



Nalmefene for the treatment of alcohol dependence: a current update

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Abstract

To date, few pharmacotherapies have been established for the treatment of alcoholism. There is a plethora of research concerning the involvement of the opioid-endorphin system in mediating the reinforcing effects of alcohol. The opioid antagonist naltrexone has been found to be effective in alcohol treatment. In addition, the mu-opioid antagonist and partial kappa agonist nalmefene was recently approved by the European Medicines Agency for the treatment of alcoholism. The relevant studies followed a harm-reduction, 'as needed' approach and showed a reduction in alcohol consumption with nalmefene 20 mg rather than increased abstinence rates, (which was not the primary goal of the relevant studies). The available literature is reviewed and discussed. Nalmefene appears to be a safe and effective treatment for alcohol dependence.

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Introduction

In December 2012, Selincro, containing the opioid antagonist nalmefene as the active substance, was approved by the European Medicines Agency (EMA) for the treatment of alcoholism. This critical review presents the rationale for using nalmefene in this indication and the data available so far. Publications were identified through a Medline search with the terms 'nalmefene' AND 'alcohol' (66 hits) or 'alcohol dependence' (52 hits). This work is also an extension of the previous analysis on the use of opioid antagonists in alcohol dependence, which included the first three studies on nalmefene (Rosner et al., 2010a).

Background

Apart from nicotine dependence, alcohol use disorders are still by far the most frequent substance disorders worldwide (Rehm et al., 2009; Wittchen et al., 2011). While abuse (harmful use) is characterized by the somatic or psychiatric problems (and, in DSM only, social problems) induced by alcohol intake, ICD-10 and DSM-IV define alcohol dependence by a cluster of somatic, psychological and behavioural symptoms (Soyka and Kuefner, 2008; Soyka, 2013). The recently published DSM-5 has abandoned the categorical distinction between abuse

and dependence and follows a dimensional approach: 11 symptoms are given for substance use disorders; four or more positive symptoms constitute a severe substance use disorder, two or three a moderate one.

Prevalence estimates for alcohol use disorders range between 7–10% in European countries and the US (Grant et al., 2004; Kessler et al., 2005; Rehm et al., 2005; Pirkola et al., 2006). Global prevalence rates of alcohol use disorders among adults are estimated to range between 0–16%, with the highest prevalence rates being found in Eastern Europe (World Health Organization, 2011). In Europe, 137 000 deaths per year are associated with alcohol consumption, including 39 000 cases of liver cirrhosis, 13 000 cases of psychiatric and neurological disorders, 11 000 cases of cardiovascular disorders, 26 000 cases of malignant disorders and 18 000 suicides (for a review, see Soyka, 2013). The net burden caused by alcohol consumption in EU countries is 1 in 7 deaths in men and 1 in 13 deaths in women (Rehm et al., 2013) and the economic burden due to alcoholism is enormous (Laramee et al., 2013).

Multiple psychosocial and psychotherapeutic approaches are used to treat alcoholism, including cognitive-behavioural therapies, motivational enhancement, contingency management, 12-step therapies and family therapy and case management, among many others (Miller and Wilbourne, 2002; Berglund et al., 2003; Prendergast et al., 2006; Soyka et al., 2008; Magill and Ray, 2009). However, relapse to heavy drinking is very frequent after conventional alcohol therapies, with abstinence rates only a little higher than 40% (Soyka, 2013).

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A number of meta-analyses have proven the efficacy of alcohol treatment in general (Hester and Miller, 1995; Miller and Wilbourne, 2002), but empirical research suggests that allocation of patients to different treatments according to individual patient profiles is very difficult (Project MATCH Research Group, 1997).

