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Nalmefene for the treatment of alcohol use disorders: recent data and clinical potential

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ABSTRACT

Introduction: Few pharmacotherapies are available for alcoholism. Numerous studies indicate the involvement of the opioid-endorphin system in mediating the reinforcing effects of alcohol via dopaminergic neurons. The opioid antagonist naltrexone was found to be effective in alcohol treatment, and the European Medicines Agency has now approved the mu-opioid antagonist und partial kappa agonist nalmefene.

Areas covered: This article presents background information on the chemistry of nalmefene and preclinical and clinical findings. The three relevant Phase III studies, all of which followed a harm-reduction, “as needed” approach and found reduced alcohol consumption with nalmefene 18 (20) mg, are discussed in detail.

Expert opinion: The integration of the “as needed” approach into conventional psychosocial alcohol therapies may be challenging but offers the opportunity to reach otherwise not treated patients. Nalmefene is the first medication to be approved specifically in this indication and seems to be most suitable for patients with alcohol misuse or a rather low physical dependence on alcohol who do not require immediate detoxification or inpatient treatment. Although a categorical distinction between patients who want to stop heavy drinking or drinking at all over time may be somewhat hypothetical, nalmefene offers new treatment options to patients with alcohol use disorder.

1. Introduction

ICD-10 and DSM-IV define substance use disorders (SUDs) as abuse (harmful use) or dependence, characterized by symptoms related to compulsive or excessive use of a drug (and social problems in DSM-IV only). These classifications define dependence by a cluster of somatic, psychological, and behavioral symptoms. [1,2] ICD-10 and DSM-IV follow a categorical approach, but the recently published DSM-5 has abandoned the distinction between abuse and dependence and defines SUDs as a dimensional phenotype. [3] DSM-5 specifies substance-related and addictive disorders such as alcoholism by 11 symptoms: 6 or more positive symptoms constitute a severe SUD; 4 or 5, a moderate one; and 2 to 3, a mild one.

2. Body of review

2.1. Overview of the market

SUDs are associated with high psychiatric and physical morbidity, a substantial global burden of morbidity, and premature death. [4] Numerous studies indicate that SUDs, in particular alcoholism, are common. A recent report on global statistics of addictive behaviors [4] states that 4.9% of the world adult population have an alcohol use disorder (AUD; 7.8% of men and 1.5% of women). On the global level, prevalence estimates of alcoholism range from 0% to 16%. [5] AUDs account for 9.6% of Disability Adjusted Life Years (DALYs) caused by mental and substance use disorders. [6]

Epidemiological studies estimate the prevalence of alcoholism to be 7–10% in Europe and the United States. [7–10] Recently, the U.S. National Epidemiologic Survey on Alcohol and Related Conditions II reported a 12-month and lifetime prevalence of 13.9% and 29.1%, respectively, for AUDs diagnosed with DSM-5 criteria. [11] This study found the usual percentage of untreated patients: only 19.8% of affected people had ever been treated. Common features of alcoholism include liver disorders; multiple mental and neurological conditions, such as withdrawal delirium, cognitive decline and cerebellar degeneration, cardiomyopathy, multiple gastrointestinal disorders; and a high risk for numerous carcinomas, among many others. [12] The overall mortality is high.

Multiple psychosocial and psychotherapeutic approaches are used to treat alcoholism, including cognitive–behavioral therapies, motivational enhancement, contingency management, 12-step therapies, and family therapy and case management, among many others. [13–17] A number of meta-analyses have proven the efficacy of alcohol treatment in general. [17,18] To date, allocation of patients to different treatments on the basis of individual patient profiles is difficult. [19]

Few anti-craving drugs have been established as treatment for alcoholism. [16,20–23] The putative N-methyl-D-aspartic acid (NMDA) modulator acamprosate[24,25] is marketed for relapse prevention of alcoholism and is available worldwide. Its precise mechanism of action is unclear, but many data suggest modulations of the NMDA receptor as the primary mechanism of action. [26] Meta-analyses indicate that
Acamprosate reduces relapse to heavy drinking or increases the abstinence rates in alcohol-dependent people. [23–25] Apart from disulfiram, the opioid antagonist naltrexone has been extensively studied and used for treatment of AUDs. There are numerous studies on naltrexone and recent Cochrane and meta-analyses suggest naltrexone to be effective in reducing alcohol consumption or relapse to heavy drinking rather than improving abstinence rates. [23–25,27] Both acamprosate and naltrexone have moderate effect sizes. Acamprosate is safe and usually well-tolerated. [25] Other drugs are currently being tested, including baclofen, [28,29] but none of these agents is close to being introduced to the market. [30,31]

