Extending the Treatment Options in Alcohol Dependence: A Randomized Controlled Study of As-Needed Nalmefene

Karl Mann, Anna Bladström, Lars Torup, Antoni Gual, and Wim van den Brink

Background: There is a large treatment gap in alcohol dependence, and current treatments are only moderately effective in preventing relapse. New treatment modalities, allowing for reduction of alcohol consumption as a treatment goal are needed. This study evaluated the efficacy of as-needed use of the opioid system modulator nalmefene in reducing alcohol consumption in patients with alcohol dependence.

Methods: Six hundred and four patients (placebo = 298; nalmefene = 306), ≥18 years of age, with a diagnosis of alcohol dependence, ≥6 heavy drinking days, and average alcohol consumption ≥ World Health Organization medium drinking risk level in the 4 weeks preceding screening, were randomized (1:1) to 24 weeks of as-needed placebo or nalmefene 18 mg.

Results: Patients taking placebo ($n = 289$) and patients taking nalmefene ($n = 290$) were included in the efficacy analyses. At Month 6, there was a significant effect of nalmefene compared with placebo in reducing the number of heavy drinking days (−2.3 days [95% confidence interval: −3.8 to −.8]; $p = .0021$) and total alcohol consumption (−11.0 g/day [95% confidence interval: −16.8 to −5.1]; $p = .0003$). Improvements in Clinical Global Impression and liver enzymes were larger in the nalmefene group compared with placebo at Week 24. Adverse events (most mild or moderate) and dropouts due to adverse events were more common with nalmefene than placebo. The number of patients with serious adverse events was similar in the two groups.

Conclusions: Nalmefene provides clinical benefit, constitutes a potential new pharmacological treatment paradigm in terms of the treatment goal and dosing regimen, and provides a method to address the unmet medical need in patients with alcohol dependence that need to reduce their alcohol consumption.

Key Words: Alcohol dependence, as-needed, nalmefene, opioid antagonist, placebo-controlled, reduction

With almost 15 million affected persons in the European Union and 8 million affected persons in the United States, alcohol dependence is a major public health problem (1,2). At the same time, alcohol dependence remains seriously underdiagnosed and undertreated (3). In Europe, <10% of the people diagnosed with alcohol dependence receive any treatment; the corresponding figure for the United States is approximately 25% (4). Moreover, more than two thirds of patients in abstinence-oriented treatments relapse within the first 12 months (5,6). Despite encouraging data from studies targeting reduction of alcohol intake (7–9), current pharmacological treatments for alcohol dependence are approved only for relapse prevention. However, <30% of patients treated with acamprosate were continuously abstinent after 12 months of treatment (10), and two thirds of patients treated with naltrexone had experienced at least one heavy drinking day after 16 weeks of treatment (2). Despite all this, prevailing opinions hold abstinence as the primary treatment goal (11), although abstinence-oriented treatments might not be desirable or acceptable to many patients (12).

In such an unsatisfactory situation, new evidence-based treatment modalities are needed (13–15) to address this unmet medical need in patients at risk of alcohol-related harm. Reduction of alcohol consumption as a treatment goal has been heavily debated within the scientific community (16,17). Clinicians increasingly support reduction of alcohol consumption as a valuable treatment option to reduce the consequences of harmful alcohol consumption and attract patients who are currently not inclined to seek treatment (11,13,18–20).

Reduction of alcohol consumption is associated with reduced risk of morbidity and mortality in patients with alcohol dependence (21). Allowing patients to choose between abstinence or reduction as their treatment goal might enhance engagement with the treatment, ultimately leading to better treatment outcomes (22,23). Patients might also reconsider abstinence once they are engaged in therapy (24), even though abstinence is not always necessary to benefit from treatment.

Nalmefene is an opioid system modulator, with antagonist activity at the μ and δ receptors and partial agonist activity at the κ receptor (25). Acute alcohol intake results in mesolimbic dopamine release (facilitated by the release of β-endorphins) (26). After repeated exposure to high doses of alcohol, neuroadaptations occur in several neurotransmitter/neuropeptide systems, including the opioid receptor system, which might lead to continued alcohol intake (27,28). The proposed mechanism of action of nalmefene is to reduce the reinforcing effects of alcohol, helping the patient to reduce drinking.

Although Anton *et al.* (29) was unable to show an effect compared with placebo, other studies of nalmefene in patients with alcohol-use disorders indicate that treatment with nalmefene is

From the Central Institute of Mental Health (KM), University of Heidelberg, Mannheim, Germany; H. Lundbeck A/S (AB, LT), Copenhagen, Denmark; Neurosciences Institute (AG), Hospital Clinic, Barcelona, Spain; and the Academic Medical Center (WvdB), Department of Psychiatry, University of Amsterdam, Amsterdam, The Netherlands.

Authors AG and WvdB contributed equally to this work.

Address correspondence to Karl Mann, M.D., Ph.D., Department of Addictive Behavior and Addiction Medicine, Ruprecht-Karls-University Heidelberg, Central Institute of Mental Health, Square J5, 68159 Mannheim, Germany; E-mail: karl.mann@zi-mannheim.de.

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associated with a reduction of heavy drinking (30–32). Furthermore, the as-needed treatment regimen seems to be a feasible approach (32). Here we present results from a recently completed phase 3 study in patients with alcohol dependence that assessed the efficacy and safety of as-needed use of nalmefene in reducing alcohol consumption, measured as the monthly changes from baseline in the number of heavy drinking days and total alcohol consumption (g/day) during a treatment period of 24 weeks.