Few pharmacotherapies have been established as anti-craving drugs to reduce relapse risk or alcohol intake in alcoholism (Heilig and Egli, 2006; Soyka et al., 2008; Spanagel and Kiefer, 2008; Soyka and Rosner, 2010). Empirical evidence is available for the efficacy of the putative N-methyl-D-aspartic acid (NMDA) modulator acamprosate and the opioid antagonist naltrexone in alcohol treatment (Rosner et al., 2010b; Maisel et al., 2013). Acamprosate is marketed for relapse prevention of alcoholism and available in many countries worldwide. Its precise mechanism of action is not fully understood, but many data suggest modulation of the NMDA receptor as the primary mechanism of action (Littleton and Ziegler, 2003). Meta-analyses indicate that acamprosate reduces relapse to heavy drinking or increases the abstinence rates in alcohol-dependent people (Rosner et al., 2010b; Maisel et al., 2013). Acamprosate is safe and usually well tolerated. The Cochrane analysis indicates that only diarrhoea is more frequent in acamprosate patients (Rosner et al., 2010b). Some more recent studies have shown negative results for acamprosate (Mann et al., 2012). Other drugs are currently being tested, including baclofen, but none of these agents is close to being introduced to the market (Davies et al., 2013; Spanagel and Vengeliene, 2013).

Neurobiological basis

Multiple lines of evidence suggest that opioid receptors are implicated in the development of alcohol use and alcoholism (Ciccocioppo et al., 2002). Altered activity of mu-opioid-receptor-mediated neurotransmission has been suggested as one of the key mechanisms underlying the reinforcement of alcohol consumption and development of alcoholism (Koob, 1992; Herz, 1997; Cowen and Lawrence, 1999; Gianoulakis, 2004; Oswald and Wand, 2004).

Three major classes of opioid receptors have been identified: mu (μ), kappa (κ) and delta (δ) opioid receptors (Gianoulakis, 2004). Mu and kappa receptors are located in the grey matter of the spinal cord, limbic system, hippocampus, thalamus, ventral striatum and the brainstem (Kuhar et al., 1973; Hiller et al., 1994; Koob and Le Moal, 2006). Delta receptors are located throughout the grey matter of the telencephalon and also the hippocampus, mostly in GABAergic neurons (Erbs et al., 2012). Beta-endorphins are endogenous ligands for the mu and delta receptors, enkephalins for the delta receptors and dynorphins predominantly for the kappa receptors (Kuhar et al., 1973; Koob and Le Moal, 2006).

Mu receptors play an essential role in mediating the analgesic and rewarding effects of opioids and, very likely, also in physical dependence (Narita et al., 2001). The μ 1 receptor subtype is linked to analgesia and euphoria, the μ 2 subtype to respiratory depression (Boom et al., 2012).

Alcohol affects many different neurotransmitter systems in the brain, including glutamate, gamma aminobutyric acid (GABA), serotonin and especially dopamine (Koob and Le Moal, 2006; Spanagel, 2009; Spanagel and Vengeliene, 2013). It stimulates the release of beta-endorphin, enkephalins and dynorphin (Koob et al., 2003; Marinelli et al., 2004, 2005, 2006; Dai et al., 2005). Opioids in the paraventricular nucleus stimulate alcohol intake (Barson et al., 2010), while blockade of the opioid receptor has been shown to decrease alcohol intake (Hubbell et al., 1986, 1988; Herz, 1997; Oswald and Wand, 2004). There is much evidence suggesting that the opioid system plays a significant role in mediating the reinforcing effects of alcohol and the associated dopamine release in the mesolimbic brain area (Belluzzi and Stein, 1977; Goeders et al., 1984; Hubbell et al., 1988; Reid, 1996; Gianoulakis, 2004; Marinelli et al., 2006; Jarjour et al., 2009). Opioid receptors in GABAergic neurons interact with dopaminergic neurons and thus mediate dopamine release (Koob and Le Moal, 2006) and midbrain dopamine neurons in the ventral tegmental area and their projections to the nucleus accumbens in the ventral striatum are believed to support reward anticipation, reinforcement and motivational processes in general (Adcock et al., 2006).

The opioidergic system has been viewed as a 'hedonic' system. Long-term changes due to substance use may include receptor densities and effector systems (Turchan et al., 1999; Chen and Lawrence, 2000) and modifications of mRNA coding for both receptors and peptides (Przewlocka et al., 1997; Rosin et al., 1999; Cowen and Lawrence, 2001).