3. Introduction to the compound

There is a clear scientific rationale for the use of opioid antagonists in alcoholism (for a review see [32]). Opioid receptors are clearly implicated in mediating the reinforcing effects of alcohol and in the development of alcoholism. [33] The mu-opioid receptor is of particular relevance. [34–38] The reinforcing effects of alcohol are in part attributed to interactions between opioid and dopaminergic signaling pathways. [39–41] Alcohol induces the release of endogenous opioids and has an indirect modulatory influence on dopamine release in the mesocorticolimbic dopamine system, being important for reward anticipation, reinforcement, and motivational processes. [42] Dopamine release in the nucleus accumbens is essential for the positively reinforcing effects of alcohol. [35]

Functional neuroimaging studies suggest that marked changes and adaptations in the opioid system are associated with chronic alcohol use. Positron emission tomography (PET) studies indicate a negative correlation between mu-opioid receptor binding and alcohol craving in recently abstinent alcohol-dependent people. [43] Heinz et al. [44] have demonstrated an increase of mu-opioid receptors in different regions of the brain, including the nucleus accumbens, and a correlation with the severity of alcohol craving, but Williams et al. [45] did not find significant differences in opioid receptor binding between alcohol-dependent people and controls (Figures 1 and 2).

4. Chemistry

Nalmefene has been shown repeatedly to be an antagonist at the mu- and delta-opioid receptors and a partial agonist at the kappa receptor (see Box 1). It is selective for the mu- and kappa-opioid receptor subtypes. [47,48] Preclinical data indicate that kappa-opioid receptor antagonism decreases dependence-induced alcohol self-administration. [49]

Nalmefene has a comparable chemical structure to naltrexone (see Figure 3). It may have a number of potential advantages relative to naltrexone, [50] i.e. a more effective binding to central opioid receptors, [51,52] a higher bioavailability [53,54] and the absence of a dose-dependent association with liver toxicity. [50]

In alcohol-dependent rats, nalmefene was found to be significantly more effective than naltrexone in suppressing alcohol intake. [49] The results were suggestive of the kappa-opioid receptor antagonism selectively decreasing alcohol self-administration. Nalmefene-induced elevation in serum prolactin in healthy volunteers was interpreted as a partial agonist effect at kappa-opioid receptors, [47] an interpretation that was also confirmed in binding assays. [47] Data from animal model studies indicate that the in vivo pharmacology of nalmefene is similar to that of naloxone and naltrexone. [55] Nalmefene has a slower onset and longer duration of action than naltrexone.

5. Pharmacodynamics

Recently, Brokso Khyll et al. [56] published data from nine phase I studies (243 participants) and other samples, including eight

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Figure 1. Effect of endorphins (adapted from [46]).
participants for whom imaging data on receptor occupancy were available, among others. Absolute oral bioavailability was estimated to be 41% without food intake and 53% with food. Simulation of the mu-opioid receptor occupancy showed a 60–90% occupancy for up to 22–24 hours after a single dose of 20 mg nalmefene. Data suggested that a single 20 mg dose of nalmefene is predicted to be above the target therapeutic occupancy for about 24 hours in about 95% of the target population.

PET data with the opioid receptor ligand (11c) carfentanil [52] indicate that nalmefene is rapidly absorbed. The mean half-life is 13.4 hours after single and repeated dosing. Nalmefene thus has a linear pharmacokinetics. Receptor occupancy was high after both 2 hours (87–100%) and 26 hours (83–100%). After 50 hours, receptor occupancy was still 48.4–72.0%, while the nalmefene plasma concentration was very low. These data indicate a slow dissociation of the drug from the mu-opioid receptor.

6. Pharmacokinetics and metabolism

Kim et al. [57] demonstrated a clearance half-life of about 28 hours for central opioid receptors and a plasma elimination half-life of 8 hours. Nalmefene has a similar but slightly better bioavailability than naltrexone. [53,54] There is no evidence for liver toxicity. [50]

7. Preclinical and clinical studies

7.1. Preclinical findings

Relatively few animal studies are available. Nalmefene was found to reduce alcohol consumption in animal models, [33,58] being even significantly more effective than naltrexone. [49] In humans, nalmefene was equally effective as naltrexone in reducing subjective responses to alcohol in non-treatment-seeking alcoholics. [59]

The effects of nalmefene on craving and other subjective responses to alcohol-related cues were assessed in a randomized clinical laboratory study [59,60] in non-treatment-seeking alcoholics (n = 125) and social drinkers (n = 90). Both nalmefene and naltrexone reduced craving, alcohol intake, and frequency to a comparable extent among the alcohol-dependent group, while no effects were observed in the social drinker group, relative to placebo.

