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Targeted Opioid Receptor Antagonists in the Treatment of Alcohol Use Disorders

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Abstract

In 1994, the US Food and Drug Administration approved the μ -opioid receptor antagonist naltrexone to treat alcohol dependence. However, treatments requiring daily administration, such as naltrexone, are inconsistently adhered to in substance abusing populations, and constant medication exposure can increase risk of adverse outcomes, e.g., hepatotoxicity. This has fostered a ‘targeted’ or ‘as needed’ approach to opioid receptor antagonist treatment, in which medications are used only in anticipation of or during high-risk situations, including times of intense cravings. Initial studies of the ability of targeted naltrexone to reduce drinking-related outcomes were conducted in problem drinkers and have been extended into larger, multi-site, placebo-controlled investigations with positive results. Another μ -opioid receptor antagonist, nalmefene, has been studied on an ‘as-needed’ basis to reduce heavy drinking in alcohol-dependent individuals. These studies include three large multi-site trials in Europe of up to 1 year in duration, and serve as the basis for the recent approval of nalmefene by the European Medicines Agency as an ‘as-needed’ adjunctive treatment for alcohol dependence. We review potential moderators of opioid receptor antagonist treatment response including subjective assessments, objective clinical measures and genetic variants. In sum, the targeted or ‘as-needed’ approach to treatment with opioid antagonists is an efficacious harmreduction strategy for problem drinking and alcohol dependence.

1 Introduction

Alcohol use disorders (AUDs)¹ are among the most prevalent substance use disorders worldwide. The World Health Organization (WHO) has listed AUDs among the highest disease morbidity and mortality burden worldwide (2.5 million deaths/year) [1] with wide-

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¹We have primarily used the Diagnostic and Statistical Manual, fifth edition (DSM-V) revised diagnosis of ‘alcohol use disorder’, which encompasses both alcohol abuse and dependence in DSM-IV-TR. However, in studies where either alcohol abuse and/or dependence were diagnosed via older DSM criteria, this terminology has been retained.

reaching neuropsychiatric, medical and psychosocial sequelae for those afflicted and their families. Four medications are currently Food and Drug Administration (FDA)-approved in the US for the treatment of alcohol dependence: disulfiram, oral naltrexone, long-acting injectable (LAI) naltrexone, and acamprosate [2]. These medications are available for the treatment of alcoholism in most European countries. Other medications, however, have been approved for the treatment of AUDs in other countries, e.g., sodium oxybate in Italy and baclofen in France.

These medications reduce the risk of relapse post-detoxification and promote less hazardous drinking in alcohol dependent patients. They may also have additional benefits across the alcohol use spectrum. A prevalent, 'at risk' population is 'problem drinkers', i.e., those with alcohol-related problems of mild-to-moderate severity but not currently meeting Diagnostic and Statistical Manual of Mental Disorders-IV-Text Revision (DSM-IV-TR) criteria for abuse or dependence. Problem drinkers comprise up to 20–30 % of the US population and are at significant risk for deleterious health consequences from excessive alcohol intake [3, 4]. They also suffer psychosocially from at-risk drinking, e.g., absenteeism/presenteeism at work and familial stress. A recent prospective study showed that at-risk problem drinkers (those drinking heavily on a weekly basis: >4 standard drinks/day for men and >3 standard drinks/day for women) were at greater risk for subsequent development of either alcohol abuse or dependence as well as serious health risks and deleterious psychosocial consequences [5].

For problem drinkers, daily compliance with a medication, especially on non-drinking days, may not be suitable or even sustainable [6]. As a result, 'targeted' or 'as needed' strategies have been proposed for harm reduction, i.e., decreasing the amount of alcohol consumed, time spent drinking and, concomitantly, recovering from the residual effects of alcohol intoxication ('hangovers', legal problems and problems with one's primary support group). Targeted medication may also be more palatable for some alcohol dependent patients to improve adherence as well as to reduce side effects and the risk of severe adverse reactions, e.g., medication-related hepatotoxicity. Several clinical trials have investigated targeted opioid receptor antagonists (naltrexone and nalmefene) as a harm-reduction strategy in problem drinkers and alcohol dependent patients. In particular, targeted nalmefene (as developed and studied by Denmark's H. Lundbeck A/S) has now been recommended for marketing in Europe by the Committee for Medicinal Products for Human Use (CHMP) under the European Medicines Agency (EMA). In this article, we will review targeted opioid receptor antagonists in AUDs, discuss potential predictors/moderators of treatment, and explore potential future directions for research with targeted treatment.

