid agonists. Through this mechanism, the pleasurable and priming effects associated with alcohol consumption may be reduced, thereby reducing risk of relapse.[39,40] However, one third of patients treated with nalmefene did relapse, there was no apparent advantage to higher nalmefene dosing, and measures of alcohol craving did not differ between nalmefene and placebo groups. Preclinical studies have shown alcohol consumption to be mediated by multiple neurotransmitters and neuromodulators, including nonopioid systems, that interact to optimize the rewarding properties of alcohol.[41] Thus, antagonism of opioid receptors alone, even in higher doses, may not entirely eliminate alcohol consumption in individuals with alcohol dependence. Additionally, much of the activity of brain reward systems occurs subcortically. Therefore, self-report measures of craving, like the OCDS or the visual craving scale, may not be sensitive to drug effects on these systems that are manifest behaviorally as nonrelapse. An earlier dose-ranging pilot study found 0- and 10-mg doses of nalmefene to be ineffective in preventing relapse, whereas a 40-mg dose significantly reduced risk of relapse,[11] as did 20- and 80-mg doses relative to administration of placebo in the present study. Preclinical studies looking at higher doses also lend support to a ceiling effect for nalmefene treatment, as was observed in the present study.[34,35] Occurrence of specific adverse drug experiences did not differ between the groups treated with 20- and 80-mg doses of nalmefene, but the 3 patients discontinuing treatment due to adverse drug experiences were assigned to treatment with 80-mg doses, suggesting that nalmefene dosing in the 20- to 40-mg/d range may be preferable for treating alcohol dependence. All patients received CBT and showed overall improvement on the percentage of days abstinent and in the number of drinks consumed per drinking day, as did patients receiving CBT in Project MATCH.[29] The skills to avoid or cope with drinking triggers learned in CBT may have contributed to the re-

duction in drinking frequency, intensity, and self-reported craving severity across treatment groups. However, those patients receiving nalmefene showed added benefit in terms of lower risk for relapse to the heavy drinking associated with negative consequences of alcoholism.

The strengths of this study include its external validity, in terms of the high proportion of screened patients who were randomized; its internal validity, as exemplified by the high rates of medication compliance, treatment retention, preservation of the double-blind element, and availability of drinking outcome data on all randomized patients; and the efficacy demonstrated by rates of nonrelapse to heavy drinking in intention-to-treat analyses, and in subgroup analyses of drinkers and subjects who completed the study.

Limitations of the study include a potential limit on generalizability due to our reliance on advertisements to recruit subjects, small sample size, and short-term duration of the trial. Survival curves and other relapse data provide no evidence of tolerance to the effects of treatment with nalmefene over the 3-month study period. However, longer-term efficacy of treatment with nalmefene is unknown. Theoretically, treatment could be discontinued in patients achieving a stable period of abstinence, with the understanding that it could always be reinstated if needed, or used to avert relapse during periods of increased risk, particularly given the rapid onset of the effect. Study findings confirm earlier reports of opioid antagonist effects on heavy drinking and support the development of nalmefene as a first-line treatment of alcohol dependence.

Accepted for publication April 29, 1999.

This study was supported in part by grant AA09560 from the National Institute on Alcohol Abuse and Alcoholism, Bethesda, Md. The nalmefene and matched placebo were provided by the Ivax Corporation, Miami, Fla.

We are indebted to the following people for their hard work and assistance in completing this project: Judy Lozano, Gloria Goldberg-Nelson, MSW, and Bobby Brandt.

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