Methods and Materials

Patients

This randomized, double-blind, placebo-controlled, parallel-group study included patients from 39 sites in Austria, Finland, Germany, and Sweden. Patients were recruited from in- and outpatient clinics, including both spontaneous referrals and referrals resulting from special advertisements; the recruitment approach was identical across all countries. Eligible patients were men and women ≥ 18 years of age with a primary diagnosis of alcohol dependence according to DSM-IV-TR (33) (assessed with Mini-International Neuropsychiatric Interview [34]) and a blood alcohol concentration <.02% at the screening visit. Exclusion criteria were <6 heavy drinking days (a day with alcohol consumption ≥60 g for men and ≥40 g for women [11]), an average alcohol consumption below medium drinking risk level according to the World Health Organization (≤40 g alcohol/day for men and ≤20 g alcohol/day for women [35]), or >14 consecutive abstinent days in the 4 weeks preceding screening, a Revised Clinical Institute Withdrawal Assessment for Alcohol (36) score ≥10 (indicating the need for medication supported detoxification), aspartate aminotransferase and/or alanine aminotransferase (ALAT) values >3× of upper normal limit, a DSM-IV Axis I disorder other than alcohol dependence or nicotine dependence, a DSM-IV antisocial personality disorder (assessed with Mini-International Neuropsychiatric Interview), or recent (within 1 week before the screening visit) treatment with opioid agonists or partial agonists. For the full list of selection criteria and disallowed recent and concomitant medication, see Supplementary Material and Methods and Table S1 in Supplement 1.

This study was designed and conducted in accordance with the principles of the Declaration of Helsinki; each site started patient inclusion only after ethics committee approval. All patients gave written informed consent.

Randomization and Concealment

At baseline (Week 0), eligible patients were assigned to 24 weeks of treatment with as-needed use of either placebo or nalmefene 18 mg (base; dose rationale in Supplementary Material and Methods in Supplement 1) in a 1:1 ratio, according to a computer generated randomization list (in blocks of 4), provided by the sponsor. Randomization for the run-out period was also done at baseline.

Patients, investigators, staff, and sponsor were blind to treatment assignment. Two sets of sealed envelopes containing study medication details for each patient were prepared. One set was kept by the sponsor, and one set was kept by the investigator or pharmacist. The randomization code was only to be broken by the investigator in case of an emergency situation. Nalmefene and placebo tablets were identical in appearance.

Study Procedures

The study consisted of a 1- to 2-week screening period, a 24-week double-blind main treatment period with nalmefene or placebo, and a 4-week double-blind run-out period (to evaluate any treatment discontinuation effects) during which nalmefene-treated patients were randomized to placebo or nalmefene (1:1) and placebo-treated patients continued with placebo. A safety follow-up was scheduled 4 weeks after completion or dropout.

Patients were instructed to take one tablet on each day they perceived a risk of drinking alcohol (as-needed dosing), preferably 1 to 2 hours before anticipated time of drinking. Tablets could be taken up to once daily and were supplied in wallet cards with space for the patient to record the date of study medication intake. The Timeline Follow-Back (37) was used to obtain estimates of daily drinking as well as to record daily medication intake.

In addition, all patients took part in a motivational and adherence-enhancing intervention (BRENDA [38]) to support them in changing their behavior and to enhance adherence to treatment, starting at randomization and subsequently at all scheduled visits. No treatment goal was defined (i.e., both abstinence and reduction were accepted); no information was collected on individual treatment goals.

Assessments of efficacy and safety were performed at screening (Week –1 or Week –2), baseline, Weeks 1, 2, and 4, followed by monthly assessments. For a full description of timing of assessments, see Table S2 in Supplement 1.

Monthly drinking variables were derived from the Timeline Follow-Back (37) that provided information of daily number of standard drinks. To define standard drinks, a conversion card was provided. The conversion of recorded standard drinks to grams was performed by a statistical programmer with the following country-specific factors: Austria 10 g; Finland 12 g; Germany and Sweden 14 g.

At screening, patients reported their daily drinking over the previous month (= 28 consecutive days). At subsequent visits, they reported drinking since the previous visit.

The predefined co-primary outcome measures were change from baseline in heavy drinking days and total alcohol consumption (grams/day) at Month 6. The predefined key-secondary outcome measure was drinking risk level response (from very high drinking risk level at baseline to medium drinking risk level or below, or from high or medium drinking risk level at baseline to low drinking risk level or below) at Month 6.

Clinical status was based on Clinical Global Impression—Severity of Illness and Global Improvement scales (CGI-S and CGI-I [39]), and alcohol dependence symptoms were based on Alcohol Dependence Scale (40) and Drinker Inventory of Consequences (41). Liver function variables related to efficacy included γ-glutamyltransferase (GGT) and ALAT.

Secondary outcome measures reported here are Week 24 CGI-S and CGI-I scores and GGT and ALAT values. The GGT and ALAT values were analyzed as log-transformed values instead of as log-transformed changes from baseline, as specified in the protocol.

Other secondary variables will be reported elsewhere. For the full list of outcome variables, see Supplementary Material and Methods in Supplement 1.

Safety assessments consisted of evaluation of adverse events (including pretreatment and treatment-emergent adverse events), clinical safety laboratory tests, vital signs, weight, electrocardiograms, and Profile of Mood States. To capture any signal related to psychiatric adverse events, a group of selected adverse events was predefined (see Supplementary Material and Methods in Supplement 1). Adverse events potentially related to suicide were identified with the substandardized Medical Dictionary for Regulatory Activities query "suicide/self-injury."