2 Search Methods

For this narrative review, Medline/PubMed was searched using the following keywords in isolation and conjunction: 'naltrexone', 'nalmefene', 'opioid receptor antagonist', 'opioid receptor blocker', 'alcohol', 'alcohol dependence', 'alcohol use disorder', 'problem drinking', 'at-risk drinking', 'targeted', 'targeted treatment', 'mu-opioid receptor gene', '*OPRM1*', and '*OPRM1A118G*'. Based on the prior knowledge of the authors, we also searched the names of several critical investigators who have published studies on targeted

opioid antagonists in AUDs. Finally, the results of two Lundbeck A/S phase III trials with targeted nalmefene have now been published in peer-reviewed journals [7, 8], a final phase III trial remains unpublished. We have evaluated and discuss this data as publically presented in biomedical meetings, e.g., poster abstracts.

3 Opioid Receptor Antagonists: Naltrexone/Nalmefene

3.1 Efficacy of Daily Administration in Relapse Prevention

The μ -opioid receptor antagonist naltrexone is among the most extensively studied treatments for alcohol dependence and should be considered first-line pharmacologic management. Naltrexone and its major metabolite, 6- β -naltrexol, are μ - and κ -selective, and to a lesser extent δ -opioid receptor antagonists with high central nervous system (CNS) penetrance [9, 10]. The plasma half-life of naltrexone is approximately 4 hours (13 h for 6- β -naltrexol) with a bioavailability of 5–40 %; hence, naltrexone is administered twice daily, although an [^{11}C]-carfentanil positron emission tomography (PET) study revealed more prolonged μ -opioid receptor occupancy with single and repeated clinically relevant dosing [11]. Naltrexone is hepatically metabolized by dihydrodiol dehydrogenases as well as glucuronidation, and has been associated with rare cases of hepatotoxicity; therefore, it should be prescribed with caution in those with liver disease. Alcohol increases endogenous opioid release in key areas of the brain's reward circuitry (i.e., the ventral tegmentum and nucleus accumbens) and subsequently facilitates dopaminergic neurotransmission [12]. Naltrexone counteracts the alcohol-induced increase in dopaminergic neurotransmission in the nucleus accumbens by blocking opioidergic inhibition of GABAergic inhibitory interneurons in the ventral tegmentum, and by blocking opioidergic stimulation of dopamine release in the nucleus accumbens [12].

The multi-site combined pharmacotherapies and behavioral interventions for alcohol dependence (COMBINE) study, a 2001 meta-analysis, and a more recent Cochrane review all support the efficacy of naltrexone, and indicate that daily naltrexone promotes a greater number of days abstinent and fewer heavy drinking days (HDD) than placebo [13–16]. In all of the relevant studies, medication was administered on a daily basis regardless of drinking risk, with only small-to-moderate effect sizes. Naltrexone is not efficacious for all alcohol dependent patients as evidenced by several published negative trials comparing the medication to placebo [17, 18]. As mentioned above, there is also a once-monthly LAI preparation that was developed to improve adherence, especially in patients who do not desire abstinence. In randomized, placebo-controlled trials for the treatment of alcohol dependence, LAI naltrexone was safe, tolerable, and modestly efficacious on drinking-related measures over a once-monthly placebo injection [14, 19].

Biochemically, nalmefene has a substituted methylene ($\text{C}=\text{CH}_2$) for naltrexone's ketone ($\text{C}=\text{O}$) at its 6-position [20]. Nalmefene also has a greater bioavailability (40–50 %) and a longer plasma half-life (8–10 h) than naltrexone [21–23]. Although nalmefene is likewise metabolized in the liver by glucuronidation (inactive) and dealkylation (little bioactivity) with decreased clearance in liver disease [24], there is no dose-dependent hepatotoxicity with oral nalmefene, which increases its safety profile in patients with hepatic dysfunction [23].

Nalmefene appears to bind the μ -opioid receptor with similar affinity to naltrexone, and binds somewhat more avidly at δ - and κ -opioid receptors [9, 25]. Nalmefene's main mechanism of action in alcohol dependence is thought to be similar to naltrexone and likely related to its antagonism of opioid receptors, particularly the μ -opioid receptor. However, the greater affinity of nalmefene at δ - and κ -opioid receptors could suggest a subtle mechanistic difference that may be clinically relevant as modulating δ - and κ -opioid receptors is known to affect drinking behavior in mammals [26].

There is preliminary evidence of prolonged μ -opioid receptor occupancy with both single and repeated dosing of nalmefene [11]. Several PET studies have demonstrated the importance of μ -opioid receptor occupancy in reducing alcohol craving [27, 28] and opioid receptor antagonists' ability to modulate mesolimbic dopamine release from the ventral tegmental area onto the nucleus accumbens. A PET study with a μ -opioid receptor-specific ligand demonstrated hypothalamic–pituitary–adrenal underactivity in early abstinence—it required *twice* the amount of exogenous naloxone to produce as much cortisol secretion in alcohol-dependent patients as in healthy volunteers [29]. Also, in contrast to healthy subjects who demonstrated an inverse correlation between cortisol levels and μ -opioid receptor binding availability, there was no significant relationship between peak cortisol level and μ -opioid receptor binding potential in recently detoxified alcohol dependent subjects [29].

