Nalmefene for the management of alcohol dependence: review on its pharmacology, mechanism of action and meta-analysis on its clinical efficacy

Article *in* European neuropsychopharmacology: the journal of the European College of Neuropsychopharmacology · November 2016
DOI: 10.1016/j.euroneuro.2016.10.008

CITATIONS
9

READS
132

7 authors, including:

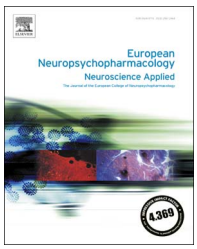
Antoni Gual
Hospital Clínic de Barcelona
332 PUBLICATIONS **3,612** CITATIONS
SEE PROFILE

Robert Swift
Brown University
82 PUBLICATIONS **1,763** CITATIONS
SEE PROFILE

Wim van den Brink
Academisch Medisch Centrum Universiteit van Amsterdam
873 PUBLICATIONS **21,527** CITATIONS
SEE PROFILE

European Neuropsychopharmacology (▮▮▮▮) ▮, ▮▮▮–▮▮▮

www.elsevier.com/locate/euroneuro



Nalmefene for the management of alcohol dependence: review on its pharmacology, mechanism of action and meta-analysis on its clinical efficacy

Karl Mann[a,*], Lars Torup[b], Per Sørensen[c], Antoni Gual[d], Robert Swift[e], Brendan Walker[f], Wim van den Brink[g]

[a]*Central Institute of Mental Health, Medical Faculty Mannheim, University of Heidelberg, Germany*
[b]*Novo Nordisk Foundation, Copenhagen, Denmark*
[c]*H. Lundbeck A/S, Valby, Denmark*
[d]*Neurosciences Institute, Hospital Clinic, IDIBAPS, Barcelona, Spain*
[e]*Center for Alcohol and Addiction Studies, Brown University, and the Providence VA Medical Center, Providence, RI, USA*
[f]*Laboratory of Alcoholism and Addictions Neuroscience, Washington State University, WA, USA*
[g]*Department of Psychiatry, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands*

Received 12 April 2016; received in revised form 5 October 2016; accepted 29 October 2016

KEYWORDS
Nalmefene;
Alcohol;
Alcohol dependence;
Preclinical;
Clinical;
Meta-analysis

Abstract
Nalmefene, a mu- and delta-opioid receptor (MOR, DOR) antagonist and a partial kappa-opioid receptor (KOR) agonist, is approved in the European Union and other countries for the reduction of alcohol consumption in alcohol dependent patients with a high drinking risk level according to WHO ("target population"). This review presents an overview of nalmefene's pharmacology, its mechanisms of action and a meta-analysis on its efficacy in reducing alcohol consumption. The review was based on a systematic search of the literature. Random effects meta-analyses were performed on published and unpublished trials directed at drinking reduction using the changes in heavy drinking days (HDDs) and daily total alcohol consumption (TAC) from baseline to the primary endpoint. For each included study and each dose, Hedges' g was used as an unbiased estimator of the standardised mean differences between nalmefene and placebo.
Preclinical data suggests that nalmefene counters alcohol-induced dysregulations of the MOR/endorphine and the KOR/dynorphin system. Evidence further suggests that reduced alcohol consumption is an effective treatment strategy that appeals to patients not ready for abstinence. Finally, meta-analyses confirmed the efficacy of 20 mg nalmefene for reducing

*Correspondence to: Medical Faculty Mannheim, Ruprecht-Karls-University Heidelberg, Central Institute of Mental Health, Square J5, 68159 Mannheim, Germany.
E-mail address: karl.mann@zi-mannheim.de (K. Mann).

http://dx.doi.org/10.1016/j.euroneuro.2016.10.008

Please cite this article as: Mann, K., et al., Nalmefene for the management of alcohol dependence: review on its pharmacology, mechanism of action and meta-analysis.... European Neuropsychopharmacology (2016), http://dx.doi.org/10.1016/j.euroneuro.2016.10.008

HDDs in the ITT population (Hedge's g = −0.20; 95% CI −0.30 to −0.09) and the target population (Hedge's g = −0.33; 95% CI −0.48 to −0.18).
Similar results were seen for TAC.
Several meta-analyses, including this new meta-analysis, support nalmefene's efficacy in reducing alcohol consumption. In conclusion, because it does not require abstinence, this treatment has the potential to motivate more patients for treatment and thus helps to address a major public health concern.

1. Introduction

The objectives of this review on nalmefene are threefold: (1) an overview of its pharmacology; (2) an overview of its mechanisms of action; and (3) a meta-analysis of randomized controlled trials (RCTs) on its efficacy in the treatment of alcohol dependent patients. In the overview of the preclinical and clinical pharmacology of nalmefene we emphasize its similarities and differences to other opioid antagonists, such as naltrexone. Nalmefene is an antagonist at the mu and delta opioid receptors and, in contrast to naltrexone, is a partial agonist at the kappa-opioid receptor. Evidence suggests that this distinctly different kappa-opioid receptor (KOR) profile may confer nalmefene with specific therapeutic properties, in addition to the blockade of positive reinforcement that it shares with the classical opioid antagonists. Nalmefene is currently the only pharmacological treatment approved for the reduction of alcohol consumption (and not abstinence) in patients with alcohol dependence in the European Union and in several other countries, including Switzerland, Australia, Turkey, Russia, Israel and Hong Kong. Therefore, the second goal of this review is to discuss the rationale for harm reduction/controlled drinking as a clinically beneficial outcome. For the third goal, we describe the results of a systematic review and meta-analysis performed on the data from clinical trials examining the efficacy of nalmefene in reducing alcohol consumption, including both published and unpublished data. Concerning the safety profile of nalmefene we refer to a recently published paper focusing on this topic (van den Brink et al., 2015) and a recent meta-analysis discussing risks and benefits of nalmefene (Palpacuer et al., 2015). This meta-analysis does not address the nalmefene approved patient population (target population: alcohol dependent patients with at least high drinking risk levels according to the World Health Organization (WHO) (2000) which is of focus in our review, however.

