

Drugs for relapse prevention of alcoholism: ten years of progress

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Multiple neurochemical pathways are involved in mediating craving and relapse to alcohol. Opioidergic and glutamatergic systems have a key role in alcoholism, as demonstrated by the clinically effective compounds naltrexone and acamprosate acting through these systems. The dopaminergic system has long featured in alcoholism research; hitherto disappointing results from clinical studies could improve following the discovery that dopamine D3 receptor antagonism produces consistent and robust results in preclinical studies. Corticotropin-releasing factor signalling and the endocannabinoid system integrate stress-related events and thereby mediate relapse behaviour. Overall, these new targets have yielded several compounds that are undergoing clinical testing. However, the heterogeneity in treatment response makes it necessary to characterize genetic and protein markers and endophenotypes for individualized pharmacotherapy.

Health and socioeconomic consequences of alcoholism

Alcoholism is one of the most prevalent neuropsychiatric diseases, having an enormous health and socioeconomic impact. Chronic alcohol consumption contributes to a multiplicity of medical indications, including addiction and damage to organ function. Alcohol use and misuse affects all social groups, and in an estimate of factors responsible for the global burden of disease, alcohol contributes to 3.2% of all deaths worldwide [1]. Moreover, the percentage of the total disability-adjusted life years (DALYs – calculated by adding the years of life lost due to premature mortality and the years of life lost due to living with disability) of the world population caused by chronic alcohol consumption has been estimated to be as great as 4.0% (AIDS, in comparison, accounts for 2.2%).

Addiction to alcohol entails not only deleterious consequences to the physical and psychological health of afflicted individuals, but also serious societal and economic fallouts in the form of criminality, decreased productivity and increased healthcare costs. As a consequence, on a worldwide scale, typically 6% of the gross domestic product of an industrialized nation is spent on alcohol use and misuse (i.e. the cost of treatment for and consequences of addiction) [1].

Modelling alcohol craving and relapse in animals

Addictive behaviour associated with alcoholism is characterized by craving for alcohol, loss of control over consumption, and the development of tolerance and dependence, while simultaneously the repertoire of social functioning unrelated to intake behaviour declines dramatically. Moreover, alcoholism is a chronic relapsing disease; even after long periods of abstinence from alcohol, the risk of relapse remains great. Whereas prevention of relapse was often considered the ultimate treatment goal in the past, in recent years there has been a conceptual shift towards the reduction of hazardous drinking. From a clinical view, this shift enables a more pragmatic treatment focused on the reduction of harm caused by alcohol intake and improvement in social functioning.

Characteristics of an addictive behavioural syndrome, such as alcohol-seeking behaviour and relapse-like drinking, can be modelled satisfactorily in laboratory animals. In both humans and animals, potent triggers of relapse are stress, conditioned cues and priming doses of alcohol. The most common procedure to study alcohol-seeking behaviour in animals, representing one dimension and a measurable translation of craving, is the so-called reinstatement model [2]. In this procedure, an animal is trained to self-administer alcohol and is then subjected to extinction – that is, the animal is tested under conditions of nonreinforcement until operant responding is extinguished. Following extinction, conditioned stimuli, stress or alcohol priming can reinstate alcohol-seeking behaviour. Importantly, the reinstatement model has been pharmacologically validated. Thus, acamprosate and naltrexone are known to reduce craving and relapse in alcohol-dependent patients and can also reduce or even block reinstatement of alcohol-seeking behaviour induced by either conditioned cues or alcohol priming [3,4].

The deprivation model, another animal model, enables the study of relapse behaviour [5]. Alcohol-experienced animals show a transient increase in alcohol intake after a period of forced abstinence, which is termed the ‘alcohol deprivation effect’ (ADE). The ADE can be observed in numerous species including mice, rats, monkeys and humans, and shows a great degree of reliability. The fact that the clinically effective antirelapse drugs acamprosate and naltrexone also reduce or even abolish the ADE [6] lends predictive value to this animal model for the development of novel and better drugs as treatments for relapse.