The higher affinity of nalmefene at the κ -opioid receptor may be responsible for its distinctive neurophysiological effects: increased hypothalamic–pituitary–adrenal axis activation via increased adrenocorticotrophic hormone [30] and cortisol secretion and decreased alcohol self-administration in alcohol dependent rats with intra-nucleus accumbens infusion presumably through dynorphin/ κ -opioid receptor positive neurons [31]. An *in vitro* study of Chinese hamster ovary cells stably expressing cloned human κ -opioid receptors suggested that nalmefene may have some partial agonist activity at the κ -receptor, though it is not clear that this occurs *in vivo* [32].

Although there has been one negative multi-site trial with daily nalmefene [33], the majority of studies report positive clinical effects [23, 34–36] and the drug has excellent pharmacokinetic/dynamic properties for targeted administration [11].

3.2 Efficacy of Targeted Naltrexone in Problem Drinking

As discussed, one alternative strategy is to limit medication usage in problem drinkers to days/situations where he or she is at higher risk of heavy/heavier drinking, i.e., weekends, parties, etc. Several studies have shown that this ‘as needed’ alternative strategy decreases alcohol intake and reduces harm (Table 1). Kranzler et al. [37] first reported that open-label naltrexone (50 mg) ‘as needed’ 2–5 times/week decreased drinking-related measures, e.g., amount of drinks per drinking day, in a sample of 21 early problem drinkers. The first reported randomized, placebo-controlled trial enrolled 121 non-abstinent outpatients [38]. The subjects were first randomized to either a coping-based cognitive therapy ($n = 67$) or supportive psychotherapy ($n = 54$) and either daily naltrexone 50 mg/day ($n = 63$) or placebo ($n = 58$) for 12 weeks. After these 12 weeks, subjects were instructed to take their study medication only when craving alcohol for an additional 20 weeks. The coping skills/naltrexone group had the best drinking-related outcomes in both daily and targeted phases

compared with the coping skills/placebo arm, e.g., 27 % (coping skills/naltrexone) versus 3 % (coping skills/placebo) did not relapse to heavy drinking. Interestingly, naltrexone did not separate from placebo when paired with supportive psychotherapy. Therefore, combined cognitive-based psychotherapy and naltrexone was most efficacious in this trial. Although this study suggested that naltrexone decreased drinking when taken only 'as needed', due to the lead-in phase, carry-over effects from daily naltrexone administration could not be conclusively ruled out.

To redress this potential confound, Kranzler and colleagues [39] replicated the initial report in a randomized, double-blind, placebo-controlled trial in a much larger sample of early problem drinkers. In this study of 153 treatment-seeking subjects (>24 drinks/week for men and >18 drinks/week for women), subjects were randomized to one of four treatment arms (daily naltrexone, daily placebo, targeted naltrexone or targeted placebo) for a total of 8 weeks. Daily naltrexone or 'as needed' medication also reduced the number of HDDs and number of drinks/day [40]. However, this effect diminished over time in the targeted groups as the number of available tablets decreased in the final weeks (as the subjects were provided a finite supply). Both targeted naltrexone *and* targeted placebo reduced daily drinking to a greater extent than daily naltrexone and placebo (with greater effect size for targeted naltrexone than targeted placebo) [40]. This study was the first indication that targeted therapy may be more effective than daily administration in a short-term study for reducing drinking-related measures.

In another replication trial, 163 heavy drinkers were randomized to either placebo or naltrexone (50 mg/day) and instructed to take the study medication only before potentially high-risk drinking situations. In the final week of this 12-week protocol, targeted naltrexone decreased the mean number of daily drinks in men [41]. A subtle interaction effect of sex was observed on the secondary outcome measure of 'drinks per drinking day', such that females on naltrexone did not reduce their drinking over time. From the viewpoint of clinically meaningful changes, men appeared to benefit significantly by reducing their quantities closer to the US National Institute on Alcohol Abuse and Alcoholism (NIAAA) 'non-hazardous' guidelines. Nevertheless, the definition of problem drinking used in this study allowed the recruitment of subjects that met alcohol dependence criteria (albeit of a milder severity) and most (95.1 %) of subjects met DSM-IV criteria for alcohol dependence (mean of 3.6 of the 7 diagnostic criteria). In this trial, targeted naltrexone was well tolerated, the study completion rate was high, and there were no statistically significant differences in retention due to adverse events.

Finally, in a lengthy open-label trial of disulfiram (200 mg/day), acamprosate (1,998 mg/day) and naltrexone (50 mg/day) with both 12-week continuous and 52-week targeted phases, there were no significant differences between the groups in time to first HDD and days to first relapse but total days abstinent were significantly greater in the targeted disulfiram group relative to the other two groups [42]. There were no differences between the naltrexone and acamprosate groups in either phase.