Functional neuroimaging studies suggest that marked changes and adaptations in the opioid system are associated with chronic alcohol use. Positron emission tomography (PET) studies indicate a negative correlation between mu-opioid receptor binding and alcohol craving in recently abstinent alcohol-dependent people (Bencherif et al., 2004). Heinz et al. (2005) have demonstrated an increase of mu-opioid receptors in different regions of the brain, including the nucleus accumbens, and a correlation with the severity of alcohol craving.

Nalmefene – pharmacology, preclinical and clinical findings and pharmacogenetics

Nalmefene is an antagonist at the mu- and delta-opioid receptor (DeHaven-Hudkins et al., 1990; Emmerson et al., 1994) and a partial agonist at the kappa receptor (Bart et al., 2005a) and has been studied for use in substance use disorders, especially alcoholism, since the 1990s.

Nalmefene has a comparable chemical structure to naltrexone (Swift, 2013) but was proposed to offer a number of potential advantages relative to naltrexone (Mason et al., 1999), including a more effective binding to central opioid receptors (Emmerson et al., 1994; Ingman et al., 2005), a higher bioavailability (Gal et al., 1986; Dixon et al., 1987) and the absence of a dose-dependent association with liver toxicity (Mason et al., 1999). There is no evidence of significant activity at any other receptor type (for review see Niciu and Arias, 2013). Chronic nalmefene administration does not change dopamine receptor function, as shown by animal PET studies (Unterwald et al., 1997).

Nalmefene is a potent antagonist at the opioid receptor and is selective for the mu- and kappa-opioid receptor subtypes (Michel et al., 1985; Bart et al., 2005a). Preclinical data indicate that kappa-opioid receptor antagonism decreases dependence-induced alcohol self-administration (Walker and Koob, 2008). The relatively higher affinity of nalmefene at the kappa-receptor may be responsible for the increased hypothalamic-pituitary-adrenal axis activation via increased adrenocorticotrophic hormone (Schluger et al., 1998). There is a close interaction between the opioid system and stress system in alcoholism, and naltrexone and nalmefene may have different effects on the systems (Emsley et al., 2013).

In alcohol-dependent rats nalmefene was found to be significantly more effective in suppressing alcohol intake than naltrexone (Walker and Koob, 2008). The results were suggestive of the kappa-opioid receptor competitive antagonism selectively decreasing alcohol self-administration. Nalmefene-induced elevation in serum prolactin in healthy volunteers was interpreted as a partial agonist effect at kappa-opioid receptors (Bart et al., 2005a), while binding assays confirmed nalmefene's affinity for kappa-opioid receptors (Bart et al., 2005a). Data from animal model studies indicate that the *in vivo* pharmacology of nalmefene is similar to that of naloxone and naltrexone (Osborn et al., 2010). Nalmefene has a slower onset and longer duration of action than naltrexone.

Pharmacokinetics and pharmacodynamics

Nalmefene has a similar chemical structure to naltrexone but may somehow bind more tightly to opioid receptors (Emmerson et al., 1994; Ingman et al., 2005).

In a PET study with the opioid receptor ligand (11c) carfentanil, Ingman et al. (2005) evaluated the pharmacokinetics of nalmefene (20 mg) after single and 7-d repeated dosing in 12 healthy volunteers. The regions of interest were the thalamus, caudate nucleus and frontal cortex, with the occipital cortex as reference region. Central mu-opioid receptor occupancy was measured 2, 26, 50 and 74 h after completion of each dosing schedule. The results indicated that nalmefene was rapidly absorbed. The mean half-life was 13.4 h after single and

repeated dosing. Nalmefene, thus, has linear pharmacokinetics. Receptor occupancy was high 2 h (87–100%) and also 26 h (83–100%) after both dosing schedules. After 50 h receptor occupancy was still 48.4–72.0%, while the nalmefene plasma concentration was very low. These results suggest a slow dissociation of the drug from the mu-opioid receptor.