Power Calculation

The sample size calculation was based on a standard deviation for the change from baseline in number of heavy drinking days of 7 days and the change from baseline in total alcohol consumption of 36.5 g/day and a correlation of .7 between heavy drinking days and total alcohol consumption. With a significance level of 5%, 300 patients in each treatment group would provide a power of 90% for detecting a difference between the treatment groups of 3 heavy drinking days and 12 g/day in total alcohol consumption, accounting for an expected drop-out rate of 35% at Month 6.

Statistical Analysis

Three datasets were prespecified in the study protocol.

The "all-patients-randomized set," comprising all randomized patients, was used to calculate the incidence of serious adverse events, to account for any pretreatment serious adverse events.

The "all-patients-treated set," comprising all randomized patients but excluding from the dataset those with no recorded study medication intake and all study medication returned. This dataset was used for all remaining safety analyses.

The "full-analysis set," comprising all patients in the all-patients-treated set with at least one valid postbaseline assessment of alcohol consumption, was used for all efficacy analyses.

Baseline for drinking variables in the main treatment period was defined as the month preceding the screening visit. For all other variables, baseline was defined as the assessment at the screening visit.

Primary Analysis

The co-primary outcome measures were analyzed with mixed model repeated measures, with the baseline score as covariate, and site, sex, time, and treatment as fixed effects; baseline score × time interaction and treatment × time interaction were also included in the model. Various sensitivity analyses were performed (Supplementary Methods and Materials in Supplement 1).

Key Secondary Analysis

The null hypothesis of no difference in treatment effect on heavy drinking days and total alcohol consumption had to be rejected to proceed with formal testing of the key-secondary outcome measure, which was analyzed by logistic regression by month, with country, sex, baseline drinking risk level, and treatment as fixed effects, with nonresponse imputation for missing values. The odds ratio of nalmefene compared with placebo with 95% confidence interval (CI) and corresponding p value based on the likelihood ratio test was estimated from the model. Various sensitivity analyses were performed (Supplementary Methods and Materials in Supplement 1).

Secondary Analyses

The secondary outcome measures were analyzed with similar models as used for the coprimary variables. The CGI-S baseline score was included as a covariate in the model for CGI-I.

A post hoc analysis was performed by a nonparametric log-rank test to test whether there was a difference in withdrawal rate between the treatment groups in the main treatment period.

Adverse events were coded with the lowest level term according to Medical Dictionary for Regulatory Activities, version 13.0.

The principal statistical software used was SAS, version 9.2 (SAS Institute Inc., Cary, North Carolina).

Results

Study Sample

From December 2008 to February 2010, 770 patients were screened, of whom 604 were randomized (Figure S1 in Supplement 1). There were no clinically relevant differences in baseline demographic or clinical characteristics between the groups (Table 1). All but one patient were Caucasian, two thirds were men, and the mean age was 52 years. Mean age of onset of alcohol problems was 38 years.

In the month before screening, patients had on average 20 heavy drinking days and drank on average 85 g of alcohol/day. The mean CGI-S score of 4, the Drinker Inventory of Consequences score of 35, and the Alcohol Dependence Scale score of approximately 12 confirmed that these were moderately ill patients with significant adverse consequences of drinking. Mean values of liver parameters were close to or slightly above the reference ranges. The vast majority of patients had not previously been treated for either alcohol dependence (424 [70%] of 604) or alcohol withdrawal symptoms (491 [81%] of 604).

The all-patients-treated set comprised 598 patients, and the full-analysis set comprised 579 patients. Importantly, 102 of these patients (18%) reduced their drinking to <6 heavy drinking days/month or below medium drinking risk level already in the period between screening and randomization (Table 1).

During the main treatment period, 91 (31%) of the placebo-treated patients and 160 (53%) of the nalmefene-treated patients dropped out of the study. The dropout rate was significantly different between the groups ($p < .0001$); the most frequent primary reason was withdrawal of consent in the placebo group and adverse events in the nalmefene group (Figure S1 in Supplement 1). Two hundred patients (68%) in the placebo and 138 (46%) in the nalmefene group completed the study.

On average, patients receiving placebo took study medication on nearly two thirds of the days in the main treatment period, whereas patients receiving nalmefene took study medication on almost half of the days (Table S3 in Supplement 1).

Efficacy

The mean number of heavy drinking days decreased from 19 to 8 days/month, and the mean total alcohol consumption decreased from 84 to 33 g/day in the nalmefene group at Month 6 (Table 2). In the placebo group, the mean number of heavy drinking days decreased from 20 to 11 days/month, and the mean total alcohol consumption decreased from 85 to 45 g/day at Month 6.