2. Preclinical neuropsychopharmacology of nalmefene

Nalmefene, an opioid receptor ligand with higher affinity for μ- and κ-opioid receptors (MOR and KOR) than for δ-opioid receptors (DOR) (Bart et al., 2005; Michel et al., 1985), has an antagonist effect at the MOR and DOR, but a partial agonist effect at the KOR (Bart et al., 2005). The endogenous opioid system has been extensively studied in relation to alcohol reinforcement, reward and relapse as one of the earliest approved treatments for alcohol dependence was an opioid receptor antagonist (i.e., naltrexone; see Heilig and Egli, 2006 for review). Blockade of opioid system signaling with selective antagonists for the MOR and DOR has been shown to reduce alcohol self-administration (ASA) in non-dependent rodents (Stromberg et al., 1998); (Hyytia and Kiianmaa, 2001); (Kissler et al., 2014), whereas KOR-selective antagonists generally show no effect on non-dependent ASA (for review, see Walker et al., 2012). Consequently, MORs and DORs, but not KORs, are considered viable targets to reduce the positive reinforcing effects of alcohol. In non-dependent rats, nalmefene dose-dependently reduces ASA, presumably due to MOR antagonism (June et al., 1998; June et al., 2004; Nealey et al., 2011; Kissler et al., 2014) in a manner that was shown to be equipotent to naltrexone (Walker and Koob, 2008). However, accumulating evidence suggests that in alcohol dependent or withdrawing animals, increased expression of dynorphin A (DYN), the endogenous ligand for the KOR (Chavkin et al., 1982) and/or amplified KOR signaling contribute to the negative reinforcing effects of alcohol by promoting dysphoric states that can drive excessive alcohol consumption and promote relapse to alcohol during abstinence (Markou et al., 1998, Koob, 2009; Walker, 2012). Under conditions of chronic alcohol use, MOR signaling is attenuated and DYN/KOR system activity is exacerbated (for example, see Walker et al., 2012 and Kissler et al., 2014). The observation that nalmefene was significantly more effective at reducing escalated ASA than naltrexone in dependent rats was putatively attributed to a KOR mechanism and confirmed by the finding that a selective KOR antagonist ameliorated excessive ASA during withdrawal (Walker and Koob, 2008). Subsequent investigations into KOR-mediated behaviors in alcohol dependence have established DYN/KOR system contributions to multiple phenotypes of alcohol dependence in humans and animals, including deficits in motivation, affect and executive function (Bazov et al., 2013; Berger et al., 2013; Walker and Kissler, 2013; Kissler and Walker, 2016). Recent findings highlight the differences in the effects of MOR/DOR and KOR antagonists on non-dependent and alcohol-dependent ASA (Kissler et al., 2014): intra-amygdalar infusion of MOR/DOR antagonists dose-dependently reduced non-dependent ASA but not escalated ASA in dependent animals, whereas KOR antagonists reduced escalated ASA in dependent animals without altering non-dependent use. Owing to the combined MOR antagonist/KOR partial agonist properties, nalmefene was shown to reduce ASA in both alcohol non-dependent and alcohol-dependent conditions. Noteworthy

Please cite this article as: Mann, K., et al., Nalmefene for the management of alcohol dependence: review on its pharmacology, mechanism of action and meta-analysis.... European Neuropsychopharmacology (2016), http://dx.doi.org/10.1016/j.euroneuro.2016.10.008

is that KOR antagonism, including the functional antagonism that nalmefene could provide under heightened DYN tone in dependence (Kissler et al., 2014), reduces escalated ASA to pre-dependent 'social' levels of drinking in rats during acute withdrawal (Walker et al., 2011) and protracted abstinence (Kissler and Walker, 2016), which is consistent with reduced-risk drinking in humans.

3. Clinical pharmacology of nalmefene

Nalmefene is rapidly absorbed following administration of a single dose (18 mg free base), with a peak plasma concentration (C_{max}) of 16.5 ng/ml achieved within 1.5 h (time to peak plasma concentration, T_{max}) and a total exposure (area under the curve, AUC) of 131 ng h/ml. Nalmefene has an absolute bioavailability of 41%, and shows plasma binding of approximately 30%, with an estimated volume of distribution of 3200 L. Nalmefene has an oral clearance of 169 L/h and a terminal half-life ($T_{1/2}$) of approximately 12.5 h. Based on *in vitro* studies, no clinically relevant interactions are anticipated with alcohol or with drugs metabolized by the most common CYP450 and UGT enzymes (Selincro Product Characteristic 2013). A positron emission tomography (PET) study has shown that, following rapid absorption, nalmefene attained very high receptor occupancy at μ-opioid receptors (87–100%) 3 h after dosing, which persisted 26 h after dosing (83–100%), (Ingman et al., 2005). The decline in receptor occupancy occurred more slowly than the decline in the plasma concentrations of nalmefene and its metabolites (Ingman et al., 2005). Since nalmefene is a mu-opioid antagonist, it will block the effect of opioid analgesics, and may precipitate opioid withdrawal in patients chronically taking opioids (Donnerstag et al., 2015).

4. Reduced drinking as an alternative endpoint

Abstinence from alcohol has (until recently) been the prevailing goal in the treatment of alcohol dependence. Although this approach has been challenged repeatedly, abstinence remains the primary treatment goal in most countries around the world. Empirical research into controlled drinking (reduced alcohol consumption), a harm-reduction strategy, started with a landmark study by Sobell and Sobell (1973). Using cognitive behavioral therapy, they showed the feasibility of reduced drinking; a finding replicated by an independent controlled study (Sanchez-Craig et al., 1984). Nevertheless, much controversy remained on controlled drinking as an acceptable approach when treating (severely) alcohol dependent patients (Sobell and Sobell, 1995; Sobell and Sobell, 2011; van Amsterdam and van den Brink, 2013).

Meanwhile, the clinical benefits of reducing heavy drinking to moderate drinking was supported by longitudinal studies demonstrating that patients could sustain moderate drinking over time and had reduced alcohol problems compared to heavy drinkers (Gual et al., 2013); In the US, Project MATCH showed that those drinking moderately at the end of the 4 month psychosocial treatment maintained moderate drinking and showed good clinical outcomes one or more years later (Maisto et al., 2007). Based on initial work by Sinclair and colleagues (reviewed in 2001) placebo controlled medication trials in actively drinking patients were undertaken. Some of the early proof-of-concept studies used the opioid antagonist naltrexone (Heinälä et al., 1999) and the anti-epileptic medication topiramate (Johnson et al., 2003, 2007) and showed a consistent reduction of alcohol consumption in the active medication group and to some extent in the placebo group. Along these lines a recent meta-analysis of medications used in alcohol treatment found that opioid antagonists showed better efficacy for reducing alcohol consumption than for maintaining abstinence (Jonas et al., 2014).

Alcohol dependence has the widest treatment gap (82%) in mental health care (Kohn et al., 2004), mainly because patients are reluctant to endorse abstinence (Marlatt and Witkiewitz, 2002; National Survey on Drug Use & Health, SMA 2013). About half of alcohol-dependent individuals who eventually seek treatment mention reduction of consumption over abstinence as their preferred treatment goal (Heather et al., 2010; Hodgins et al., 1997). In their guideline, the European Medicines Agency (EMA, 2010) acknowledges the value of a harm reduction treatment strategy of fewer heavy drinking days and lower total alcohol consumption as an interim step towards abstinence (EMA, 2010). Similarly, the US Food and Drug Administration (FDA) recently identified reduced heavy drinking as a beneficial clinical outcome in their published draft guidance on preferred clinical outcomes for alcohol dependence treatment studies (FDA, 2015).