3.3 Efficacy of Targeted Nalmefene in Alcohol Dependence

The first large ($n = 403$), multi-site, randomized, placebo-controlled trial of targeted nalmefene was reported in 2007 (Table 1) [43]. In this 28-week trial, subjects were instructed to take the study medication (nalmefene 10–40 mg vs. placebo) up to once daily if they suspected an imminent risk of drinking. All subjects received only minimal behavioral intervention (based on the BRENDA² model of assessment and psychosocial intervention [44, 45] directed at improving medication adherence), and subjects were not required to endorse a goal of abstinence. 93 % of subjects were alcohol dependent. HDDs were reduced with targeted nalmefene compared with placebo, with the nalmefene group reducing their HDDs on average by ~42 versus ~30 % in the placebo group (number needed to treat ~9). γ -Glutamyltransferase (GGT) and alanine aminotransferase (ALT) (liver function tests affiliated with hepatobiliary dysfunction in alcoholism and other conditions) levels were significantly reduced in the nalmefene group compared with placebo. Following the 28-week treatment phase, a subgroup of the nalmefene subjects were subsequently randomized to continue nalmefene or switch to placebo for another 24 weeks, and subjects who remained on nalmefene continue to benefit while subjects randomized to placebo tended to relapse to their prior baseline drinking.

The first phase III study (ESENSE1 [Efficacy of Nalmefene in Alcohol Dependence], [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00811720) identifier: NCT00811720) was a 6-month, randomized, double-blind, placebo-controlled study of targeted nalmefene (20 mg) conducted at 39 sites in Austria, Finland, Germany, and Sweden. The second phase III study (ESENSE2; [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00812461) identifier: NCT00812461) was another half-year, randomized, double-blind, placebo-controlled study of targeted nalmefene with an international European enrolment. The final phase III long-term safety and cost effectiveness study (SENSE; [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00811941) identifier: NCT00811941) was a full-year, randomized, double-blind, placebo-controlled study with continued international European enrolment.

A total of 1,997 alcohol-dependent patients were randomized in the three phase III trials: 604 patients in ESENSE1 (placebo: $n = 298$, targeted nalmefene: $n = 306$), 718 in ESENSE2 (placebo: $n = 360$, targeted nalmefene: $n = 358$), and 675 in SENSE (placebo: $n = 166$, targeted nalmefene: $n = 509$) [46–49]. All subjects also received a combination of motivational counseling and psychoeducation to promote adherence (BRENDA) with both reduction and abstinence as acceptable treatment goals. The primary outcome measures were the same in the two 6-month trials (ESENSE1/2): reduction in the monthly number of HDDs and the total alcohol consumption (TAC). The primary objective of SENSE was to evaluate safety/tolerability over a longer time (52 weeks), but, like the other two studies, SENSE also evaluated efficacy at 6 months (and also at 1 year). Numerous alcohol-related secondary outcomes, e.g., total number of dependence symptoms, liver function and clinical status (as assessed by the Clinical Global Improvement [CGI] scale) were also included in each of these trials.

²BRENDA is a brief psychosocial treatment modality for alcoholism that includes several key components, and the acronym is formed from these components: Biopsychosocial evaluation, Report to the patient on assessment, Empathic understanding of the patient's situation, Needs collaboratively identified by the patient and treatment provider, Direct advice to the patient on how to meet those needs, Assess reaction of the patient to advice and adjust as necessary for best care.

In ESENSE1 and 2, targeted nalmefene reduced the number of HDDs ($p < 0.05$ in both studies) and TAC (ESENSE1, $p < 0.05$; ESENSE2, $p = 0.088$) at study endpoint (the results of these studies are described in more detail below). In SENSE, targeted nalmefene was again superior to placebo ($p < 0.05$) in reducing the number of HDDs and TAC at the majority of the time points, including the 1-year primary outcome (albeit targeted nalmefene did not separate from placebo at a 6-month interim analysis in contrast to ESENSE1/2) [46–49]. Mann et al. [7] recently published an article detailing the results of ESENSE1 with preliminary cardiac safety data [50]. The primary results of ESENSE2 were also recently published [8]. Prior to these two peer-reviewed publications, the results of the three phase III trials were presented in abstracts/posters at international alcohol conferences, and we obtained information on the SENSE trial from these sources [46–49].