Previously, Kim et al. (1997) showed a clearance half-life of 28.7 ± 5.9 h for central opioid receptors and a plasma elimination half-life of 8.30 ± 0.34 h. Again, the regions of interest were the thalamus, caudate nucleus, putamen and cerebral cortex. Nalmefene has an oral bioavailability of about 40% (Gal et al., 1986; Dixon et al., 1987; Ingman et al., 2005; European Medicines Agency, 2013). There is no evidence for liver toxicity (Mason et al., 1999). The opioid kappa receptor system may be of relevance for motivational aspects of alcoholism and for mood disorders/depression (Walker and Koob, 2008; Walker et al., 2011, 2012).

Nalmefene is rapidly absorbed (Dixon et al., 1987). Tolerance of single doses of 20–300 mg daily or 10–40 mg twice daily is usually good (Dixon et al., 1987; Mason et al., 1994). There is no evidence of any serious adverse drug reactions in hepatic or other body systems.

In the Anton et al. study (2004, see below) the 20 mg group experienced more insomnia, dizziness and confusion, while the 5 mg group also showed more dizziness and the 40 mg group more nausea than the placebo group. Most symptoms were mild and improved over time. Outcome parameters concerning alcohol intake did not differ between groups.

Preclinical findings

Nalmefene was found to reduce alcohol consumption in animal models (June et al., 1998; Ciccocioppo et al., 2002). Walker and Koob (2008) examined the effects of naltrexone, nalmefene and nor-binaltorphimine on alcohol consumption in nondependent and dependent rats. Nalmefene was found to be significantly more effective in suppressing ethanol intake than naltrexone in ethanol-dependent animals. In a human study, nalmefene was equally effective as naltrexone in reducing subjective responses to alcohol in non-treatment seeking alcoholics (Drobes et al., 2004).

The effects of nalmefene on craving and other subjective responses to alcohol-related cues were assessed in a clinical laboratory study (Drobes et al., 2003, 2004). Non-treatment-seeking alcoholics and social drinkers were randomly assigned to receive nalmefene (titrated to 40 mg per day), naltrexone (titrated to 50 mg per day) or placebo for 7 d before they attended an alcohol challenge clinical laboratory session in which an alcoholic drink was provided in a bar-like setting. Both nalmefene and naltrexone reduced craving, drinking amounts and frequency to a comparable extent among the alcohol-dependent group, while no effects were observed in the

Table 1. Design and outcomes of randomized clinical trials on nalmefene for drinking problems

Authors (Year)	Country	N	Dosing (mg/d)	Treatment duration (wk)	Reduction in heavy drinking	Reduction in number of drinking days	Reduction in number of drinks or amount of alcohol per drinking day
Mason et al. (1994)	USA	21	0, 10, 40	12	$p \leq 0.05$ (40 mg group only)	$p < 0.05$	$p \leq 0.05$ in both groups
Mason et al. (1999)	USA	105	0, 20, 80	12	$p \leq 0.02$ no difference between the two doses	n.s.	n.s.
Anton et al. (2004)	USA	270	0, 5, 20, 40	12	n.s.		
Karhuvaara et al. (2007)*	Finnland	403	0, 10–40	28	$p = 0.01$	$p \leq 0.05$	$p \leq 0.01$ G-GT also decreased significantly ($p < 0.01$)
Gual et al. (2013)*	Europe	718	20 vs. placebo	24		Fewer 'heavy drinking days' ($p = 0.01$)	No significant reduction in alcohol consumption
Mann et al. (2013)*	Europe	604	20 vs. placebo	24	$p < 0.05$		$p = 0.003$
van den Brink et al. (2013) (Pooled analysis of data from the Mann et al. (2013) and Gual et al. (2013) studies)	Europe	667	20 vs. placebo	24	$p < 0.0001$		$p < 0.0001$ for total alcohol consumption in patients not reducing alcohol after initial assessment

n.s. = not significant ($p > 0.5$); G-GT: gamma-glutamyl transferase.