5. A Systematic literature review and meta-analysis on the efficacy of nalmefene

5.1. Experimental procedures

5.1.1. Study selection

A systematic literature review was conducted to identify studies evaluating nalmefene for the reduction of alcohol consumption in adult, alcohol-dependent patients and to evaluate efficacy. The following databases were searched concatenated: Medline (incl. Medline In-Process), EMBASE, PsychInfo via the provider ProQuest and the clinical study reports available for nalmefene manufacturer-sponsored studies (European Public Assessment Report 2012). The search was not limited by date. The search was conducted using a combination of search terms and keywords for alcoholism, nalmefene, and terms related to the study design (e.g., randomized controlled trial [RCT]). The full search strategy is presented in supplementary materials. The PICOS (population/patients, intervention, comparison, outcomes, study design) inclusion and exclusion criteria strategy was used to assess titles and abstracts for the systematic review at screening level 1 and full-text assessment at screening level 2. The level 2 study selection was divided in two parts: 2a intention-to-treat (ITT) (or modified ITT if used in the original publication) population analyses; and 2b patient population and intervention according to the nalmefene label as defined by the EMA (target population: alcohol dependent patients with at least high drinking risk levels according to the World Health Organization (WHO, 2000). Furthermore, at level 2 the selection was restricted to studies reporting change from baseline in alcohol consumption. Studies only reporting alcohol consumption at endpoint (i.e. not change from baseline) were excluded for methodological reasons as these should not be combined with change from baseline values when analyzing standardized mean differences (Higgins & Green, 2011). Studies designed to prevent relapse to (heavy) drinking and therefore did not report on reduction of alcohol consumption were excluded.

Please cite this article as: Mann, K., et al., Nalmefene for the management of alcohol dependence: review on its pharmacology, mechanism of action and meta-analysis.... European Neuropsychopharmacology (2016), http://dx.doi.org/10.1016/j.euroneuro.2016.10.008

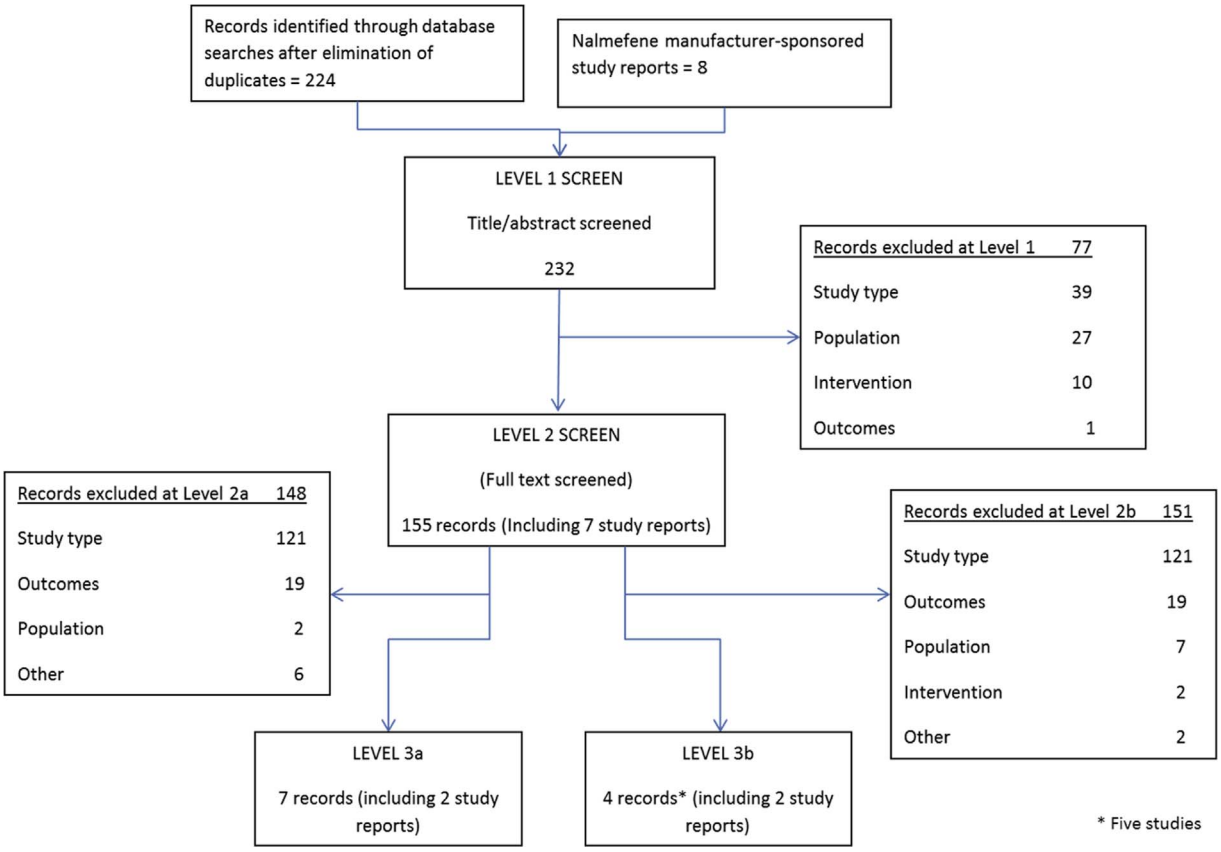


Figure 1 Flow Diagram for Identification Process in the Systematic Review of nalmefene studies.

5.1.2. Outcomes and data extraction

The outcome analysed was the change from baseline in the number of HDDs to the primary endpoint assessment (if defined in the study protocol) or to the final assessment. The endpoint varied between studies from month 3 to month 7 after randomization. The definition of a HDD (for men, a day with alcohol consumption $\geq$ 60 g or $\geq$ 64 g; for women, a day with alcohol consumption $\geq$ 40 g or $\geq$ 48 g) differed slightly between studies.

For identified studies, data was extracted from the publication or from the clinical study report. As the Mixed Model for Repeated Measures (MMRM) approach was used as primary analysis in the majority of studies, and because this methodology appropriately handles missing data, results based on MMRM analysis was preferred. In the absence of MMRM results, observed case data was used because analysis results based on a single imputation method (e.g. ANCOVA-BOCF) tend to underestimate the variance of the treatment effect and Witkiewitz et al. (2014) has illustrated how single imputation led to biased estimates of the treatment effect for continuous heavy drinking outcomes in alcohol clinical trials.