In ESENSE1, there was a significant main effect of treatment on the number of HDDs (-2.3 days [95 % CI -3.8 to -0.8]; $p = 0.0021$) and TAC (-11.0 g/day [95 % CI -16.8 to -5.1]; $p = 0.0003$) [7]. There were also statistically significant improvements in CGI-S scores (-0.4 [95 % see above CI -0.6 to -0.2]; $p = 0.0004$) and CGI-I scores (-0.3 [95 % CI -0.5 to -0.2]; $p = 0.0005$). Liver function tests were also decreased in the nalmefene group compared with placebo: GGT ratio nalmefene-to-placebo 0.8 (95 % CI 0.8–0.97; $p = 0.0094$); ALT ratio nalmefene-to-placebo 0.9 (95 % CI 0.84–0.98; $p = 0.0109$) (although statistically significant, the change in group means in liver function tests was probably not clinically meaningful). Mostly mild-to-moderate adverse events (dizziness, nausea, fatigue, and headache) and trial discontinuation were more common in the nalmefene group. However, serious adverse events were similar in both groups (naltrexone: 18 [5.9 %], placebo: 20 [6.7 %], including two patients on placebo who died by suicide during the protocol)). Viewed differently, targeted nalmefene decreased the mean number of HDDs/month from 19 to 7 and reduced the mean TAC/day from 84 to 30 g/day at month 6; in comparison, placebo reduced the mean number of HDDs/month from 20 to 10 days and the mean TAC/day from 85 to 43 g/day at the end of protocol, which translated into a small-to-moderate effect size in this large clinical trial (see Table 1).

In ESENSE2, targeted nalmefene again significantly reduced HDDs/month at month 6 (the mean change in HDDs/month: -1.7 days/month, 95 % CI -3.1 to -0.4 , $p = 0.012$) [48]. There was an advantage for nalmefene over placebo on TAC, which was significant at month 1 but trended by month 6 (-5.0 g/day, 95 % CI -10.6 to 0.7 , $p = 0.088$) [8]. The nalmefene group again had numerically greater improvements in CGI scores ($p = 0.111$) and liver function tests ($p = 0.049$) compared with placebo [8]. The mean number of HDDs decreased from approximately 20 to 7 days/month and the mean TAC decreased from 93 to 30 g/day in the targeted nalmefene group at month 6 [8]. Likewise, in the placebo group, the mean number of HDDs decreased from 18 to 8 days/month and the mean TAC decreased from 89 to 33 g/day [8]. Dropouts and adverse events were not significantly different between the groups [8].

In SENSE, targeted nalmefene significantly reduced HDDs and TAC/month across most study time points, including after 1 and 13 months, though the differences were not statistically significant at 6 months [49]. Comparison at month 13 showed that nalmefene was superior to placebo on both primary endpoints, HDD/month reduction (-1.6 days/

month, 95 % CI -2.9 to -0.3 ; $p = 0.017$) and TAC reduction (-6.5 g/day, 95 % CI -12.5 to -0.4 ; $p = 0.036$). The absolute mean number of HDDs in the targeted nalmefene group decreased from 15 to 5 days/month at month 6, and further decreased to 3 days/month out to 1 year. The mean TAC decreased from 75 g/day at baseline to 22 g/day at month 6 with a further decrease to 16 g/day at 1 year. In the placebo group, the mean number of HDDs decreased from a baseline 15 to 6 days/month while the mean TAC decreased from 75 to 27 g/day at 6 months with no significant further decline in both end-points to 1 year. Significant advantages were observed for nalmefene on several secondary endpoints: CGI, GGT, and ALT ($p < 0.05$). Taken together, these results suggest that nalmefene treatment produces statistically significant differences for at least a year.

The overall safety profile of targeted nalmefene in all three trials with approximately 2,000 subjects was consistent with observations in prior studies of targeted opioid receptor antagonists in AUDs. The most frequently reported adverse effects were all relatively mild and time-limited: dizziness, headache, nausea/vomiting, insomnia, and fatigue/somnolence. Finally, as with most other neuropsychiatric medications, the majority of these events had an onset within days of initiation and tended to abate over time.

Finally, H. Lundbeck A/S has published safety and tolerability data. Short-term (1 week) results demonstrate no clinically significant effects of both 20 and 80 mg/day nalmefene on salient electrocardiogram intervals, i.e., no QTc prolongation and T wave morphology aberrations [50].

As displayed in the table, the effect size of nalmefene is small when compared with placebo. In moderate length protocols (6 months and less), substantial placebo effects are not uncommon in large randomized controlled trials for alcoholism [51]. The longer-term efficacy of nalmefene will be clearer once the peer-reviewed results of SENSE are published and (although obviously not placebo-controlled) during post-marketing surveillance in Europe. At this point, however, there is insufficient data to recommend targeted treatment with nalmefene over other opioid receptor antagonists (i.e., naltrexone) for alcohol dependence.

4 Predictors/Moderators of Targeted Response

In order to better ascertain the clinical neuroscience of opioid receptor dysfunction in AUDs and predict treatment outcomes, several potential predictors/moderators of targeted response have been studied, which we have broken down for convenience into subjective measures, objective assessments and pharmacogenomics studies.

4.1 Subjective Measures

In a secondary analysis of the above-cited study of 153 non-dependent/early problem drinkers randomized to four treatment arms, mood and drinking expectancies moderated drinking-related outcomes with targeted naltrexone [52]. As revealed by structured nightly diaries, there was an increased desire to drink in all treatment arms during both positive and negative emotional states, and targeted naltrexone attenuated the behavioral association between drinking and reward [52].