* 'as needed' approach.

social drinker group, relative to placebo. Like naltrexone, nalmefene reduces the subjective 'high' feeling after alcohol consumption (Drobes et al., 2004).

Clinical findings

To date, six randomized controlled trials have been published on the efficacy of nalmefene in alcohol treatment (Mason et al., 1994, 1999; Anton et al., 2004; Karhuvaara et al., 2007; Gual et al., 2013; Mann et al., 2013) (see Table 1). The first was a pilot study with a small sample size (Mason et al., 1994) in which 21 alcohol-dependent subjects were randomly assigned to 12 wk of double-blind treatment with 40 mg nalmefene, 10 mg nalmefene or placebo. Patients also attended Alcoholics Anonymous (AA) support groups and were encouraged to visit other psychosocial therapies, but no such treatment was provided in the study. Compared with placebo, nalmefene significantly decreased the number of drinks per drinking day in both dosing groups ($p \leq 0.05$). An additional, significant effect on heavy drinking was observed in the higher (40 mg) dosing group, while there was a non-significant trend of a higher proportion of abstinent days in the nalmefene groups. This effect was more marked in the subsequent studies. Nalmefene was well tolerated and no serious adverse drug reactions occurred.

The same group (Mason et al., 1999) later studied 105 patients who were assigned in a 12-wk study to receive 80 mg nalmefene ($n = 35$), 20 mg nalmefene ($n = 35$) or

placebo ($n = 35$). Cognitive behavioural therapy was additionally provided. Significant effects on rates of heavy drinking were shown in both nalmefene groups. Heavy drinking rates were also found to be significantly reduced when the analysis was limited to the sampler subgroup, indicating that non-abstinent patients (who had at least one drink during the trial) also benefit from treatment to a similar degree. Differences in other outcomes, such as percentage of abstinent days and the number of drinks consumed per drinking day were not statistically significant. Again, no unexpected serious adverse events were recorded and rates of adverse events did not differ between both dosing groups. The authors stated that the comparatively high patient dropout rate in the 80 mg-dosing group indicates that a lower dosing of 20 to 40 mg per day may be preferable.

The results of a multicentre trial did not find significant effects on drinking outcomes for nalmefene (Anton et al., 2004). The trial evaluated 3 doses of nalmefene (5, 20 and 40 mg) in a double-blind comparison with placebo over a 12-wk treatment period. A total of 270 recently detoxified alcohol-dependent subjects were enrolled. Motivational enhancement therapy with individualized treatment goals of total abstinence or drinking reduction was additionally provided. Both the nalmefene and placebo groups showed a reduction in heavy drinking days, craving and gamma-glutamyl transferase and carbohydrate-deficient transferrin concentrations over time. The 20 mg group experienced more insomnia, dizziness and

confusion, while the 5 mg group also showed more dizziness and the 40 mg group more nausea than the placebo group. Most symptoms were mild. Outcome parameters concerning alcohol intake did not differ between groups. Although there were more symptoms of mild-to-moderate nausea, insomnia and dizziness in the nalmefene groups than in the placebo group, the drug was well tolerated and adverse experiences did not result in excessive trial termination.

Positive findings were obtained in a Finish multicentre, randomized, placebo-controlled trial by Karhuvaara et al. (2007). This study shows significant effects on various drinking outcomes in a sample of heavy drinkers ($N=403$). Concomitant psychosocial intervention was minimal. The risk of heavy drinking decreased significantly compared to the placebo group, as did the levels of serum alanine aminotransferase and gamma-glutamyl transferase. The most common adverse events associated with nalmefene were nausea, insomnia, fatigue, dizziness and alcoholic hangover.

The efficacy of nalmefene was studied in two recent large, adequately powered European randomized controlled trials (Gual et al., 2013; Mann et al., 2013). In contrast to the above-mentioned trials, these studies used an 'as needed' approach with nalmefene 18 (20) mg *vs.* placebo. They followed a harm reduction approach, i.e. abstinence was not the primary goal but reduction of heavy drinking days. No fixed dosing regime was used. The patients could decide whether to take the drug or not on a daily basis, depending on whether they were anticipating alcohol exposure or not. The medication was taken on about half of the days during treatment.