The co-primary efficacy analyses showed a statistically significantly superior effect of nalmefene compared with placebo in the change from baseline to Month 6 in heavy drinking days (group difference: −2.3 days/month [95% CI: −3.8 to −.8]; $p = .0021$) and total alcohol consumption (group difference: −11.0 g/day last month [95% CI: −16.8 to −5.1]; $p = .0003$) (Table 2). All sensitivity analyses (except for the baseline observation carried forward analysis) confirmed the results (Table S4 in Supplement 1). A statistically significant reduction in the number of heavy drinking days and total alcohol consumption in favor of nalmefene was observed already at Month 1 and throughout the main treatment period (Figure 1). The changes in heavy drinking days and total

Table 1. Demographic Data and Baseline Clinical Characteristics of All Randomized Patients

Patients Randomized	Placebo (n = 298)	Nalmefene (n = 306)
Race		
Caucasian	297 (99.7%)	306 (100%)
Sex		
Women	96 (32.2%)	102 (33.3%)
Age (yrs)	52.1 (9.0)	51.0 (10.1)
Body Mass Index (kg/m^2)	26.6 (4.2)	26.6 (4.2)
Age at the Onset of Drinking Problems	37.7 (12.2)	37.9 (13.1)
Drinking Risk Level[a]		
Unknown	0 (.0%)	1 (.3%)
Low	2 (.7%)	1 (.3%)
Medium	60 (20.1%)	68 (22.2%)
High	119 (39.9%)	114 (37.3%)
Very high	117 (39.3%)	122 (39.9%)
Total Monthly Heavy Drinking Days[a]	19.5 (7.0)	19.5 (7.3)
Total Alcohol Consumption (g alcohol/day)[a]	84.1 (41.5)	84.8 (42.1)
Clinical Global Impression–Severity of Illness Score	3.96 (1.52)	4.02 (1.48)
γ-Glutamyltransferase (IU/L)[b]	53.7	51.7
Alanine Aminotransferase (IU/L)[b]	29.1	29.2
Mean Corpuscular Volume (fL)[b]	96.6	97.0
Percentage Carbohydrate-Deficient Transferrin (%)	2.49 (1.26)	2.60 (1.44)
Drinker Inventory of Consequences Total Score	35.0 (18.1)	35.8 (18.7)
Alcohol Dependence Scale Total Score	12.2 (4.88)	12.9 (5.85)
Previously Treated for Alcohol Dependence		
Yes	89 (29.9%)	91 (29.7%)
Previously Treated for Alcohol Withdrawal		
Yes	53 (17.8%)	60 (19.6%)
Family History of Alcohol Problems		
Yes	179 (60.1%)	191 (62.4%)
<6 Heavy Drinking Days or Drinking Risk Level < Medium at Randomization[c]		
Yes	58 (20.1%)	44 (15.2%)

All-patients-randomized set; N = 604. Data are mean (SD) or number of participants (%).
[a]On the basis of Timeline Follow-Back data from the month preceding the screening visit.
[b]Geometric mean.
[c]Patients having <6 heavy drinking days or a drinking risk level below medium in the period between screening and randomization, extrapolated to 4 weeks; percentages on the basis of the full-analysis set.

alcohol consumption from Month 6 were small and nonsignificant in the run-out period (Table S5 in Supplement 1).

The key secondary analysis of drinking risk level response was statistically significant in favor of placebo (odds ratio = .70; Table S6 in Supplement 1). However, sensitivity analyses showed a greater proportion of responders with nalmefene than with placebo.

A decrease in the CGI-S score from baseline to week 24 was observed in both treatment groups (Figure S2 in Supplement 1), with greater mean improvement (group difference: −.4 [95% CI: −.6 to −.2]; p = .0004) in the nalmefene group than in the placebo group. In addition, there was a difference in the CGI-I score at week 24 in favor of the nalmefene group (group difference: −.3 [95% CI: −.5 to −.2]; p = .0005).

For GGT and ALAT, the analyses also showed improvements from baseline in both treatment groups, with greater reduction from baseline to week 24 in the nalmefene group than in the placebo group (GGT, p = .0094; ALAT, p = .0109 [Table S7 in Supplement 1]).

Safety and Tolerability

During the main treatment period, 198 (67%) of the patients in the placebo group and 246 (81%) of the patients in the nalmefene group had treatment-emergent adverse events

Table 2. Baseline Values and Coprimary Efficacy Analysis at Month 6 in "Full-Analysis Set"

	Baseline Value				Adjusted Change from Baseline to Month 6					
	Placebo		Nalmefene		Placebo		Nalmefene		Difference to Placebo	
Efficacy Variable	n	Mean ± SD	n	Mean ± SD	n	Mean ± SE	n	Mean ± SE	Mean	p
Number of Heavy Drinking Days	289	19.6 ± 6.9	290	19.4 ± 7.3	213	−8.9 ± .6	152	−11.2 ± .6	−2.3 [−3.8 to −.8]	.0021
Total Alcohol Consumption (g/day)		85 ± 42		84 ± 42		−39.7 ± 2.2		−50.7 ± 2.4	−11.0 [−16.8 to −5.1]	.0003

N = 578. Baseline values were based on observed cases; changes from baseline and differences to placebo were based on mixed model repeated measures values.