4.2 Objective Assessments

Other potential moderators of opioid receptor antagonist efficacy in AUDs have been investigated. Although the efficacy data is mixed [14, 17, 53–55], female sex is associated with decreased rewarding effects of alcohol in women treated with daily naltrexone [56]. Overall, while there may be subtle differences in daily naltrexone treatment response for females, the drug appears to reduce drinking and provide clinical benefit, and should be considered a viable treatment option for both sexes. Sex was a significant moderator in the most recent study with targeted naltrexone in problem drinkers and, overall, males appeared to benefit from targeted naltrexone while females did not [41]. A previous study of targeted naltrexone did not observe a moderating effect of sex [40].

Family history of alcohol dependence was a positive predictor of heavy drinking reduction ($p = 0.05$) in a double-blind, randomized, placebo-controlled study of 100 mg/day naltrexone ($n = 121$ naltrexone, $n = 62$ placebo) [57]. Another sample of 336 male alcoholics treated with either naltrexone and psychotherapy or psychotherapy alone for 3 months also revealed that subjects with a family history of alcohol dependence maintained abstinence over 28 days relative to subjects without a family history of alcoholism ($\chi^2 = 5.714$, $p = 0.017$) [58]. Next, 92 nontreatment-seeking alcohol-dependent patients received naltrexone (50 or 100 mg/day) or placebo for 6 days followed by an alcohol challenge session [59]. Family history-positive males decreased drinking during challenge sessions relative to males without a family history of alcoholism ($p < 0.05$) [59]. A secondary data analysis of 128 alcoholics treated for 12 weeks with 50 mg/day naltrexone demonstrated that having a higher percentage of relatives with problem drinking predicted an augmented personal response to naltrexone [60]. However, a post hoc assessment of 603 alcohol-dependent subjects from COMBINE revealed no effect of alcoholism family history on naltrexone treatment response across three outcome measures: percentage of days abstinent, drinks per drinking day and percentage of HDDs [61]. Inconsistent results for the moderating effect of alcoholism family history on naltrexone response support pharmacogenomic hypotheses, suggesting that specific genetic variants are probably more important than a general family history of alcoholism in driving the response to treatment. Additionally, the moderating effect of alcoholism family history on naltrexone treatment response has only been studied with daily and not targeted administration paradigms.

Although a complete discussion is beyond the scope of this review on targeted treatment, several other moderators correlate with daily treatment efficacy. First, as revealed by Monterosso et al. [57], subjects with high levels of alcohol craving have augmented anti-drinking effects with naltrexone. Next, sweet taste preference correlated with positive treatment response in a sample of 78 alcohol-dependent patients treated for 32 weeks with either daily naltrexone or placebo [62]. However, in another sample, although sweet taste preference alone did not correlate with efficacy, it interacted with high craving to predict more robust anti-alcohol effects [63]. Again, these predictors correlate with positive outcomes with *daily* naltrexone treatment but remain untested in targeted paradigms.

4.3 Pharmacogenetics

The genetics of naltrexone response, particularly at the μ -opioid receptor gene *OPRM1*, has been studied in AUDs [64–66]. A single nucleotide polymorphism (SNP) in *OPRM1* (A118G $\rightarrow$ Asn40Asp amino acid substitution) has drawn particular attention. *OPRM1* A118G has demonstrated pharmacogenetic effects in preclinical studies, but the results of pharmacogenetic analyses of treatment trials have unfortunately yielded inconsistent results (for a review of pharmacogenetic treatment studies in AUDs, see Arias and Sewell [67]). A total of 158 problem drinkers were randomized to receive either daily or targeted naltrexone 50 mg ($n = 81$) or matching placebo ($n = 77$) for 12 weeks. Subjects then called an interactive voice response system each evening with craving scores and their drinking behavior during the previous day. Several potential moderators (genotype, medication, desire to drink, and interactive effects) were examined. On high craving days, individuals with the 118G (Asp40) allele had greater nighttime drinking than 118A (Asn40) homozygotes ($p = 0.019$), and this effect was attenuated by oral naltrexone [68]. A secondary data analysis of pharmacogenetic response was also conducted in 272 subjects from a multi-site, randomized, placebo-controlled trial of targeted nalmefene [69]. Two SNPs in *OPRM1* (including A118G), two SNPs in *OPRD1*, and one SNP in *OPRK1* (which, respectively, encode the μ , δ , and κ -opioid receptors) were genotyped and analyzed for potential moderators. There was no statistically significant moderating effect of genotype on any of the drinking outcomes.