The subgroup of patients with at least high drinking risk levels according to the WHO at both screening and randomisation was of special interest, as it corresponds to the target patient population to be treated with nalmefene according to the nalmefene label (European Summary of Product Characteristics, Selincro; European Medicines Agency, 2013). For the studies that could evaluate the efficacy in this patient population, the change from baseline in the number of HDDs was analysed using the definition of HDDs as reported in the pivotal trials of Nalmefene (Mann et al., 2013; Gual et al., 2013; van den Brink et al., 2014). Data for this subgroup of patients was extracted from the publications or was available from re-analyses in case the subgroup was not considered in the publication. In accordance with the European Medicine Agency guideline on alcohol dependence (EMA, 2010), the pivotal trials of nalmefene were designed to include reductions in HDD and in total alcohol consumption (TAC) as co-primary endpoints for the target population. Therefore we will also briefly describe the meta-analysis results for change in TAC in the target population.

5.1.3. Statistical analysis

For each study identified, the mean difference between each nalmefene dose and placebo was standardised using the pooled within-groups standard deviation in the study. Hedges' g was used as an unbiased estimator of the standardised mean difference. Random-effects meta-analyses were performed to estimate the combined difference between each nalmefene dose and placebo using study level data, thus the standardised outcome for each treatment in each study (using the pooled within-groups standard deviation in the study) was used as the dependent variable in the analyses. Random-effects models were used as they allow for between-study heterogeneity and provide more conservative estimates in the presence of heterogeneity. All analyses were performed in SAS version 9.4 using PROC MIXED.

6. Results from the systematic literature and meta-analysis

6.1. Studies selected

The literature search yielded 232 relevant citations. A total of 77 records were excluded at level 1 screening of titles/abstracts, and a further 148 and 151 articles were respectively excluded at the level 2a and 2b full-text article screening stage (see flow diagram Figure 1). After applying

the screening criteria for level 2a, 7 records describing 7 studies were included. Four records describing 5 studies were included after applying screening criteria for level 2b. Two single-site, (relatively) small randomized placebo controlled studies on nalmefene were excluded at level 2b because the reported (positive) outcomes did not include reduction in the number of heavy drinking days (Mason et al., 1994; Mason et al 1999). Details on study characteristics, data source and data extracted for statistical analyses are provided in the Supplementary material Tables S1a and S1b.

6.2. Meta-analyses results

ITT population (see Figure 2): The 5 mg and 10 mg doses of nalmefene were only included in one study each, of limited sample size. Based on the individual study results, the effect size (Hedges' g) for the change from baseline in the number of HDDs was −0.06 and 0.10 for the 5 mg and 10 mg dose of nalmefene, respectively, whereas for the 20 mg and 40 mg dose of nalmefene, Hedges' g ranged from −0.07 to −0.30 and −0.06 to −0.28, respectively. The random effects meta-analyses estimated the overall effect size as −0.20 (95% CI: −0.30 to −0.09) and −0.16 (95% CI: −0.47 to 0.14) for the 20 mg and 40 mg dose of nalmefene, respectively. The between-studies variance was estimated to be zero in both meta-analyses, indicating that there was no heterogeneity in the treatment effect between studies, thus study results were very consistent.

Target population (see Figure 3): The effect size for the change from baseline in the number of HDDs was consistent across the individual study results (ranging from −0.22 to −0.43) and the estimate of the overall effect size from the random effects meta-analysis was −0.33 (95% CI: −0.48 to −0.18) for 20 mg dose versus placebo. The random effects meta-analysis on the change from baseline in TAC was consistent with the results for HDDs and led to a similar estimate of the treatment effect for the 20 mg dose versus placebo in the target population: (−0.35; 95% CI: −0.51 to −0.20) (data on file).

7. Discussion

This review provides an overview of the pharmacology, mechanisms of action and clinical efficacy of nalmefene in reducing alcohol consumption in the treatment of alcohol dependence. Nalmefene shares mu and delta opioid antagonism with naltrexone, but has a different profile at the kappa-opioid receptor. Preclinical studies with nalmefene suggest that kappa-opioid properties of the drug may normalize a chronically dysregulated KOR-dynorphine system. The review also shows that reduction strategies can be successful in reducing the risk of harm due to excessive alcohol use in alcohol dependent patients. Finally, the systematic literature review identified 7 placebo-controlled studies testing the effect of nalmefene in alcohol dependent patients and the meta-analysis estimated the efficacy of 20 mg nalmefene for reducing HDDs: overall