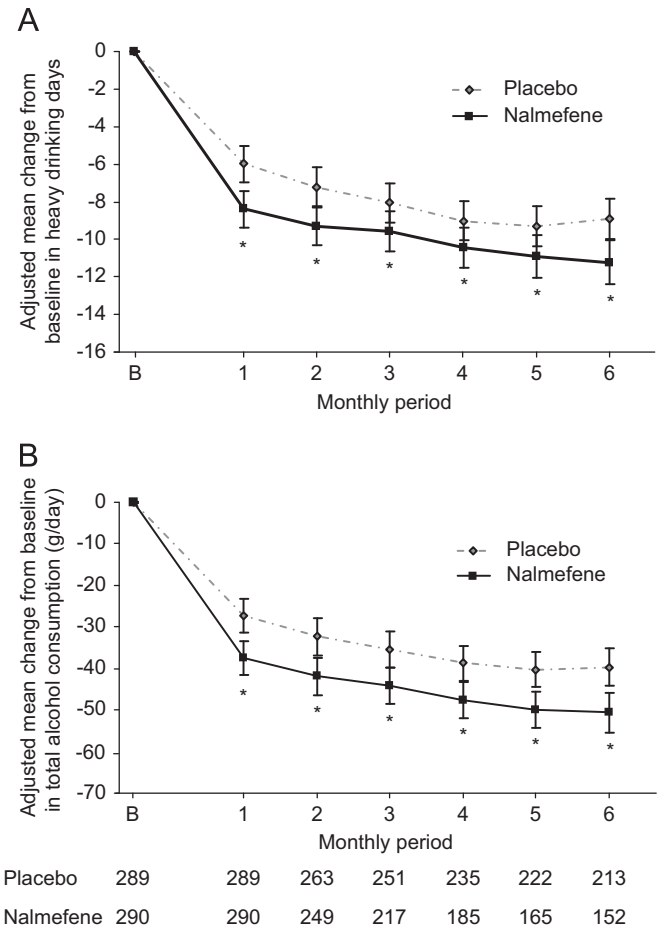

Figure 1. Change in alcohol consumption. **(A)** Adjusted mean change from baseline (on the basis of mixed model repeated measures analysis) in monthly heavy drinking days. **(B)** Adjusted mean change from baseline (on the basis of mixed model repeated measures analysis) in monthly total alcohol consumption (g/day). Baseline data for heavy drinking days and total alcohol consumption were derived from the Timeline Follow-Back for the month preceding the screening visit. Patient numbers contributing to each monthly period are shown below the x-axis for each treatment group. *$p < .05$ (difference to placebo). Bars indicate 95% confidence intervals. B, baseline.

(Table 3). Of the most common treatment-emergent adverse events (incidence ≥5%) dizziness, nausea, fatigue, sleep disorder, insomnia, vomiting, and hyperhidrosis had an incidence two times higher in the nalmefene group than in the placebo group. However, the vast majority of the most common adverse events in the nalmefene group were mild or moderate and occurred within 1 day after the first dose of study medication. Ninety-one patients dropped out due to treatment-emergent adverse events during the main treatment period: 22 (7%) in the placebo group and 69 (23%) in the nalmefene group (Table 3; Table S8 in Supplement 1). Treatment-emergent adverse events with an incidence ≥2% leading to dropout comprised dizziness, nausea, fatigue, and headache in the nalmefene group.

Serious adverse events were reported for 38 patients (including 3 patients with pretreatment serious adverse events): 20 patients in the placebo group and 18 patients in the nalmefene group. No serious adverse event was reported in more than one patient in a treatment group, except for alcoholism (two patients in each group), completed suicide (two patients taking placebo), and convulsion (two patients taking placebo). Most of the serious adverse events were considered not related to study medication by the investigator. There was no pattern in the distribution of serious adverse events across system organ classes, and no indication of specific serious adverse events occurring in the nalmefene group.

Table 3. Adverse Events in All-Patients-Treated Set

	Placebo ($n = 296$)	Nalmefene ($n = 302$)
Treatment-Emergent Adverse Events[a]	198 (66.9)	246 (81.5)
Treatment-Emergent Adverse Events (≥5%)		
Dizziness	23 (7.8)	83 (27.5)
Nausea	18 (6.1)	83 (27.5)
Fatigue	25 (8.4)	53 (17.5)
Headache	27 (9.1)	36 (11.9)
Nasopharyngitis	37 (12.5)	34 (11.3)
Sleep disorder	1 (.3)	32 (10.6)
Insomnia	10 (3.4)	30 (9.9)
Vomiting	8 (2.7)	24 (7.9)
Hyperhidrosis	5 (1.7)	16 (5.3)
Treatment-Emergent Adverse Events Leading to Dropout[a]	22 (7.4)	69 (22.8)
Treatment-Emergent Adverse Events Leading to Dropout (≥2%)		
Dizziness	0 (.0)	16 (5.3)
Nausea	0 (.0)	16 (5.3)
Fatigue	0 (.0)	10 (3.3)
Headache	0 (.0)	9 (3.0)
Serious Adverse Events[b]	20 (6.7)[c]	18 (5.9)

$N = 598$. Data are numbers of patients (%).
[a]In the main treatment period.
[b]In the entire study period; percentages based on the "all-patients-randomized set."
[c]Including two patients that died in the main treatment period.

As mentioned, two patients died during the study: a 36-year-old man and a 47-year-old man (both taking placebo) committed suicide in the main treatment period. In addition, five patients were identified with potentially suicide-related adverse events (two taking placebo, and one taking nalmefene in the main treatment period; one in the placebo-placebo group, and one in the nalmefene-placebo group in the run-out period). However, these suicide-related events were identified as intentional overdoses of the study medication to obtain increased efficacy, and the events were not related to suicide or self-injury.

Nine patients (two taking placebo, seven taking nalmefene) had one of the selected psychiatric adverse events; none was serious, and all the patients fully recovered.

There were no apparent trends in the incidence of potentially clinically significant clinical safety laboratory values, apart from the incidences of potentially clinically significant liver test values (GGT, ALAT, and aspartate aminotransferase), which were lower in the nalmefene than in the placebo group.

No clinically relevant changes over time or differences between the treatment groups were seen in the vital signs, weight, electrocardiogram parameters, or Profile of Mood States total scores.