7.2. Clinical studies

Some randomized controlled trials are available for the efficacy of nalmefene in alcohol treatment [50,61–65] (see
Table 1). In a pilot study with a small sample size, [65] nalmefene significantly decreased the number of drinks per drinking day in both dosing groups compared with placebo ($p \leq 0.05$).

Mason et al. [50] studied 105 patients in a 12-week study comparing the effects of 80 mg nalmefene ($n = 35$), 20 mg nalmefene ($n = 35$), and placebo ($n = 35$) with cognitive behavioral therapy. Rate of heavy drinking was significantly decreased in both nalmefene groups ($p = 0.023$). No unexpected serious adverse events were recorded and rates of adverse events did not differ between both dosing groups. The higher patient drop-out rate in the 80-mg group indicated that a lower dosing of 20–40 mg/day may be preferable.

In a multicenter trial, Anton et al. [61] evaluated three doses of nalmefene (5, 20, and 40 mg) in a double-blind comparison with placebo over a 12-week treatment period ($N = 270$). Both the nalmefene and placebo groups showed a similar reduction in heavy drinking days, craving and secondary parameters. The 20-mg group experienced more insomnia, dizziness, and confusion, whereas the 5-mg group showed more dizziness than the placebo group and the 40-mg group more nausea. Most symptoms were mild. Outcome parameters concerning alcohol intake did not differ significantly between groups.

In contrast, a Finish multicenter, randomized, placebo-controlled trial by Karhuvaara et al. [63] in a sample of heavy drinkers ($N = 403$) obtained positive findings. Significant effects on various drinking outcomes were found, including the risk of heavy drinking ($p < 0.01$). The most common adverse events associated with nalmefene were nausea, insomnia, fatigue, dizziness, and alcoholic hangover.

The efficacy of nalmefene was further studied in three large European randomized controlled trials, [62,64,66] all of which used an ‘as needed’ approach to compare nalmefene 18 (20 mg with placebo. Reduction of heavy drinking days, not abstinence, was the primary goal in all three studies. No fixed dosing regime was used and the patients could take the drug on the basis of their own needs and expectations (see Table 1).

The study by Mann et al. [64] evaluated the long-term safety and tolerability of as-needed use of 20 mg nalmefene versus placebo over 52 weeks in 579 patients with alcohol dependence. It found a significant reduction of daily alcohol consumption and a reduction of heavy drinking days. The number of patients who discontinued treatment was significantly higher in the nalmefene group, and the main side effects were nausea, sedation, and vertigo. With respect to secondary parameters, liver values decreased significantly more in the nalmefene group than in the placebo group.

The study by Gual et al. [62] used a similar design and included 718 patients (358 in the nalmefene group). The co-primary efficacy analyses showed a significantly superior effect of nalmefene compared to placebo in the change from baseline to month 6 in heavy drinking days and a better but non-significant effect in reducing total alcohol consumption.

In the study by van den Brink et al., [66] 675 patients were randomized to 52 weeks of as-needed treatment with nalmefene 18 mg or placebo. A total of 112 (68%) participants in the placebo group and 310 (62%) in the nalmefene group completed the study. At month 6, the primary outcome parameters did not differ between the two groups. At month 13, nalmefene was more effective than placebo with respect to both the reduction of heavy drinking days and the reduction of total alcohol consumption. In patients with high/very high alcohol-drinking risk levels (defined according to the World Health Organization criteria [67] as men who drink >60 g/day and women who drink >40 g/day), the reduction of total alcohol consumption showed a significant effect at both month 6 and month 13. Serious adverse events were rare in both the placebo (5.4%) and the nalmefene groups (6.9%). The baseline alcohol level of 70 g/day was moderate and lower than in the other two studies. [62,64]

Table 1 Numbers needed to treat for nalmefene ranged between 6 and 10. [68]

Possible ECG changes or risk of QT prolongation after treatment with nalmefene were excluded in a study by Matz et al. [69]

8. Secondary analyses

8.1. Pharmacogenetics

Over 100 variants of the mu-opioid receptor gene have been identified. [70,71] The most common and clinically relevant single nucleotide polymorphism is A118G, which results in an amino acid exchange at position 40 from asparagine to aspartate. [72] Animal and experimental data suggest a relevant role for OPRM1 A118G variations in moderating effects of opioid antagonism on alcohol reward and consumption [73] and alcohol-induced euphoria, [74] as do some clinical data. [75] A meta-analysis supported the role of the A118G polymorphism of the OPRM1 gene and treatment response to naltrexone. [76] Another meta-analysis suggested that this effect can be seen in Asians but not Caucasians. [77]
Few data on pharmacogenetics are available for nalmefene. A post hoc analysis [78] of the Karhuvaara et al. [63] study did not identify main or moderating effects of the genotypes on drinking outcomes.