5 Conclusions

There is a growing body of literature on targeted opioid receptor antagonist treatment in AUDs as one of the few evidence-based psychopharmacological strategies for ‘as needed’ treatment. As mentioned, this strategy may be more palatable for non-dependent problem drinkers with high cravings and a family history of alcohol dependence who acknowledge difficulties controlling drinking but seek harm reduction instead of total abstinence. Targeted treatment may also be preferable in alcohol-dependent patients who are chronically treatment non-adherent and refuse LAI naltrexone. Harm-reduced drinking below NIAAA guidelines reduces the incidence of alcohol intoxication, decreases the intensity of alcohol withdrawal and abrogates psychosocial dysfunction that can cripple patients and their families. Additionally, targeted instead of daily medications may also minimize the risk for adverse effects, e.g., hepatotoxicity, with chronic daily opioid receptor antagonists (and fear of side effects is a major barrier to prescribing evidence-based medications for AUDs in clinical practice) [70].

Targeted nalmefene is now approved for the treatment of alcohol dependence in Europe. The overall effects size on HDDs and TAC appears small (see Table 1) but may be clinically significant in this often chronic, non-adherent, and treatment-resistant population. Though the effect size for targeted naltrexone appears to be more robust than for targeted nalmefene (see effect sizes in Table 1), it is difficult to draw any firm conclusions because of the relatively few number of studies overall and the smaller size of the targeted naltrexone samples. There are also differences in psychosocial/behavioral regimens between the published naltrexone and nalmefene studies that may have contributed to effect size

differences, possibly via interaction between cognitive-behavioral therapy (CBT)-based skills as opposed to the modified BRENDA in most targeted naltrexone versus targeted nalmefene studies, respectively. The type or minimal required 'dose' of psychosocial treatment is an interesting area for future study with targeted opioid receptor antagonists.

In conclusion, the preponderance of evidence supports the use of targeted opioid antagonists in the spectrum of AUDs from early problem drinking to alcohol dependence. While these treatments appear to be efficacious with a small-to-moderate effect size in studied primary outcomes, study results have not been reported in terms of percentage of subjects with no HDDs or relapse rate for any heavy drinking, which is now considered to be a preferred benchmark by the FDA. Nonetheless, as discussed here, clinicians may find the targeted treatment approach beneficial for selected patients. As initiated by Arias et al. [69], identifying novel predictors/moderators and biomarkers of targeted opioid receptor antagonist treatment is critical for the field, which will permit a more personalized decision tree for targeted opioid receptor antagonist therapy. Future studies may also examine the targeted approach with other medications with established (e.g., acamprosate) or preliminary (e.g., gamma-hydroxybutyric acid or butyrate (GHB) and baclofen) efficacy in the treatment of alcohol dependence.

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Table 1
Targeted opioid receptor antagonist treatment in alcohol use disorders

Study	Design	Behavioral intervention	Sample size/group distribution	Primary/secondary outcomes	Effect size(s)
Naltrexone					
<i>Positive studies</i>					
Kranzler et al. [37]	Prospective, single-site, open-label study of brief psychotherapy and NTX 2–59×/week for 4 weeks + 3 months post-treatment follow-up	Initial choice of abstinence vs. ‘sensible’ drinking → 4 weekly sessions of manualized combination cognitive coping skills training during first month	21 treatment-seeking early problem drinkers (non-dependent) NTX 50 mg/day 2–59×/week prior to anticipated high-risk situations	Days drinking, drinks/drinking day, HDDs, craving score, GGT level, ASI (alcohol desire questionnaire) score	Unable to calculate as no placebo/comparison group
Heinala et al. [38]	Prospective, single-site, double-blind, parallel group randomized controlled trial over 12 weeks daily + 20 weeks targeted administration of psychotherapy vs. supportive tx and NTX vs. placebo (4 tx arms)	Weeks 1, 2, 5 and 12: cognitive coping: manualized group cognitive-behavioral therapy with focus on harm reduction, supportive: group psychotherapy with focus on complete abstinence	121 non-abstinent alcohol-dependent subjects tx with cognitive coping skills ($n = 67$) vs. supportive tx ($n = 54$) and NTX 50 mg/day ($n = 63$) vs. placebo ($n = 58$)	% relapse to heavy drinking at 32 weeks (12 weeks daily treatment + 12 weeks of targeted treatment)	% relapse to heavy drinking at 32 weeks (coping/NTX vs. coping/placebo): Cohen's $d = 0.70$ (95 % CI 0.19–1.20)
Kranzler et al. [39]	Prospective, single-site, double-blind, parallel group, randomized controlled trial over 8 weeks daily vs. targeted tx and NTX vs. placebo (4 tx arms)	Biweekly structured/manual-based counseling sessions (combination psychoeducation, coping skills and cognitive strategies)	150 early problem drinkers tx with daily NTX 50 mg/day ($n = 33$), targeted NTX 50 mg/day ($n = 42$), standing placebo ($n = 39$) and targeted placebo ($n = 36$)	Days drinking/HDDs at week 5	HDDs at week 5: Cohen's $d = 0.86$ (95 % CI 0.36–1.37)
Kranzler et al. [41]	Prospective, single-site, double-blind, parallel group, randomized controlled trial over 12 weeks of daily vs. targeted tx and NTX vs. placebo (4 tx arms)	Biweekly structured/manual-based counseling sessions (combination psychoeducation, coping skills and cognitive strategies)	163 non-dependent early problem drinkers tx with daily vs. targeted tx and NTX 50 mg/day vs. placebo	Drinks/day at week 8 Drinks/drinking day at week 8	No. of drinks/drinking day at week 8: Cohen's $d = 0.02$ (95 % CI -0.46 to 0.49) → significant effects for sex in subgroup analysis
<i>Negative studies</i>					
Laaksonen et al. [42]	Prospective multi-site, open-label randomized (1:1:1) NTX, ACA, DIS trial in 2 phases: 12-week continuously supervised medication → targeted medication for up to 52 and 67-week follow-up period (119 weeks/2.5 years total)	Brief (first 4 weeks) combined cognitive-behavioral, motivational and psychoeducational approach emphasizing harm reduction (alternative psychosocial interventions, e.g. Alcoholics Anonymous, permitted)	243 treatment-seeking alcohol-dependent subjects tx with NTX 50 mg/day, ACA 1998 mg/day and DIS 200 mg/day + brief-manual-based cognitive behavioral tx	<i>Primary:</i> Time to first HDD, time during the first 3 months to the first drinking day <i>Secondary:</i> Abstinent days/week, average weekly alcohol intake, AUDIT, SADD and QoL	Time to first HDD after continuous medication: no statistically significant difference between ACA, DIS and NTX; abstinent days/week: DIS > NTX ($p = 0.0006$) and ACA ($p = 0.0015$)
Nalmefene					