Discussion

This study provides evidence for the clinical benefit of nalmefene as-needed in patients with alcohol dependence.

Patients in the study were predominantly middle-aged men, with most having a high or very high drinking risk level. Patients with significant withdrawal symptoms were not eligible for participation, and thus some of the most severe alcohol-dependent patients had to be excluded. However, all patients drank excessively, with a mean of 85 g alcohol/day and 19 of the 28 days with heavy drinking in the month before screening. The study population is comparable to patients that are likely to present in primary care (42).

Nalmefene was superior to placebo in reducing the number of heavy drinking days and total alcohol consumption at Month 6; a statistically significant difference in the number of heavy drinking days and total alcohol consumption in favor of nalmefene was observed already at Month 1 and was maintained throughout the treatment period. Compared with baseline, there was a considerable reduction in alcohol consumption in both treatment arms: total alcohol consumption decreased by approximately 60% in the nalmefene group and by approximately 47% in the placebo group. The differences between nalmefene and placebo of approximately 2 heavy drinking days/month and 11 g alcohol/day are clinically relevant, because evidence from epidemiological data have shown that every heavy drinking day carries an increased risk of accidents, aggression, suicide, and cardiac arrest (43), and any reduction in alcohol consumption for a person who consumes more than 10 g of alcohol/day will reduce the annual and lifetime risk of an alcohol-related death (21). Furthermore, the reduction in alcohol consumption after treatment with nalmefene was accompanied by improvements in the CGI scores—which reflect the global clinical judgment of the outcome by an expert clinician—and in significantly greater decreases in GGT and ALAT relative to placebo.

The adverse event profile was as expected on the basis of existing data (29–32) and reflects the pharmacological profile of nalmefene. The number of patients with and the types of serious adverse events were similar in the two groups. Overall, as-needed use of nalmefene was safe and well-tolerated and no safety issues were raised in this study.

Despite their drinking problems having started on average 14 years before study entry, 70% of the patients had never been treated for their alcohol dependence. The nalmefene treatment paradigm thus addresses an unmet medical need, because it obviously has the potential to engage patients at risk of alcohol-related harm who might otherwise not have sought help. Nalmefene does not require the patients to achieve and maintain complete abstinence. The combination of alcohol reduction as a treatment goal and the as-needed dosing concept would be suitable for patients not willing or able to fully abstain from alcohol and might also constitute an important motivational factor, because it engages and empowers patients with alcohol dependence in active and responsible management of their illness. However, all currently approved treatments are indicated for relapse prevention. Although as-needed use ("targeted use") of nalmefene (32), acamprosate (44), disulfiram (44), and naltrexone (44–47) has been studied previously in patients with alcohol use disorders, the current study is the largest randomized controlled study of the as-needed use approach in alcohol-dependent patients to date.

There are also some limitations of this study. Firstly, there was a substantial nonspecific treatment response, partly present before randomization, leaving limited room for further improvements with nalmefene in these patients. Nevertheless, nalmefene provided a statistically significant larger reduction in the number of heavy drinking days and total alcohol consumption, which confirms the pharmacological effect of nalmefene.

Secondly, the dropout rate was higher in the nalmefene group compared with the placebo group. There was no indication, on the basis of demographic data and baseline clinical characteristics, that the patients in the nalmefene group that dropped out from the study differed from completers.

Several sensitivity analyses were performed to evaluate how different assumptions for handling missing data influenced the results. The sensitivity analyses for the co-primary outcome measures were consistently in favor of nalmefene, except for the baseline observation carried forward approach. This approach assumes that all patients immediately return to their baseline values after treatment dropout. However, published data do not support this assumption, because many patients can maintain reduced alcohol consumption after the end of treatment (48). Furthermore, short-term data from the randomized run-out period in the current study suggest that the effect is not lost on short term, and complete loss of effect is not likely.

Thirdly, the proportion of responders was, on the basis of the key secondary responder analysis, statistically significantly lower in the nalmefene group compared with the placebo group at Month 6. However, this effect was due to the differential dropout rate and the nonresponse imputation of missing values. Similar to baseline observation carried forward, this approach can be considered very conservative, because all withdrawn patients are considered nonresponders, irrespective of the value of total alcohol consumption at the time of dropout. The results of the sensitivity analyses were consistently in favor of nalmefene.

Finally, the results from this study should be interpreted in view of the fact that the study population was limited by the selection criteria (e.g., patients with significant axis I comorbidity were excluded). However, this is directly in line with the European Medicines Agency guideline on the development of medicinal products for the treatment of alcohol dependence (11).

In conclusion, nalmefene treatment addresses a significant unmet medical need, given the widespread social and economic consequences—both for the individual and for society—of alcohol dependence. Nalmefene as-needed constitutes a potential new pharmacological treatment paradigm, both in terms of the treatment goal and in terms of the dosing regimen, and has the potential to help those patients with alcohol dependence for whom abstinence is not a desirable or acceptable goal to proactively seek and to engage them in treatment, thereby leading to clinically relevant benefits.

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ClinicalTrials.gov: Nalmefene Efficacy Study I: Randomised, Double-blind, Placebo-controlled, Parallel-group, Efficacy Study of 20 mg Nalmefene, as Needed Use, in Patients With Alcohol Dependence; http://clinicaltrial.gov/ct2/show/NCT00811720?term=NCT00811720&rank=1; NCT00811720.

Supplementary material cited in this article is available online.