### 8.2. Secondary and pooled analyses

A number of secondary and pooled analyses have been performed of the three major long-term studies with nalmefene described above. [79,80]

A subgroup analysis of the two 6-month phase III studies [62,64] indicated that patients who did not reduce their drinking before randomization benefitted more from nalmefene. [79] In addition, reductions in liver enzymes were greater in the nalmefene group. In contrast to the Mann et al. study, [64] the incidence of adverse events leading to dropout in the Gual et al. study [62] was similar in both groups. [79]

### 9. Safety and tolerability

An analysis of the pooled data of the two 6-month studies [62,64] and the 12-month study [66] looked at the total population (placebo, n = 824; nalmefene, n = 1123) and patients with high/very high drinking risk levels at screening and randomization (placebo, n = 374; nalmefene, n = 450). [80] The analysis found that in the total population 62.7% of the patients on placebo and 74.7% of those on nalmefene had treatment-emergent adverse events (TEAEs) and 47 (5.9%) of the patients on placebo and 149 (13.9%) of those on nalmefene dropped out because of TEAEs. There was no evidence for an increased suicide risk associated with nalmefene. The higher incidence of psychiatric events in the nalmefene group was mainly due to confusional states. Other frequent TEAEs in the nalmefene group in the total population were nausea (22% vs. 5.9%), dizziness (18.2% vs. 5.5%), insomnia (13.4% vs. 5.4%), headache (12.3% vs. 8.3%), and vomiting (8.7% vs. 2.3%). Although there was a higher incidence of TEAEs and associated dropouts, overall nalmefene was well tolerated and no major safety issues were identified. [80]

Another secondary analysis of data from two randomized controlled clinical trials, [62,64] and a comprehensive meta-analysis [81] as an indicator for mortality risk showed that the reduction of alcohol intake in the nalmefene group was associated with an 8% reduction in mortality risk. [82]

Francois et al. [83] performed a pooled post hoc analysis on a subgroup of patients with at least a high drinking level (>60 g in men, >40 g in women) who had participated in the Mann et al. [64] and Gual et al. [62] studies (N = 667). At week 24, nalmefene had a superior effect compared to placebo in improving quality of life, measured by the SF-36: scores were significantly correlated to reductions in heavy drinking days and total alcohol consumption.

To date, no randomized studies have compared the efficacy of naltrexone and nalmefene. Recently, Soyka et al. [84] performed an indirect meta-analysis of randomized controlled studies on these two medications. The group used a random effects model to measure effects and compare them between the two medications and included 4 placebo-controlled studies with nalmefene and 13 with naltrexone. In brief, the analysis showed a statistically significant advantage of nalmefene over naltrexone in the two patient-relevant outcome efficacy criteria, quantity and frequency of drinking. Both drugs had a benign safety profile. This indirect meta-analysis may indicate an advantage of nalmefene over naltrexone in the treatment of alcohol dependence, at least in certain treatment settings (‘as needed’) or subgroups of patients. Sex differences were not part of this analysis. There are some data suggesting that naltrexone may be more effective in men than women, as demonstrated in some but not all clinical studies. [85] Women may also be more sensitive to the effects of naltrexone. [86] Thirty percent of patients included in the nalmefene studies were female and 23% of those included in the naltrexone studies. [87]

Cost–benefit and economic aspects play an enormous role in medicine today. The U.K. National Institute for Health and Care Excellence (NICE) invited the manufacturer of nalmefene, Lundbeck, to submit evidence of its clinical and cost-effectiveness. [88] The University of Sheffield was commissioned to act as the independent evidence group and to produce a critical review on this issue. In brief, the appraisal committee concluded from the data presented that nalmefene, in conjunction with psychosocial support, was a cost-effective use of NHS resources compared with psychosocial support alone for treating patients with alcohol dependence drinking at high risk level, without physical withdrawal symptoms and not requiring immediate assisted withdrawal from alcohol.