Study	Design	Behavioral intervention	Sample size/group distribution	Primary/secondary outcomes	Effect size(s)
<i>Positive studies</i>					
Karhuvaara et al. [43]	Prospective, multi-site, double-blind, parallel group, randomized controlled trial over 28 weeks (with 24-week randomized withdrawal extension) of nalmefene vs. placebo	Modified BRENDA with little psychoeducational component	403 non-dependent heavy drinkers tx with nalmefene 10–40 mg/day (<i>n</i> = 242) vs. placebo (<i>n</i> = 161)	Mean change in monthly no. of HDD at 28 weeks	Mean monthly no. of HDD at 28 weeks: Cohen's <i>d</i> = 0.15 (95 % CI -0.11 to 0.41)
Mann et al. [7, 46, 47]	Prospective, multi-site (Europe), double-blind, parallel group, randomized controlled trial over 6 months	Modified BRENDA without establishment of tx goals	579 treatment-seeking alcohol-dependent patients tx with nalmefene 18 mg/day (<i>n</i> = 290) vs. placebo (<i>n</i> = 289)	Mean change in monthly no. of HDD, TAC over 6 months	Mean change in monthly no. of HDD: Cohen's <i>d</i> = 0.22 (95 % CI 0.01–0.43) TAC: Cohen's <i>d</i> = 0.30 (95 % CI 0.09–0.51)
Gual et al. [8, 48]	Prospective, multi-site (Europe), double-blind, parallel group, randomized controlled trial over 6 months	Same as ESENSE1/SENSE	718 treatment-seeking alcohol-dependent patients tx with nalmefene 18 mg/day (<i>n</i> = 329) vs. placebo (<i>n</i> = 326)	Mean change in monthly no. of HDDs, TAC over 6 months	Mean change in monthly no. of HDDs: Cohen's <i>d</i> = 0.27 (95 % CI 0.08–0.46) TAC: Cohen's <i>d</i> = 0.17 (95 % CI -0.02 to 0.35)
van den Brink et al. [49]	Prospective, multi-site (Europe), double-blind, parallel group, randomized (3:1) controlled trial over 1 year	Same as ESENSE1/2	675 treatment-seeking alcohol-dependent patients tx with nalmefene 18 mg/day (<i>n</i> = 509) vs. placebo (<i>n</i> = 166)	Long-term safety, tolerability over 1 year Mean monthly no. of HDD, TAC over 1 year	Unable to calculate based on available unpublished data
<i>Negative studies</i>					
None	N/A	N/A	N/A	N/A	N/A

ACA acamprosate, ASI addiction severity index, AUDIT alcohol use disorder identification test, BRENDA Biopsychosocial evaluation, Report to the patient on assessment, Empathic understanding of the patient's situation, Needs collaboratively identified by the patient and treatment provider, Direct advice to the patient on how to meet those needs, Assess reaction of the patient to advice and adjust as necessary for best care, CI confidence interval, DIS disulfiram, GGT gamma-glutamyltransferase, HDD heavy drinking day, NTX naltrexone, QoL quality of life, SADD severity of alcohol dependence data, TAC total alcohol consumption, tx treated/treatment