Both animal models have been combined with the use of different alcohol-preferring rat lines (Table 1). This is a

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Table 1. Alcohol-preferring rat lines developed to study putative anticraving and antirelapse compounds^a

Line	Breeder	Daily intake 10% EtOH (g/kg/day)	Generation	Publications
UChA/UChB	University of Santiago, Chile	4–7	>100	57
AA/ANA	NPHI, Helsinki, Finland	5–6	>90	>100
P/NP	Indiana University, USA	5–8	>50	>100
HAD/LAD	Indiana University, USA	9.5	>35	85
sP/sNP	University of Cagliari, Italy	6	>45	>100
msP	University of Camerino, Italy	7–8	>50	42
WHP/WLP	IPN, Warsaw, Poland	9	>27	9

Abbreviations: IPN, Institute of National Remembrance; NPHI, National Public Health Institute.

^aDifferent alcohol-preferring and non-preferring rat lines have been developed over the last 50 years. These lines are very powerful animal models for testing putative anti-craving and anti-relapse compounds, especially when combined with the ADE and reinstatement model.

powerful approach as, for example, the ADE in alcohol-preferring (P) rats is marked by excessively raised alcohol intake with elevated blood alcohol levels [7]. Also, studies of knockout mice in either the reinstatement or ADE model provide precise information about genes involved in alcohol craving and relapse [8]. However, mice show an elevated rate of spontaneous lever responding, especially during extinction, and only in a few studies has a reliable reinstatement response been established [9]. The measurement of an ADE in mice on a C57BL/6J background is also challenging because these animals already exhibit a markedly elevated basal alcohol intake [10].

In conclusion, there seems to be a good correspondence between events that induce craving and relapse in alcohol-dependent patients and those that provoke similar behavioural phenomena in laboratory animals. Even more important, the pharmacology that underlies craving and relapse seems to include the same pathways in rodents and humans, giving us an ideal basis for the development of novel pharmacotherapies.

Opioidergic compounds and nociceptin: preclinical and clinical findings

The clinically used opioid receptor antagonists naltrexone and nalmefene interfere with alcohol consumption through the blockade of opioid receptors [6]. A recent meta-analysis of 2861 subjects in 24 randomized controlled trials (RCTs) demonstrated that naltrexone significantly decreased, by 36%, the relative risk of relapse compared with placebo [11]. In both humans [12] and laboratory animals [3] naltrexone was shown to reduce cue reactivity, suggesting that this effect is mediated, at least partly, by an attenuation of the mesolimbic response to alcohol-associated cues. However, because opioid antagonistic compounds seem to have a more general balancing effect on reduced impulsive control (e.g. in pathological gambling [13]) it is suggested that a subgroup of alcohol-dependent patients with reduced impulsivity control – the early-onset, predominantly male and novelty-seeking subgroup summarized as Cloninger type 2 – could especially benefit from treatment with naltrexone [14]. However, in contrast to cue-induced craving or reinstatement, stress-induced reinstatement of alcohol-seeking is not influenced by naltrexone [15].

Because naltrexone acts mainly through mu opioid peptide (MOP) receptors whereas nalmefene has selectivity for MOP and kappa opioid peptide (KOP) receptors and somehow has more pronounced effects on alcohol consumption [16], it is suggested that KOP receptors also have a role in alcohol relapse and craving. However, the application

of the KOP receptor antagonist norbinaltorphimine (nor-BNI) did not reduce the ADE, neither under home cage nor operant conditions [17]. In yet another animal model, where raised alcohol consumption is initiated by prior alcohol vapour exposure – the so-called dependence-induced excessive drinking model [18] – nor-BNI treatment actually decreased alcohol intake [16], supporting the hypothesis that in the alcohol-dependent brain the dynorphin–KOP receptor system is dysregulated. Further studies are needed, especially with regard to the application of KOP receptor ligands during reinstatement testing, to make a definite conclusion on whether KOP receptors are a promising target for the treatment of alcoholism.

