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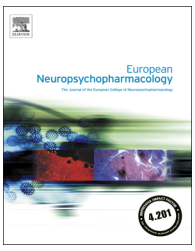

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A randomised, double-blind, placebo-controlled, efficacy study of nalmefene, as-needed use, in patients with alcohol dependence

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Abstract
This study evaluated the efficacy of as-needed use of the opioid system modulator nalmefene in reducing alcohol consumption in patients with alcohol dependence. Seven hundred and eighteen patients (placebo=360; nalmefene=358), ≥18 years of age, with a diagnosis of alcohol dependence, ≥6 heavy drinking days and an average alcohol consumption ≥WHO medium drinking risk level in the 4 weeks preceding screening, were randomised (1:1) to 24 weeks of as-needed placebo or nalmefene 18 mg/day.
The co-primary efficacy analyses showed a significantly superior effect of nalmefene compared to placebo in the change from baseline to month 6 in heavy drinking days (group difference: −1.7 days/month [95% CI −3.1; −0.4]; p=0.012) and a better but not significant effect in reducing total alcohol consumption (group difference: −5.0 g/day last month [95% CI −10.6; 0.7]; p=0.088). A subgroup analysis showed that patients who did not reduce their drinking prior to randomisation benefitted more from nalmefene. Improvements in Clinical Global Impression and reductions in liver enzymes were greater in the nalmefene group than in the placebo group. Adverse events were more common with nalmefene; the incidence of adverse events leading to dropout was similar in both groups.
This study provides evidence for the efficacy of nalmefene, which constitutes a new pharmacological treatment paradigm in terms of treatment goal (reduced drinking) and dosing regimen (as-needed), in alcohol dependent patients unable to reduce alcohol consumption on their own.

1. Introduction

Europe has the highest overall consumption of alcohol (World Health Organization, 2010), and in general, the European Union can be characterised by a lower proportion of abstainers

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and a higher proportion of the population drinking more than 20 g of pure alcohol per day than the rest of the world (World Health Organization, 2011). Worldwide, the European region suffers the highest impact of alcohol with 6.5% of all deaths and 11.6% of all disability-adjusted life years attributable to alcohol (Rehm et al., 2009).

Most of the alcohol-attributable mortality is due to alcohol dependence, presumably by means of heavy drinking (Rehm et al., 2013). Approximately 15 million persons in the European Union are alcohol-dependent (Wittchen et al., 2011). There is a large treatment gap, with less than 10% of people in Europe with a diagnosis of any alcohol disorder (including alcohol dependence) actually receiving any treatment (Alonso et al., 2004).

Reduction of alcohol consumption is increasingly accepted as a viable treatment goal (European Medicines Agency, 2010; Luquiens et al., 2011). However, the three currently registered pharmacological treatments for alcohol dependence are indicated only for the maintenance of abstinence following detoxification.

A large proportion of patients in abstinence-oriented treatments experience relapses (Anton et al., 2006; Mann et al., 2004; Merkx et al., 2011; Miller et al., 2001), and abstinence-oriented treatments might not be desirable or acceptable to many patients (Gastfriend et al., 2007; Marlatt and Witkiewitz, 2002). Allowing patients to choose between abstinence and reduced drinking as their treatment goal may enhance engagement with the treatment, ultimately leading to better treatment outcomes for the population at large (Adamson et al., 2010; Heather et al., 2010). Furthermore, research has shown that any reduction in alcohol consumption for a person who consumes more than 10 g of alcohol per day will reduce the annual and lifetime risk of alcohol-related death (Rehm et al., 2011).

Therefore, there is clearly a need for new pharmacological treatments allowing for reduction of alcohol consumption as a treatment goal.

Nalmefene is an opioid system modulator, which in several studies in patients with alcohol use disorders has been associated with a reduction of heavy drinking. Although Anton et al. (2004) were unable to show a reduction in alcohol use compared to placebo, other studies in patients with alcohol-use disorders indicate that treatment with nalmefene causes a reduction of heavy drinking (Karhuvaara et al., 2007; Mason et al., 1994, 1999). A recently published large phase 3 study in patients with alcohol dependence showed that nalmefene, taken on an as-needed basis was superior to placebo in reducing alcohol consumption (Mann et al., 2013).

Here, we present results from another recently completed phase 3 study in patients with alcohol dependence that assessed the efficacy and safety of as-needed use of nalmefene in reducing alcohol consumption, measured as the monthly changes from baseline in the number of heavy drinking days (days in last month) and mean total alcohol consumption (g/day in last month) during a treatment period of 24 weeks.

2. Experimental procedures

2.1. Patients

This randomised, double-blind, placebo-controlled, parallel-group study included patients from 57 sites in Belgium, the Czech Republic, France, Italy, Poland, Portugal, and Spain. Patients were recruited from in- and out-patient clinics, from the study site's patient pool, and by spontaneous referrals to the study site. Advertisements were used in the Czech Republic, France, Italy, and Spain. Eligible patients were men and women aged ≥18 years with a primary diagnosis of alcohol dependence according to Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR™ [American Psychiatric Association, 2000]) (assessed using the Mini-International Neuropsychiatric Interview [MINI; Lecrubier et al., 1997]) and a blood alcohol concentration <0.02% at the screening visit. Exclusion criteria were (a) <6 heavy drinking days in the 4 weeks before screening (European Medicines Agency, 2010; a day with alcohol consumption ≥60 g for men and ≥40 g for women), (b) an average alcohol consumption below medium drinking risk level according to the World Health Organization (WHO) in the 4 weeks before screening (≤40 g alcohol/day for men and ≤20 g alcohol/day for women; World Health Organization, 2000), (c) >14 consecutive abstinent days in the 4 weeks preceding screening, (d) a score ≥10 on the revised version of the Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar; Sullivan et al., 1989), indicating the need for medication supported detoxification, (e) aspartate aminotransferase or alanine aminotransferase (ALAT) values >3 times of upper normal limit, (f) a current DSM-IV Axis I disorder other than alcohol dependence (except nicotine dependence), (g) a DSM-IV Axis II antisocial personality disorder (assessed using the MINI) or (h) recent (within 1 week prior to the screening visit) treatment with opioid agonists or partial agonists. For the full list of selection criteria, see Supplementary material.

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

2.2. Randomisation and blinding

At baseline (week 0), eligible patients were assigned to 24 weeks of treatment with as-needed use of either placebo or nalmefene 18 mg (base) in a 1:1 ratio, according to a computer generated randomisation list (in blocks of 4), provided by the sponsor. Randomisation for the run-out period was also done at baseline.

Patients, investigators, staff and the sponsor were blind to treatment assignment. Two sets of sealed envelopes containing study medication details for each patient were prepared. One set was kept by the sponsor and one set by the investigator or pharmacist. The randomisation code was only to be broken by the investigator in case of an emergency situation. The randomisation code was not broken for any patient during the study. Nalmefene and placebo tablets were identical in appearance.

2.3. Procedures

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

Patients were instructed to take one tablet on each day they perceived a risk of drinking alcohol (as-needed dosing), preferably 1–2 h prior to the anticipated time of drinking. Tablets could be taken up to once daily and were supplied in wallet cards with space for the patient to record the date of study medication intake. The Timeline Follow-back (Sobell and Sobell, 1992) was used to obtain estimates of daily drinking as well as to record daily medication intake. In addition, all patients took part in a motivational and adherence-enhancing intervention (BRENDA [Volpicelli et al., 2001;