1. Wittchen HU, Jacobi F, Rehm J, Gustavsson A, Svensson M, Jönsson B, *et al*. (2011): The size and burden of mental disorders and other disorders of the brain in Europe 2010. *Eur Neuropsychopharmacol* 21: 655–679.
2. Anton RF, O'Malley SS, Ciraulo DA, Cisler RA, Couper D, Donovan DM, *et al*. (2006): Combined pharmacotherapies and behavioral interventions for alcohol dependence: The COMBINE study: a randomized controlled trial. *JAMA* 295:2003–2017.
3. Schuckit MA (2009): Alcohol-use disorders. *Lancet* 373:492–501.
4. Kohn R, Saxena S, Levav I, Saraceno B (2004): The treatment gap in mental health care. *Bull World Health Organ* 82:858–866.
5. Miller WR, Walters ST, Bennett ME (2001): How effective is alcoholism treatment in the United States? *J Stud Alcohol* 62:211–220.
6. Merkx MJ, Schippers GM, Koeter MW, Vuijk PJ, Oudejans SC, Stam RK, *et al*. (2011): Guidelines for allocating outpatient alcohol abusers to levels of care: Predictive validity. *Addict Behav* 36:570–575.
7. Chick J, Lehert P, Landron F, Plinius Maior Society (2003): Does acamprosate improve reduction of drinking as well as aiding abstinence? *J Psychopharmacol* 17:397–402.
8. Slattery J, Chick J, Cochrane M, Craig J, Godfrey C, Macpherson K, *et al*. (2002): Health technology assessment of prevention of relapse in alcohol dependence. *Consultation Assessment Report*. Glasgow, UK: 1–295.
9. Berglund M, Thelander S, Salaspuro M, Franck J, Andréasson S, Ojehagen A (2003): Treatment of alcohol abuse: An evidence-based review. *Alcohol Clin Exp Res* 27:1645–1656.
10. Mann K, Lehert P, Morgan MY (2004): The efficacy of acamprosate in the maintenance of abstinence in alcohol-dependent individuals: Results of a meta-analysis. *Alcohol Clin Exp Res* 28:51–63.
11. European Medicines Agency (EMEA) (2010): Guideline on the development of medicinal products for the treatment of alcohol dependence. EMEA/CHMP/EWP/20097/2008. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/03/WC500074898.pdf.
12. Gastfriend DR, Garbutt JC, Pettinati HM, Forman RF (2007): Reduction in heavy drinking as a treatment outcome in alcohol dependence. *J Subst Abuse Treat* 33:71–80.
13. Heilig M, Goldman D, Berrettini W, O'Brien CP (2011): Pharmacogenetic approaches to the treatment of alcohol addiction. *Nat Rev Neurosci* 12:670–684.
14. Mann K, Hermann D (2010): Individualised treatment in alcohol-dependent patients. *Eur Arch Psychiatry Clin Neurosci* 260(suppl 2): S116–S1120.
15. Anton RF, Litten RZ, Falk DE, Palumbo JM, Bartus RT, Robinson RL, *et al*. (2012): The Alcohol Clinical Trials Initiative (ACTIVE): Purpose and goals for assessing important and salient issues for medications development in alcohol use disorders. *Neuropsychopharmacology* 37: 402–411.
16. Sobell MB, Sobell LC (1976): Second year treatment outcome of alcoholics treated by individualized behavior therapy: Results. *Behav Res Ther* 14:195–215.
17. Sobell MB, Sobell LC (1995): Controlled drinking after 25 years: How important was the great debate? *Addiction* 90:1149–1153.
18. Luquiens A, Reynaud M, Aubin HJ (2011): Is controlled drinking an acceptable goal in the treatment of alcohol dependence? A survey of French alcohol specialists. *Alcohol Alcohol* 46:586–591.
19. National Institute for Health and Clinical Excellence (NICE) (2011): NICE clinical guideline 115. Alcohol use disorders: Diagnosis, assessment and management of harmful drinking and alcohol dependence. Available at: http://publications.nice.org.uk/alcohol-use-disorders-diagnosis-assessment-and-management-of-harmful-drinking-and-alcohol-cg115.
20. Johnson BA, Rosenthal N, Capece JA, Wiegand F, Mao L, Beyers K, *et al*. (2007): Topiramate for treating alcohol dependence: A randomized controlled trial. *JAMA* 298:1641–1651.
21. Rehm J, Zatonksi W, Taylor B, Anderson P (2011): Epidemiology and alcohol policy in Europe. *Addiction* 106(suppl 1):11–19.
22. Heather N, Adamson SJ, Raistrick D, Slegg GP, UKATT Research Team GP (2010): Initial preference for drinking goal in the treatment of alcohol problems: I. Baseline differences between abstinence and non-abstinence groups. *Alcohol Alcohol* 45:128–135.
23. Adamson SJ, Heather N, Morton V, Raistrick D, UKATT Research Team D (2010): Initial preference for drinking goal in the treatment of alcohol problems: II. Treatment outcomes. *Alcohol Alcohol* 45: 136–142.
24. Hodgins DC, Leigh G, Milne R, Gerrish R (1997): Drinking goal selection in behavioral self-management treatment of chronic alcoholics. *Addict Behav* 22:247–255.
25. Bart G, Schluger JH, Borg L, Ho A, Bidlack JM, Kreek MJ (2005): Nalmefene induced elevation in serum prolactin in normal human volunteers: Partial kappa opioid agonist activity? *Neuropsychopharmacology* 30:2254–2262.
26. Herz A (1997): Endogenous opioid systems and alcohol addiction. *Psychopharmacology* 129:99–111.
27. Koob GF (2013): Theoretical frameworks and mechanistic aspects of alcohol addiction: Alcohol addiction as a reward deficit disorder. *Curr Top Behav Neurosci* 13:3–30.
28. Nealey KA, Smith AW, Davis SM, Smith DG, Walker BM (2011): Kappa-opioid receptors are implicated in the increased potency of intra-accumbens nalmefene in ethanol-dependent rats. *Neuropharmacology* 61:35–42.
29. Anton RF, Pettinati H, Zweben A, Kranzler HR, Johnson B, Bohn MJ, *et al*. (2004): A multi-site dose ranging study of nalmefene in the treatment of alcohol dependence. *J Clin Psychopharmacol* 24: 421–428.
30. Mason BJ, Ritvo EC, Morgan RO, Salvato FR, Goldberg G, Welch B, *et al*. (1994): A double-blind, placebo-controlled pilot study to evaluate the efficacy and safety of oral nalmefene HCl for alcohol dependence. *Alcohol Clin Exp Res* 18:1162–1167.
31. Mason BJ, Salvato FR, Williams LD, Ritvo EC, Cutler RB (1999): A double-blind, placebo-controlled study of oral nalmefene for alcohol dependence. *Arch Gen Psychiatry* 56:719–724.
32. Karhuvaara S, Simojoki K, Virta A, Rosberg M, Löyttyniemi E, Nurminen T, *et al*. (2007): Targeted nalmefene with simple medical management in the treatment of heavy drinkers: A randomized double-blind placebo-controlled multicenter study. *Alcohol Clin Exp Res* 31:1179–1187.
33. American Psychiatric Association (APA) (2000): *Diagnostic and Statistical Manual of Mental Disorders. 4th ed., ext Revision (DSM-IV-TR)*. Washington, DC: American Psychiatric Association.
34. Lecrubier Y, Sheehan DV, Weiller E, Amorim P, Bonora I, Harnett Sheehan K, *et al*. (1997): The Mini International Neuropsychiatric Interview (MINI). A short diagnostic structured interview: Reliability and validity according to the CIDI. *Eur Psychiatry* 12:224–231.
35. World Health Organization (WHO) (2000): *International Guide for Monitoring Alcohol Consumption and Related Harm*. WHO/MSD/MSB/00.4. Available at: http://whqlibdoc.who.int/hq/2000/who_msd_msb_00.4.pdf.
36. Sullivan JT, Sykora K, Schneiderman J, Naranjo CA, Sellers EM (1989): Assessment of alcohol withdrawal: The revised clinical institute