The nociceptin (orphanin FQ) peptide receptor (NOP receptor) is a G-protein-coupled receptor with great similarity to MOP, KOP and delta opioid peptide (DOP) receptors. Its endogenous ligand, nociceptin (orphanin FQ), however, does not bind to opioid receptors. This neuropeptide system has an antistress and anxiolytic-like function, and reductions in both stress- and cue-induced reinstatement of alcohol-seeking behaviour following intracerebroventricular administration of nociceptin have been demonstrated [19,20]. Moreover, in alcohol-preferring rats, elevated doses of buprenorphine reduced alcohol intake through activation of NOP receptors [21]. These results are in line with clinical evidence showing that opioid addicts under buprenorphine treatment reduce their alcohol intake [22].

Ro 64-6198, a fully non-peptide agonist at NOP receptors with an affinity similar to that of nociceptin, reduces the ADE under operant conditions, whereas NBHZ [naloxonebenzoylhydrazone, or ([5 α]-4,5-epoxy-3,14-dihydroxy-17-[2-propenyl]-morphinan-6-ylidene) hydrazide benzoic acid], a NOP receptor antagonist, augments the ADE [23], suggesting that endogenous nociceptin is involved in relapse behaviour. An association between genetic variations of the NOP gene and alcoholism [24] further points to the potential of NOP receptor non-peptide agonists as antirelapse medications.

Glutamatergic compounds: preclinical and clinical findings

The clinically used ‘antiglutamatergic’ compound acamprosate has been examined in 17 RCTs comprising 4087 subjects. This meta-analysis found a significant (17%) decrease in relative risk of relapse compared to placebo [25]. The trials with a negative outcome, most prominently the US COMBINE trial [26], could provide valuable information on treatment strategies. Whereas positive acamprosate studies included alcohol-dependent patients

Box 1. Mode of action of acamprosate

The antiglutamatergic effects of alcohol intake result in an upregulation of glutamatergic neurotransmission following chronic exposure. During alcohol withdrawal this results in a transitional hyperglutamatergic state associated with craving (Figure 1). Acamprosate exerts its actions through an interaction with NMDA and possibly mGlu5 receptors. Acamprosate can restore the imbalance between excitatory and inhibitory neurotransmission and reduces the hyperglutamatergic state. Hence, it should be called an 'antiglutamatergic' compound.

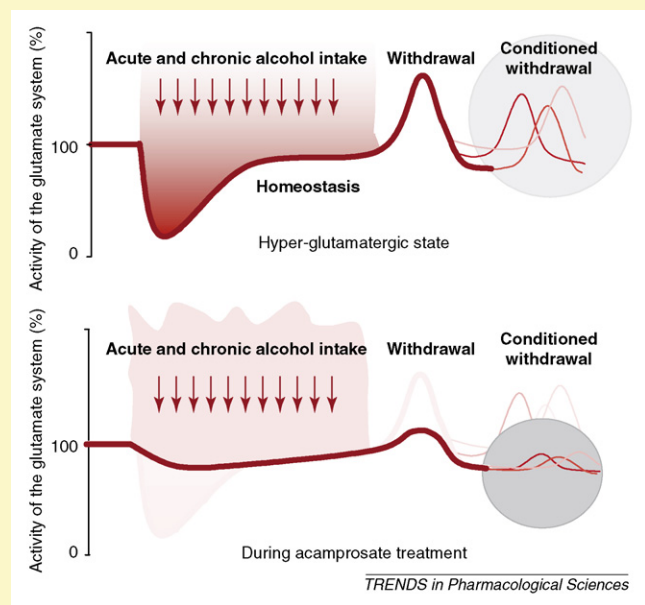


Figure 1. The antiglutamatergic action of acamprosate.

during medically supervised detoxification (generally in inpatient settings), ~98% of patients included in the COMBINE study exhibited no withdrawal syndrome requiring treatment [27]. Several mechanisms of action have been proposed for acamprosate; however, the most convincing evidence has been obtained in relation to the glutamatergic system [6] (for mode of action see Box 1). In particular, it has been demonstrated that this compound acts through attenuation of a 'hyperglutamatergic state' that underlies acute and protracted alcohol withdrawal, and is associated with alcohol craving and relapse [28] (Box 1).