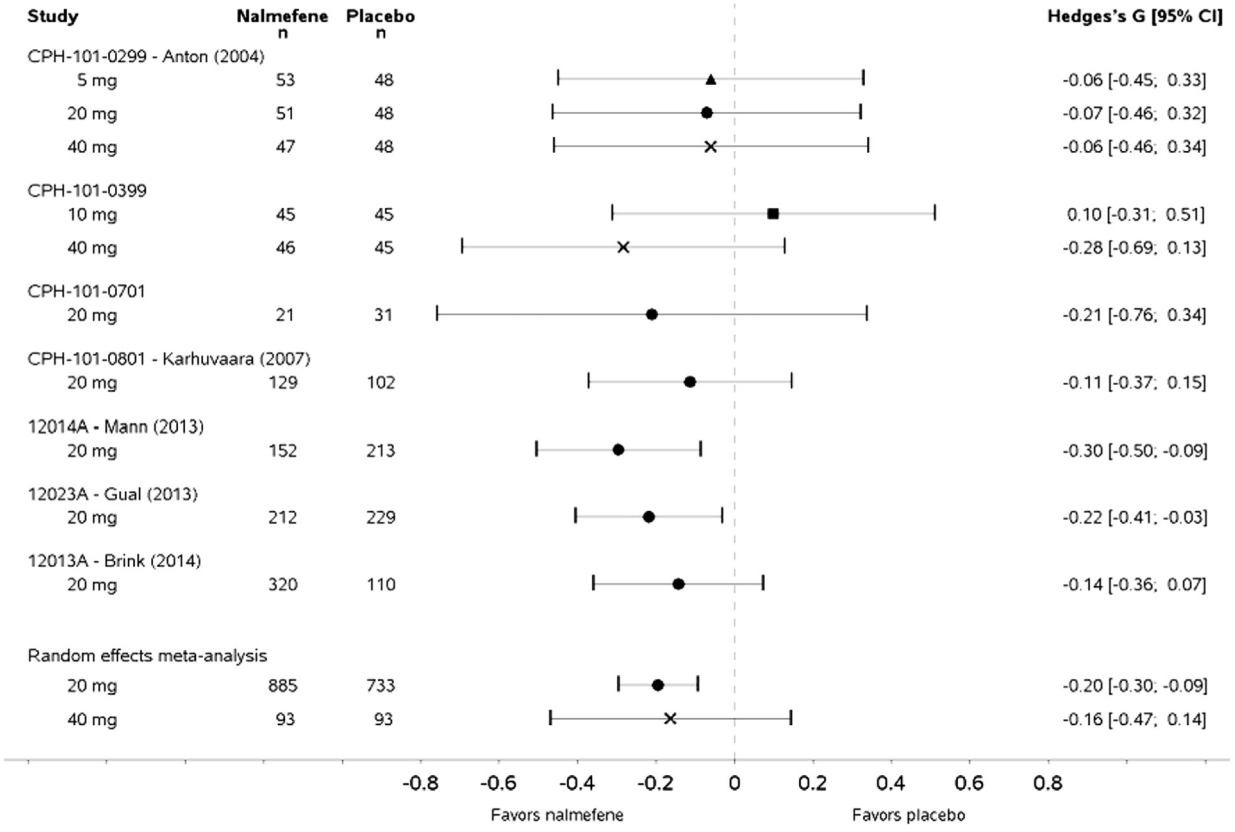


Figure 2 Meta-analysis of change from baseline in monthly HDDs; nalmefene versus placebo – ITT population. N: The number of patients at endpoint assessment.

Please cite this article as: Mann, K., et al., Nalmefene for the management of alcohol dependence: review on its pharmacology, mechanism of action and meta-analysis.... European Neuropsychopharmacology (2016), http://dx.doi.org/10.1016/j.euroneuro.2016.10.008

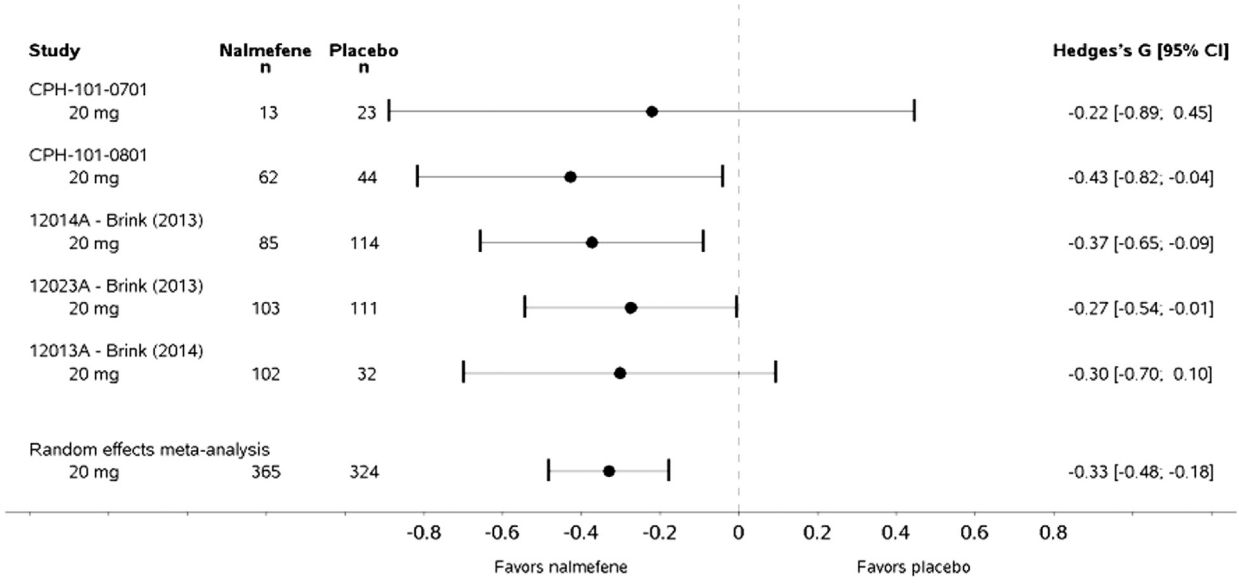


Figure 3 Meta-analysis of change from baseline in monthly HDDs; nalmefene versus placebo – Target Population. N: The number of patients at endpoint assessment.

effect size in ITT population: Hedge's g= −0.20; 95% CI −0.30 to −0.09; overall effect size in target population: Hedge's g= −0.33; 95% CI −0.48 to −0.18. This overall effect size for reducing HDDs in the ITT population is similar to the one in the primary analysis of the meta-analysis by Palpacuer et al. (2015). The main difference between our results and those from Palpacuer et al. (2015) is that we also report the results for the nalmefene target population as it was approved by the EMA and thus essential for those who want to prescribe nalmefene according to the registered indication.

Our meta-analysis has some limitations. First, the evidence for efficacy at the 5 and 10 mg dose is weak, as each dose was included in only one study with a small sample size. Second, the included studies differed considerably in study characteristics (e.g. treatment duration, dose); however patient characteristics were similar in terms of age, sex and baseline drinking as illustrated in Supplementary material Tables S1a and S1b. Moreover, the treatment effect (nalmefene versus placebo) for individual studies was generally consistent throughout the treatment period, thus the between-study differences in endpoint of analysis are unlikely to have influenced the results of the meta-analyses. Third, this meta-analysis has a focus on reduction in alcohol consumption, endpoints that are recognized by the EMA guideline as appropriate endpoints to address intermediate harm reduction. This differs from the meta-analysis by Palpacuer et al. (2015) that also addressed health outcomes, including mortality. However, as pointed out by Roerecke et al. (2015), the clinical relevance in terms of reduced mortality cannot be established based on time-limited efficacy and/or safety trials lasting up to 12–15 months. Moreover, several health outcomes have already been published for the nalmefene target population in Aubin et al. (2015). Fourth, there are results on the nalmefene patient population approved by EMA which was defined post-hoc. The credibility and interpretation of the results based on a subgroup of patients depend on the plausibility of the findings and replication of evidence across studies (Hemmings, 2014). It is well-known that non-specific treatment effects prior to randomisation can introduce heterogeneity (Johnson et al., 2003; Mann et al., 2012) and this provides a plausible explanation for the heterogeneity observed, within each study in the ITT population, which led to the identification of the nalmefene target population (see European Public Assessment Report 2012 and van den Brink et al., 2013). Moreover, there was no imbalance in baseline characteristics between treatment groups in the target population in each of the studies and the evidence for efficacy in the target population was replicated consistently across studies, thus concluding based on results from the target population meta-analysis is justified. A frequently mentioned barrier for the use of medications in alcohol dependence treatment has been a perceived low efficacy of pharmacotherapy (Thomas et al., 2003). However the effect sizes reported in the target population are well in the range for approved medicinal products in general medicine and psychiatry, including alcohol dependence (Leucht et al., 2012; Aubin et al., 2015). In addition, Aubin et al. performed various responder analyses based on drinking variables, physician and patient reported outcomes from the nalmefene pivotal trials to provide a better insight into the clinical relevance of nalmefene treatment in patients with alcohol dependence. Across the various responder definitions, odds ratios (OR) ranged from 1.79 to 2.44 and numbers-needed-to-treat (NNT) ranged from 6 to 10 (Aubin et al., 2015).