withdrawal assessment for alcohol scale (CIWA-Ar). *Br J Addict* 84: 1353–1357.
37. Sobell LC, Sobell MB (1992): Timeline follow-back: A technique for assessing self-reported ethanol consumption. In: Litten RZ, Allen JP, editors *Measuring Alcohol Consumption: Psychosocial and Biological Methods*. Totowa, New Jersey: Humana Press, 41–72.
38. Starosta AN, Leeman RF, Volpicelli JR (2006): The BRENDA Model: Integrating psychosocial treatment and pharmacotherapy for the treatment of alcohol use disorders. *J Psychiatr Pract* 12:80–89.
39. Guy, W, editor (1976): *ECDEU Assessment Manual for Psychopharmacology. Publication No 76–338*. Rockville, Maryland: National Institute of Mental Health.
40. Skinner HA, Horn JL (1984): *Alcohol Dependence Scale: Users Guide*. Toronto, Canada: Addiction Research Foundation.
41. Miller WR, Tonigan JS, Longabaugh R (1995): *The Drinker Inventory of Consequences (DrInC): An Instrument for Assessing Adverse Consequences of Alcohol Abuse. Project MATCH Monograph Series*. Rockville, Maryland: National Institute on Alcohol Abuse and Alcoholism.
42. Willenbring ML, Massey SH, Gardner MB (2009): Helping patients who drink too much: An evidence-based guide for primary care clinicians. *Am Fam Physician* 80:44–50.
43. Rehm J, Baliunas D, Borges GL, Graham K, Irving H, Kehoe T, *et al*. (2010): The relation between different dimensions of alcohol consumption and burden of disease: An overview. *Addiction* 105: 817–843.
44. Laaksonen E, Koski-Jännes A, Salaspuro M, Ahtinen H, Alho H (2008): A randomized, multicentre, open-label, comparative trial of disulfiram, naltrexone and acamprosate in the treatment of alcohol dependence. *Alcohol Alcohol* 43:53–61.
45. Kranzler HR, Tennen H, Penta C, Bohn MJ (1997): Targeted naltrexone treatment of early problem drinkers. *Addict Behav* 22:431–436.
46. Kranzler HR, Armeli S, Tennen H, Blomqvist O, Oncken C, Petry N, *et al*. (2003): Targeted naltrexone for early problem drinkers. *J Clin Psychopharmacol* 23:294–304.
47. Kranzler HR, Tennen H, Armeli S, Chan G, Covault J, Arias A, *et al*. (2009): Targeted naltrexone for problem drinkers. *J Clin Psychopharmacol* 29:350–357.
48. Project MATCH Research Group A (1998): Matching alcoholism treatments to client heterogeneity: Project MATCH three-year drinking outcomes. *Alcohol Clin Exp Res* 22:1300–1311.