The mode of action of acamprosate provides a good rationale for the glutamatergic hypothesis of alcoholism [29] and suggests further that the blockade of ionotropic glutamate receptors should also reduce relapse and craving. In fact, memantine and neramexane – both *N*-methyl-D-aspartate (NMDA) receptor channel blockers – can dose-dependently reduce the ADE [30]. Both compounds produce ethanol-like effects in animals and humans and attenuate cue-induced craving in a dose-related fashion in alcohol-dependent patients [31], providing a new concept in substitution therapy for alcoholism. A recent RCT with neramexane in 236 alcohol-dependent patients, however, did not improve abstinence rates (G.A. Wiesbeck *et al.*, unpublished). The lack of effect could be the result of the low dose. Given the concept of a substitution therapy, it is obvious that relatively elevated doses of the drug should be applied; however, because of

the relatively small therapeutic window of NMDA antagonists in alcohol-dependent patients this option is limited. NMDA receptors composed of NR1–NR3A subunits exhibit a reduced sensitivity to channel blockers compared with NR1–NR2A receptors [32]. Alcohol-preferring msP rats (Table 1) have enhanced brain levels of the NR3A subunit and are almost insensitive to neramexane treatment (V. Vengeliene *et al.*, unpublished), and markedly elevated expression levels of NR3A are also found in the brain of psychiatric patients [33], underlining our conclusion that NMDA receptor channel blockers can act as a substitution therapy in alcohol-dependent patients only when sufficient doses of these drugs are applied.

Blockade of DL- α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors also dose-dependently reduces cue-induced reinstatement behaviour and the ADE [34]. Using glutamate receptor GluA, B and C knockout mice, it was shown that the GluC receptor subunit is crucial in mediating these behaviours [8,34]. Interestingly, topiramate – an anticonvulsant compound that blocks AMPA and kainate receptors, in addition to having other sites of action – reduces relapse rates in alcohol-dependent patients and the harm of excessive drinking [35]. Moreover, in a recently published study, continuously drinking alcohol-dependent patients reach their abstinence goal significantly faster when treated with 300 mg/day topiramate compared with placebo [36].

Not only ionotropic but also metabotropic glutamate receptors hold great potential for antirelapse medication. Thus, mGlu5 receptor antagonists [MPEP (2-methyl-6-(phenylethynyl)pyridine) and MTEP (3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]-pyridine)] are effective in the reinstatement and ADE models [37] and no tolerance to their antirelapse-like effects develops because MPEP, a selective mGlu5 receptor antagonist, exhibits the same magnitude of effect in the ADE model even after multiple treatment cycles [38]. This is an important finding because tolerance to repeated acamprosate treatment has been reported [39]; however, considering the cognitive deficits repeatedly reported under mGlu5 receptor blockade [29], the clinical usefulness of these compounds has to be clarified in future studies. Activation of group II metabotropic glutamate receptors attenuates both stress- and cue-induced reinstatement behaviour [40] and also the ADE (V. Vengeliene *et al.*, unpublished). These are important findings with respect to the glutamatergic hypothesis of alcoholism [29] because activation of presynaptic mGlu2 and mGlu3 receptors can lower a hyperglutamatergic tone and thereby reduce the risk of relapse. A similar hypothesis applies to schizophrenia; furthermore, the recent milestone publication by Patil *et al.* [41] clearly demonstrates that the mGlu2/3 agonist LY404039 significantly improves both positive and negative symptoms of schizophrenia compared with placebo. These results strongly imply that mGlu2/3 agonists should also be tested in clinical trials in alcohol-dependent patients.