Despite these positive results, the EMA approval of nalmefene has recently kindled vivid criticism. Fitzgerald et al. (2016) have questioned nalmefene's approval based on a post-hoc analysis of patients with high or very high drinking levels and without alcohol reduction prior to randomization ("target population"). EMA has taken note of this critique and discussed their decision again in July 2016 at the Committee for Medicinal Products for Human Use (CHMP). Their conclusion reads as follows: "The

Please cite this article as: Mann, K., et al., Nalmefene for the management of alcohol dependence: review on its pharmacology, mechanism of action and meta-analysis.... European Neuropsychopharmacology (2016), http://dx.doi.org/10.1016/j.euroneuro.2016.10.008

Committee discussed the data and having taken into account the divergent position at time of positive opinion, concluded that the recent literature reports do not contain new information that would necessitate a re-evaluation of the benefit/risk ratio of Selincro" (European Medicines Agency, 2016).

Finally, nalmefene-related reductions in alcohol consumption are likely to be paralleled by decreases in mortality risk (Roerecke et al., 2015) and improvements in mental health (Francois et al., 2015). One may speculate that these expected improvements in mental health are caused by an amelioration of alcohol-related dysregulations of the KOR/Dynorphin system (Berger et al., 2013) by the partial KOR-agonist nalmefene, which in turn may have led to a (further) reduction of alcohol consumption. In addition, recent evidence has expanded the treatment potential of KOR-directed pharmacotherapy, because it was found that KOR/Dynorphin dysregulation produced by alcohol dependence seems to persist into protracted abstinence (Kissler and Walker, 2016) and that cues associated with KOR activation in non-dependent animals could drive escalated alcohol self-administration in a KOR antagonist-sensitive manner (Berger et al., 2013). Taken together, integrating the protracted-abstinence with the negative-affective cue-induced data, there is growing evidence supporting KOR-directed therapeutics that do not exclusively involve 'alcohol-dependent' populations, but also pre- and post-dependent populations and expand the potential utility of ligands with a KOR mechanism of action, from acute withdrawal to protracted abstinence.

8. Conclusion

Both preclinical and clinical evidence supports the efficacy of nalmefene in reducing alcohol consumption. This alcohol reduction strategy has the potential to diminish the current treatment gap and thus to help address a major public health concern.

Funding source

There was no funding for this article.

Contributors

Karl Mann, Wim van den Brink and Robert Swift drafted the manuscript. Brendan Walker provided the parts on preclinical research, Per Sørensen, Lars Torup and Antoni Gual did the meta-analysis. All authors provided important intellectual content.

Financial disclosures

Karl Mann is a consultant to Abbvie, D&A Pharma, Lundbeck, Novartis, and Pfizer. He has received speaker fees from Lundbeck. Lars Torup was employed by Lundbeck at the time of the conduct of this research. Per Sørensen is employed by Lundbeck. Antoni Gual has received honoraria and travel grants from Abbvie, Lundbeck, D&A Pharma, and Servier.

Robert Swift has received research grant funding and consulting fees from Farmaceutico CT, consulting fees and travel reimbursements from D&A Pharma, and travel reimbursements and honoraria from Lundbeck. Brendan Walker is a consultant for Lundbeck and within the last three years, has received honoraria from Lundbeck for speaking at Lundbeck-hosted scientific meetings. Wim van den Brink has received honoraria from Eli Lilly, Indivior, Lundbeck, Merck Serono, Mundipharma, Pfizer, as well as speaker fees from Lundbeck. He has also received investigator-initiated industry grants from Alkermes, and Neurotech, is a consultant to D&A Pharma, Kinnov Therapeutics, Bioproject, Indivior, Lundbeck, Merck Serono, Novartis and Mundipharma, and has received renumeration for expert testimony provided to Indivior and Mundipharma.

Acknowledgements

The authors take public responsibility for the content of the manuscript; have made substantive intellectual contributions to, and given final approval of, the submitted work.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.euroneuro.2016.10.008.

References

Aubin, H.J., Reimer, J., Nutt, D.J., Bladström, A., Torup, L., François, C., Chick, J., 2015. Clinical relevance of as-needed treatment with nalmefene in alcohol-dependent patients. Eur. Addict. Res 21, 160–168.

Bart, G., Schluger, J.H., Borg, L., Ho, A., Bidlack, J.M., Kreek, M. J., 2005. Nalmefene induced elevation in serum prolactin in normal human volunteers: partial kappa opioid agonist activity? Neuropsychopharmacol 30, 2254–2262.

Bazov, I., Kononenko, O., Watanabe, H., Kuntic, V., Sarkisyan, D., Taqi, M.M., et al., 2013. The endogenous opioid system in human alcoholics: molecular adaptations in brain areas involved in cognitive control of addiction. Addict. Biol. 18, 161–169.

Berger, A.L., Williams, A.M., McGinnis, M.M., Walker, B.M., 2013. Affective Cue-Induced Escalation of Alcohol Self-Administration and Increased 22-kHz Ultrasonic Vocalizations during Alcohol Withdrawal: role of Kappa-Opioid Receptors. Neuropsychopharmacol. 38, 647–654.

Chavkin, C., James, I.F., Goldstein, A., 1982. Dynorphin is a specific endogenous ligand of the kappa opioid receptor. Science 215, 413–415.

Donnerstag, N., Schneider, T., Lüthi, A., Taegtmeyer, A., Raetz Bravo, A., Mehlig, A., 2015. Severe opioid withdrawal syndrome after a single dose of nalmefene. Eur. J Clin. Pharmacol. 71, 1025–1026.

European Medicines Agency, 2016. Committee for medicinal products of human use /CHMP). Minutes for the meeting on 20-23 June 2016. CHMP/498012/2016. Available at: ⟨http://www.ema.europa.eu/docs/en_GB/document_library/Minutes/2016/07/WC500211429.pdf⟩ (23 September, date last accessed).

European Medicines Agency, 2013. Find medicine - Selincro. Available at: <http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002583/WC500140255.pdf> (08 November, date last accessed).

European Medicines Agency 2010. : Guideline on the development of medicinal products for the treatment of alcohol dependence. EMA/CHMP/EWP/20097/2008. February 18, 2010. Available at: ⟨http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/03/WC500074898.pdf⟩.

