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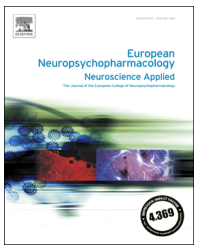

Nalmefene for the management of alcohol dependence: review on its pharmacology, mechanism of action and meta-analysis on its clinical efficacy

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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 Random effects meta-analyses were performed on published and unpublished trials directed at drinking reduction using the changes in heavy drinking days (HDDs) and daily total alcohol consumption (TAC) from baseline to the primary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

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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