Dopaminergic compounds: preclinical and clinical findings

Dopamine neurotransmission does not have a crucial role in the maintenance of alcohol drinking but it is activated

during reward expectation and conditioned cue response, and under conditions of deprivation and novelty [42]. Thus, dopamine might have a crucial role in cue-induced alcohol-seeking behaviour, suggesting a potential use of dopamine receptor antagonists as candidate medications to reduce craving. In fact, in the reinstatement model, selective antagonists for either dopamine D1, D2 or D3 receptors dose-dependently attenuate cue-induced reinstatement behaviour in rats [43,44] and mice [45]. In the ADE model, testing was restricted to the selective D3 receptor antagonist SB-277011A, which abolished relapse-like drinking behaviour [44]. However, compounds acting primarily through D1 or D2 receptors, such as tiapride, lisuride, bromocriptine and flupentixol, were either ineffective or produced opposing, relapse-promoting effects in randomized, double-blind, placebo-controlled trials. By contrast, the selective blockade of D3 receptors could result in a different clinical outcome, because: (i) D3 receptors exhibit the greatest density in the nucleus accumbens and amygdala – brain areas that are thought to be crucial for the integration and response to the presentation of alcohol-associated cues; (ii) the numbers of this receptor are enhanced in addicted patients and alcohol-dependent animals; and (iii) selective D3 receptor antagonists show a promising preclinical profile, good tolerability and a wide margin of safety. In addition, these compounds have also been tested in a variety of animal models related to nicotine, cocaine and morphine addiction with consistent and reliable results [46]. In light of these findings, clinical trials have now been initiated to test the clinical significance of D3 receptor antagonists.

Corticotropin-releasing factor (CRF) signalling and the endocannabinoid system mediate stress-induced relapse

Heilig and Koob [18] have recently summarized convincing evidence that the corticotropin-releasing factor (CRF) system with its CRF1 receptor is a key element of the neuroadaptive changes driving alcoholism and is therefore a major target for the treatment of relapse behaviour, especially under stress-related conditions. The role of the CRF system is further supported by human genetic studies showing that specific variants of the *CRFR1* gene interact with exposure to stressful life events, and can predict the onset of alcoholism [47]. Interestingly, in genetically selected alcohol-preferring msP rats, similar genetic variations of the *Crhr1* promoter were associated with an upregulation of CRF1 receptors and elevated stress sensitivity [48]. Furthermore, stress-induced reinstatement of alcohol seeking was fully blocked in msP animals by treatment with antalarmin – a CRF1 receptor antagonist [48].

From the clinical perspective it is worthwhile mentioning that the anticraving effect of naltrexone might be, at least partly, associated with its CRF-releasing effects (by disinhibition of CRF-containing neurones in the nucleus paraventricularis) because recent data suggest that the blunted stress response associated with an increased relapse risk in alcohol-dependent patients might be readjusted by CRF-stimulating effects of naltrexone [49].

A crucial role for the cannabinoid CB₁ receptor in stress-induced alcohol consumption has been shown [8,50]. However, the CB₁ receptor antagonist, rimonabant, had no effect on footshock-induced reinstatement but blocked cue-associated reinstatement behaviour [51] and the ADE in alcohol-preferring sP rats (Table 1) [52]. A first RCT with rimonabant in alcohol-dependent patients showed only a trend for less relapse behaviour (M. Soyka, unpublished). In this trial mood problems were common and use-limiting. However, given the elevated incidence of comorbid nicotine smoking in alcoholic patients and the observation that rimonabant shows some efficacy in inducing cessation of smoking [53], CB₁ receptor blockade might be beneficial for at least the group of smoking alcohol-dependent patients.

Heterogeneity in treatment response

Despite the fact that several new antirelapse compounds have entered or will enter the market, a unified treatment response cannot be expected. Addictive behaviour is the result of the genetic and epigenetic make-up of an individual, in addition to the cumulative responses to alcohol exposure and environmental perturbations over time. This complex alcohol × gene × environment interaction leads to considerable clinical heterogeneity, both in terms of symptom dimensions and severity of the disorder, and most importantly also treatment response. Thus, only 20–30% of patients respond to either naltrexone or acamprosate treatment, and it seems unlikely that any other medication would attain a greater percentage in terms of treatment response. Therefore, a real need exists for surrogate clinical readouts, either molecular (biomarkers, such as genetic markers, peripheral protein markers and metabolites) or endophenotypic, which could be used to predict treatment response.