Fitzgerald, N., Angus, K., Elders, A., de Andrade, M., Raistrick, D., Heather, N., McCambridge, J., 2016. Weak evidence on nalmefene creates dilemmas for clinicians and poses questions for regulators and researchers. Addiction 111 (8) (published online: 5 JUN 2016).

Francois, C., Rahhali, N., Chalem, Y., Sorensen, P., Luquiens, A., Aubin, H.J., 2015. The effects of as-needed nalmefene on patient-reported outcomes and quality of life in relation to a reduction in alcohol consumption in alcohol-dependent patients. PLoS One 10, e0129289.

Food and Drug Administration (FDA), 2015. , Center for Drug Evaluation and Research (CDER): Alcoholism: Developing Drugs for Treatment Guidance for Industry. Available at: ⟨http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm433618.pdf⟩.

Gual, A., He, Y., Torup, L., van den Brink, W., Mann, K., ESENSE 2 Study Group, 2013. A randomised, double-blind, placebo-controlled, efficacy study of nalmefene, as-needed use, in patients with alcohol dependence. Eur. Neuropsychopharmacol. 23, 1432–1442.

Heather, N., Adamson, S.J., Raistrick, D., Slegg, G.P., UKATT Research, Team, G.P., 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.

Heilig, M., Egli, M., 2006. Pharmacological treatment of alcohol dependence: target symptoms and target mechanisms. Pharmacol. Ther. 111, 855–876.

Heinälä, P., Alhom, H., Kuoppasalmi, K., Sinclair, D., Kiianmaa, K., Lönnqvist, J., 1999. Use of naltrexone in the treatment of alcohol dependence — a double-blind placebo-controlled Finnish trial. Alcohol Alcohol. 34, 433.

Hemmings, R., 2014. An overview of statistical and regulatory issues in the planning, analysis, and interpretation of subgroup analyses in confirmatory clinical trials. J Biopharm. Stat. 24, 4–18.

Higgins, J.P.T., Green, S. (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from ⟨www.cochrane-handbook.org⟩.

Hodgins, D.C., Leigh, G., Milne, R., Gerrish, R., 1997. Drinking goal selection in behavioral self-management treatment of chronic alcoholics. Addict. Behav. 22, 247–255.

Hyytia, P., Kiianmaa, K., 2001. Suppression of ethanol responding by centrally administered CTOP and naltrindole in AA and Wistar rats. Alcohol Clin. Exp. Res. 25, 25–33.

Ingman, K., Hagelberg, N., Aalto, S., Någren, K., Juhakoski, A., Karhuvaara, S., et al., 2005. Prolonged central mu-opioid receptor occupancy after single and repeated nalmefene dosing. Neuropsychopharmacology 30, 2245–2253.

Johnson, B.A., Ait-Daoud, N., Bowden, C.L., DiClemente, C.C., Roache, J.D., Lawson, K., et al., 2003. Oral topiramate for treatment of alcohol dependence: a randomised controlled trial. Lancet 361, 1677–1685.

Johnson, B.A., Rosenthal, N., Capece, J.A., Wiegand, F., Mao, L., Beyers, K., et al., 2007. Topiramate for treating alcohol dependence: a randomized controlled trial. JAMA 298, 1641–1651.

Jonas, D.E., Amick, H.R., Feitner, C., Bobashev, G., Thomas, K., Wines, R., Kim, M.M., Shanahan, E., Gass, C.E., Rowe, C.J., Garbutt, J.C., 2014. Pharmacotherapy for adults with alcohol use disorders in outpatient settings. A systematic review and meta-analysis. JAMA 311 (18), 1889–1900.

June, H.L., Cummings, R., Eiler, W.J., Foster, K.L., McKay, P.F., Seyoum, R., Garcia, M., McCane, S., Grey, C., Hawkins, S.E., Mason, D., 2004. Central opioid receptors differentially regulate the nalmefene-induced suppression of ethanol- and saccharin-reinforced behaviors in alcohol-preferring (P) rats. Neuropsychopharmacol 29, 285–299.

June, H.L., Grey, C., Warren-Reese, C., Durr, L.F., Ricks-Cord, A., Johnson, A., McCane, S., Williams, L.S., Mason, D., Cummings, R., Lawrence, A., 1998. The opioid receptor antagonist nalmefene reduces responding maintained by ethanol presentation: preclinical studies in ethanol-preferring and outbred Wistar rats. Alcohol Clin. Exp. Res. 22, 2174–2185.

Kissler, J.L., Walker, B.M., 2016. Dissociating motivational from physiological withdrawal in alcohol dependence: role of central amygdala kappa-opioid receptors. Neuropsychopharmacology. 41, 560–567.

Kissler, J.L., Sirohi, S., Reis, D.J., Jansen, H.T., Quock, R.M., Smith, D.G., Walker, B.M., 2014. The one-two punch of alcoholism: role of central amygdala dynorphins/kappa-opioid receptors. Biol. Psychiatry 75, 774–782.

Kohn, R., Saxena, S., Levav, I., Saraceno, B., 2004. The treatment gap in mental health care. Bull. World Health Organ 82, 858 (666).

Koob, G.F., 2009. Neurobiological substrates for the dark side of compulsivity in addiction. Neuropharmacology 56 (Suppl 1), S18–S31.

Leucht, S., Hierl, S., Kissling, W., Dold, M., Davis, J.M., 2012. Putting the efficacy of psychiatric and general medicine medication into perspective: review of meta-analyses. Br. J Psychiatry 200, 97–106.

Maisto, S.A., Clifford, P.R., Stout, R.L., Davis, C.M., 2007. Moderate drinking in the first year after treatment as a predictor of 3 year outcomes. J Stud. Alcohol Drugs 68, 419.

Mann, K., Lemenager, T., Hoffmann, S., Reinhard, I., Hermann, D., Batra, A., Berner, M., Wodarz, N., Heinz, A., Smolka, M.N., Zimmermann, U.S., Wellek, S., Kiefer, F., Anton, R.F., PREDICT Study Team, 2013. Results of a double-blind, placebo-controlled pharmacotherapy trial in alcoholism conducted in Germany and comparison with the US COMBINE study. Addict. Biol. 18, 937–946.

Mann, K., Bladström, A., Torup, L., Gual, A., van den Brink, W., 2012. Extending the treatment options in alcohol dependence: a randomized controlled study of as-needed nalmefene. Biol. Psychiatry 73, 706–713.

Markou, A., Kosten, T.R., Koob, G.F., 1998. Neurobiological similarities in depression and drug dependence: a self-medication hypothesis. Neuropsychopharmacology 18, 135–174.