Mann et al. (2013) evaluated the long-term safety and tolerability of as-needed use of 20 mg nalmefene *vs.* placebo over 52 wk in 579 patients with alcohol dependence (ClinicalTrials.gov identification number: NCT00811941). The study showed a significant reduction of daily alcohol consumption and of heavy drinking days. The number of patients who discontinued treatment was significantly higher in the nalmefene group, mostly because of withdrawal of consent in the placebo group and adverse events in the nalmefene group. The main treatment-emerging adverse events leading to dropout were nausea, dizziness, fatigue and headache and the most frequent adverse events in general were dizziness, nausea, fatigue and headache. With respect to secondary parameters, liver values decreased significantly more in the nalmefene group than in the placebo group.

Gual et al. (2013) performed a further placebo-controlled study with a similar design that included 718 patients (358 in the nalmefene group). A total of 218 patients reduced their drinking to 6 heavy drinking days/month or less or below medium drinking risk level already in the period between screening and randomization. On average, patients took study medication on 65% of the days in the main treatment period. The co-primary

efficacy analyses showed a significantly superior effect of nalmefene compared to placebo in the change from baseline to month six in heavy drinking days. A subgroup analysis showed that patients who did not reduce their drinking prior to randomization benefitted more from nalmefene. In addition, reductions in liver enzymes were greater in the nalmefene group. In contrast to the Mann et al. study, the incidence of adverse events leading to dropout was similar in both groups. Recently, van den Brink et al. (2013) presented a combined sub-analysis of data from the Gual et al. (2013) and Mann et al. (2013) studies. Since some patients had already reduced their alcohol drinking before study entry, the authors looked at patients who did not reduce their consumption after the initial assessment. The pooled analysis consisted of 667 patients (332 placebo, 335 nalmefene). There was a significant effect of nalmefene compared with placebo in reducing the number of heavy drinking days and total alcohol consumption as primary endpoints at month six. The overall efficacy of nalmefene as an 'as needed' medication in this population was larger than in the total study population.

A further safety study with nalmefene treatment over 11 yr ('Sense Study') was presented as a poster only at the Annual RSA Scientific Meeting, San Francisco, California, USA, June 23–27, 2012 and confirmed the good safety profile of nalmefene. In addition, Matz et al. (2011) did not find relevant ECG changes or QT prolongation following treatment with nalmefene.

To summarize, the data the two main studies on nalmefene as an 'as needed' medication for alcohol treatment (Gual et al., 2013; Mann et al., 2013) suggest that nalmefene does decrease the number of heavy drinking days and total alcohol consumption. The number of dropouts in the Mann et al. (2013) study, but not in the Gual et al. study (2013), was some 20% higher in the nalmefene group. Although no novel or unexpected adverse events were noted, other than the 'typical' effects seen in opioid antagonist treatment, the limited tolerance of the drug may limit its clinical acceptance. The novel 'as needed' approach is of interest and obviously accepted by many patients as a treatment option. The populations included seem to be rather moderate drinkers compared to other study populations (mean alcohol consumption of about 90 g alcohol). As stressed, with reason, by Gual et al. (2013), there is no clear-cut answer as to what constitutes a clinically relevant magnitude of heavy drinking. They mention the European Medicines Agency's guideline (European Medicines Agency, 2010) on the development of medicinal products for the treatment of alcohol dependence, which states that efficacy should also be evaluated in terms of the difference in the percentage of treatment responders. Since reduction of alcohol drinking is associated with fewer accidents and less suicide, aggression and cardiac arrest (Rehm et al., 2010), nalmefene or similar drugs may help reduce the risk for these events.