Pharmacogenomics, biomarkers and endophenotypes for improving treatment response

Response to pharmacological treatment can be influenced by genetic polymorphisms of drug target genes. In fact recently it was shown that a functional polymorphism in the MOP receptor gene is associated with enhanced alcohol consumption in male rhesus macaques [54] and that the human equivalent of this gene variant (OPRM1*A118G) predicts naltrexone efficacy, with a large effect size for naltrexone in OPRM1*A118G carriers, whereas no effect was detectable in the majority of A118A homozygotes [55,56]. Such a genetic approach can theoretically be applied to any medication that has a clear target gene (e.g. *CRFR1*). It will, however, be more complicated when multiple target genes are involved in the treatment response, as is the case for acamprosate.

In addition, novel proteomic and metabolomic approaches are becoming increasingly suitable for the development of biomarkers and the definition of endophenotypes and metabotypes. As an example, the use of miniaturized and parallelized sandwich immunoassays (i.e. multianalyte profiling) enables the accurate quantification of several hundred target proteins in human body fluids and has already been successfully applied for the identification of biomarkers for a variety

of diseases including depression and schizophrenia [57].

Using imaging techniques, it has become possible to define neurobiologically relevant endophenotypes and to correlate them with craving, relapse and treatment response. A recent positron emission tomography (PET) study using carfentanil to measure MOP receptor availability showed that abstinent alcohol-dependent patients displayed an increase in MOP receptors in the nucleus accumbens, which correlated with the severity of alcohol craving [58]. To improve the treatment response for acamprosate, glutamate spectroscopy is currently applied, and it is hoped that patients with raised glutamate levels will respond to this treatment. The most powerful approach, however, will be neuroimaging genetics [59]. Here, for example, genetic variations of target genes can be associated with the processing of alcohol-related stimuli and might thereby define subgroups of patients that ultimately respond better to treatment.

Future perspectives: systems medicine and combining pharmacotherapies

Given that multiple gene and epigenetic effects, multiple endophenotypes and a variety of environmental interactions are responsible for treatment response, it is obvious that a reductionist approach is impractical. Instead, real progress will be made by the definition of objective clinical end points for the application of individualized treatments, and by a systems medicine-oriented perspective in which the interactions and dynamics of all endogenous and environmental factors involved are centrally integrated [60].

Knowing that antirelapse compounds act through different neurochemical systems, an additional benefit might arise from combining different compounds. In fact, two clinical studies demonstrated that a combination of naltrexone and acamprosate can be more effective than either drug alone [61,62]. These findings, however, were not replicated in the COMBINE study, which included 1383 alcohol-dependent patients treated with a combination of both compounds and behavioural interventions [26]. The reason for this negative finding is most probably due to a recruitment bias of subjects with moderate severity and early stages of alcoholism, which defines a group of patients who are more responsive to naltrexone than acamprosate treatment [27,63].

In conclusion, we suggest that a 'cocktail' of different pharmacotherapies in conjunction with behavioural interventions will further improve the treatment situation. However, even if further breakthroughs in the field of pharmacological anticraving and antirelapse prevention occur in the near future, it remains questionable whether these drugs will enter the market. Thus, one major question remains, namely, why are these medications so rarely prescribed compared with other psychopharmacological therapeutics [64]? One issue might be hesitancy by the pharmaceutical industry about using appropriate marketing strategies, in addition to a continuing low level of investment in further drug development. Preclinical research can validate many good treatment targets; however, unless the pharmaceutical industry gets onboard to

bring forwards molecules with drug-like properties for these targets, no clinical development can happen. Moreover, if such molecules are brought forwards without defining the correct target populations, even effective molecules will disappoint because effect sizes will get diluted across populations – acamprosate is a good example in this respect [65].

A further problem that adds to the low prescription rates could be the view of the general public that alcoholism is a 'behavioural disorder' and as such is the sole responsibility of the affected individual. This stigma is reinforced by the majority of professionals in the addiction field including social workers, psychotherapists, members of self-help groups and counsellors, who are hesitant in promoting the use of medication [64]. The only way out of this dilemma is a more effective dissemination of information and educational marketing from public policy-makers and professional organizations. The main player in the future in this regard could be the pharmaceutical industry, but only if it resolves to conquer this potentially lucrative market, with the main beneficiaries being the patients themselves.

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