Marlatt, G.A., Witkiewitz, K., 2002. Harmreduction approaches to alcohol use: health promotion, prevention, and treatment. Addict. Behav. 27, 867–886.

Mason, B.J., Ritvo, E.C., Morgan, R.O., Salvato, F.R., 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.

Mason, B.J., Salvato, F.R., Williams, L.D., Ritvo, E.C., Cutler, R.B., 1999. A double-blind, placebo-controlled study of oral nalmefene for alcohol dependence. Arch. Gen. Psychiatry 56, 719–724.

Michel, M.E., Bolger, G., Weissman, B.A., 1985. Binding of a new opiate antagonist, nalmefene, to rat brain membranes. Methods Find. Exp. Clin. Pharmacol. 7, 175–177.

Nealey, K.A., Smith, A.W., Davis, S.M., Smith, D.G., Walker, B.M., 2011. kappa-opioid receptors are implicated in the increased potency of intra-accumbens nalmefene in ethanol-dependent rats. Neuropharmacology 61, 35–42.

Palpacuer, C., Laviolle, B., Boussageon, R., Reymann, J.M., Bellissant, E., Naudet, F., 2015. Risks and benefits of nalmefene in the treatment of adult alcohol dependence: a systematic literature review and meta-analysis of published

Please cite this article as: Mann, K., et al., Nalmefene for the management of alcohol dependence: review on its pharmacology, mechanism of action and meta-analysis.... European Neuropsychopharmacology (2016), http://dx.doi.org/10.1016/j.euroneuro.2016.10.008

and unpublished double-blind randomized controlled trials. PLoS Med. 22 (12:e1001924).

Roerecke, M., Sørensen, P., Laramée, P., Rahhali, N., Rehm, J., 2015. Clinical relevance of nalmefene versus placebo in alcohol treatment: reduction in mortality risk. J Psychopharmacol. 29, 1152–1158.

Sanchez-Craig, M., Annis, H.M., Bornet, A.R., MacDonald, K.R., 1984. Random assignment to abstinence and controlled drinking: evaluation of a cognitive-behavioral program for problem drinkers. J Consult Clin. Psychol. 52, 390–403.

Selincro® 18mg film-coated tablets (nalmefene), 2013mg. Summary of Product Characteristics. Lundbeck Limited.

Sinclair, J.D., 2001. Evidence about the use of naltrexone and for different ways of using it in the treatment of alcoholism. Alcohol Alcohol. 36, 2–10 (Review).

Sobell, M.B., Sobell, L.C., 1995. Controlled drinking after 25 years: how important was the great debate? Addiction 90, 1149–1153 (discussion 1157–1177).

Sobell, M.B., Sobell, L.C., 2011. It is time for low-risk drinking goals to come out of the closet. Addiction 106, 1715–1717.

Sobell, M.B., Sobell, L.C., 1973. Alcoholics treated by individualized behaviour therapy: one year treatment outcome. Behav. Res Ther. 11, 599–618.

Stromberg, M.F., Casale, M., Volpicelli, L., Volpicelli, J.R., O'Brien, C.P., 1998. A comparison of the effects of the opioid antagonists naltrexone, naltrindole, and beta-funaltrexamine on ethanol consumption in the rat. Alcohol 15, 281–289.

Substance Abuse and Mental Health Services Administration, 2013: Results from the, 2012. National Survey on Drug Use and Health: National Findings (Office of Applied Studies, NSDUH Series H-46, HHS Publication No. (SMA) 13–4795. Rockville, MD.

Thomas, C.P., Wallack, S.S., Lee, S., McCarty, D., Swift, R., 2003. Research to practice: adoption of naltrexone in alcoholism treatment. J Subst. Abus. Treat. 24, 1–11.

van Amsterdam, J., van den Brink, W., 2013. Reduced-risk drinking as a viable treatment goal in problematic alcohol use and alcohol dependence. J Psychopharmacol. 27, 987–997.

van den Brink, W., Aubin, H.J., Bladström, A., Torup, L., Gual, A., Mann, K., 2013. Efficacy of as-needed nalmefene in alcohol-dependent patients with at least a high drinking risk level: results from a subgroup analysis of two randomized controlled 6-month studies. Alcohol Alcohol. 48, 570–578.

van den Brink, W., Sørensen, P., Torup, L., Mann, K., Gual, A., for the SENSE Study Group, 2014. Long-term efficacy, tolerability, and safety of nalmefene as-needed in patients with alcohol dependence: a 1-year, randomised controlled study. J Psychopharmacol. 28, 733–744.

van den Brink, W., Strang, J., Gual, A., Sørensen, P., Jensen, T.J., Mann, K., 2015. Safety and tolerability of as-needed nalmefene in the treatment of alcohol dependence: results from the Phase III clinical programme. Expert Opin. Drug Saf. 14, 495–504.

Walker, B.M., Koob, G.F., 2008. Pharmacological evidence for a motivational role of kappa-opioid systems in ethanol dependence. Neuropsychopharmacology 33, 643–652.

Walker, B.M., Valdez, G.R., McLaughlin, J.P., Bakalkin, G., 2012. Targeting dynorphin/kappa opioid receptor systems to treat alcohol abuse and dependence. Alcohol 46, 359–370.

Walker, B.M., Zorrilla, E.P., Koob, G.F., 2011. Systemic kappa-opioid receptor antagonism by nor-binaltorphimine reduces dependence-induced excessive alcohol self-administration in rats. Addict. Biol. 16, 116–119.

Walker, B.M., 2012. Conceptualizing withdrawal-induced escalation of alcohol self-administration as a learned, plasticity-dependent process. Alcohol 46, 339–348.

Walker, B.M., Kissler, J.L., 2013. Dissociable effects of kappa-opioid receptor activation on impulsive phenotypes in wistar rats. Neuropsychopharmacology 38, 2278–2285.

Witkiewitz, K., Falk, D.E., Kranzler, H.R., Litten, R.Z., Hallgren, K. A., O'Malley, S.S., Anton, R.F., 2014. Alcohol methods to analyze treatment effects in the presence of missing data for a continuous heavy drinking outcome measure when participants drop out from treatment in alcohol clinical trials. Alcohol Clin. Exp. Res 38, 2826–2834 (Clinical Trials Initiative (ACTIVE)(Workgroup).

World Health Organization (WHO), 2000. International Guide for Monitoring Alcohol Consumption and Related Harm. © World Health Organization.

Please cite this article as: Mann, K., et al., Nalmefene for the management of alcohol dependence: review on its pharmacology, mechanism of action and meta-analysis.... European Neuropsychopharmacology (2016), http://dx.doi.org/10.1016/j.euroneuro.2016.10.008