Pharmacogenetics

Over 100 variants of the mu-opioid receptor gene have been identified (Lotsch and Geisslinger, 2005; Somogyi et al., 2007). The most common and clinically relevant single nucleotide polymorphism is A118G, which results in an amino acid exchange at position 40 from asparagine to aspartate (Bond et al., 1998). Genetic studies in alcoholism have provided conflicting results concerning the relevance of the functional variant 118G allele in exon 1 of the OPRM1 gene for the vulnerability risk for alcoholism (Bart et al., 2005b; Nishizawa et al., 2006; Barr et al., 2007; Gelernter et al., 2007; Job et al., 2007; van den Wildenberg et al., 2007; Koller et al., 2012). An association of variations in the kappa-opioid system with alcohol dependence has also been described (Xuei et al., 2006). The OPRM1 118G genotype may moderate the subjective and neuronal response of opioid antagonists on alcohol and alcohol cue reactivity (Ashenhurst et al., 2012; Setiawan et al., 2012; Schacht et al., 2013) and modify response to treatment with opioid antagonists such as naltrexone, although there are conflicting results (Oslin et al., 2003; McGeary et al., 2006; Gelernter et al., 2007; Anton et al., 2008, 2012; Kim et al., 2009; Koller et al., 2012; Oroszi et al., 2009; Kranzler et al., 2013). A recent meta-analysis supported the role of the A118G polymorphism of the OPRM1 gene in moderating the effect of naltrexone in patients with alcohol dependence and treatment response (Chamorro et al., 2012).

For nalmefene, a *post-hoc* analysis of the Karhuvaara et al. (2007) study (Arias et al., 2008) did not identify main or moderating effects of the genotypes on drinking outcomes.

Conclusion

Nalmefene is the first new medication for alcoholism in over a decade and one of the very few in general that was been approved for the treatment of this condition. There is a sound scientific basis and rationale for the use of opioid antagonists in alcoholism. Nalmefene has a different receptor profile than the 'pure' mu-opioid receptor antagonist naltrexone. Much fewer preclinical and clinical data are available for nalmefene (Medline count for nalmefene/alcohol was 66 hits) than for naltrexone (1617 hits). Previous studies have used different dosages of nalmefene and found that the 20 mg tablet is as effective as higher dosages but has fewer side effects.

The recent meta-analyses on opioid antagonists by Rosner et al. (2010a), which included the early nalmefene trials, and Maisel et al. (2013) indicate that opioid antagonists reduce alcohol consumption and heavy drinking days rather than promote abstinence in alcoholism. Subsequently, the two more recent studies with nalmefene followed a harm-reduction approach (Gual et al., 2013; Mann et al., 2013). Few medications have focused on a reduction in consumption (for a review, see Aubin

and Daepfen, 2013). For the first time, a so-called anti-craving drug was tested in this 'as needed' setting. The European Medicines Agency recently approved nalmefene for the treatment of alcoholism, but nalmefene is not yet marketed for use in alcohol dependence in the USA. Head-to-head comparisons with acamprosate and naltrexone are not yet available. The side effect profile of nalmefene corresponds to that typically found in opioid antagonists (Rosner et al., 2010a), with nausea probably being the most significant problem. The interesting question will be how to integrate this novel treatment strategy into conventional alcohol treatment programmes and how to identify patients who might especially benefit from this kind of treatment. Although the drug is primarily approved for treatment of alcohol dependence, one might consider testing nalmefene also in patients with alcohol misuse or harmful use to prevent them from slipping into dependence. Other areas might be relapse prevention after alcohol treatment and treatment of patients with an excessive 'binge drinking' consumption style. These clinical options remain speculative until nalmefene has been tested in these special areas. Nalmefene appears to be an effective treatment for alcohol dependence that clinically may at least have some safety advantages over naltrexone with respect to hepatotoxicity. Its partial agonist effect at the kappa receptor is of scientific interest concerning alcohol intake and depression/dysphoria but must be studied in more detail. Its effect on relapse to heavy drinking compared to naltrexone and other anti-craving compounds has to be studied in head-to-head comparisons and comparative meta-analyses.

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