### 10. Regulatory affairs

Lundbeck has licensed the drug from Biotie Therapies. In 2013, the European Medicines Agency (EMA) approved the opioid antagonist nalmefene for the treatment of alcoholism, specifically for reduction of alcohol consumption in adult patients with alcohol dependence who have a high-ranking risk level without physical withdrawal and do not require immediate detoxification. [89] Although nalmefene has been approved in most European countries, some European agencies such as the German Drug Evaluation Agency and the French and Swedish Health Agencies were critical about the additional benefit of nalmefene over conventional pharmacotherapies. [90] In the meantime, the issue of reimbursement has been solved in Germany. In the United States, an injectable form of nalmefene was approved for treatment of opioid overdose in 1995; it is not available for treatment of AUDs, [91] and the manufacturer will probably not seek approval for alcohol treatment.

### 11. Conclusion

Nalmefene is the first medication approved for alcoholism with the primary goal of reducing alcohol intake in an as needed approach. There are other studies with naltrexone that suggest this opioid antagonist also to be effective in an as needed or ‘targeted’ approach. [92–94] A clear scientific rationale exists for a role of opioid receptors in mediating the rewarding effects of alcohol. The opioid antagonist...
nalmefene has been studied extensively in alcoholism and, although data are inconsistent (as is the case for many pharmaceuticals in alcoholism), it has been shown to decrease alcohol consumption. [23,24,27,95] In contrast to naltrexone, nalmefene has a partial agonist effect at the delta receptor, [49] although the functional relevance of this partial agonist effect is a matter of debate.

Early studies used different dosages of nalmefene and found that the 18 (20) mg tablet is as effective as higher dosages but has fewer side effects.

The ‘as needed’ use of nalmefene is a novel approach to reduce heavy drinking. [96] Most evidence for its clinical efficacy comes from three recent studies with nalmefene. [62,64,66] The EMA recently approved nalmefene for the treatment of alcoholism. The overall data indicate that, despite a higher dropout rate in the nalmefene groups, alcohol drinking was reduced more than in the placebo groups.

Nalmefene has not been compared with acamprosate or in particular naltrexone in head-to-head comparisons. A recent indirect meta-analysis on naltrexone and nalmefene studies with similar methodology [84] indicates superior effects of nalmefene over naltrexone, but this finding needs to be confirmed in prospective studies. With respect to the severity of alcoholism, most patients included in the studies on nalmefene had a high but not excessive mean alcohol consumption and were not severely physical dependent on alcohol, and the concomitant psychosocial intervention alone was highly effective in reducing alcohol consumption. This type of patient is very probably the one who will benefit from such a treatment approach. There are no specific safety concerns. The side-effect profiles of nalmefene and naltrexone are similar; the most frequent side effects are nausea and other gastrointestinal effects, dizziness, insomnia, headache, fatigue, and somnolence. [66]

A number of secondary analyses and reviews are now available for nalmefene. [80,97,98] The benefits of nalmefene are still somewhat controversial. [90,99,100]

12. Expert opinion

The ‘as needed’ approach for pharmaceutical treatment of alcoholism is not entirely new and some respective data are available for naltrexone. However, nalmefene is the first medication to be approved specifically in this indication. Treatment expectations and goals are dynamic and may vary during alcohol treatment and shift from reduction of alcohol consumption to abstinence (or even back). [101] They may also be predictive for outcome of pharmacotherapy. [102] A categorical distinction between patients who want to stop heavy drinking or drinking at all over time may be somewhat hypothetical. Nevertheless, this pharmacotherapeutic tool offers new treatment options to patients with AUD, in particular non-dependent problem drinkers or people in early stages of their ‘alcoholic career.’

The integration of this novel treatment strategy into conventional psychosocial treatment programs, which are mandatory when using nalmefene, is a challenge. Whether binge-drinking patients or other specific subtypes of alcohol users may benefit more than others remains to be seen and elucidated in further studies.

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Declaration of Interest

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Papers of special note have been highlighted as either ‘of interest’ (-) or ‘of considerable interest’ (**) to readers.


Influential meta-analysis on efficacy of pharmacotherapies in alcoholism.


**Key RCT of nalmefene.**


**Key RCT on efficacy of nalmefene.**


**Key RCT on efficacy of nalmefene.**


**Important study on pharmacogenetics of mu opioid receptors.**


**Key study on efficacy and safety of nalmefene.**


**Comprehensive review on safety of nalmefene.**


89. EMA. Selincro (nalmefene): summary of product characteristics. 2011


