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REVIEW

Critical thoughts on current rodent models for evaluating potential treatments of alcohol addiction and withdrawal

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Despite years of neurobiological research that have helped to identify potential therapeutic targets, we do not have a reliable pharmacological treatment for alcoholism. There are a range of possible explanations for this failure, including arguments that alcoholism is a spectrum disorder and that different population subtypes may respond to different treatments. This view is supported by categorisations such as early- and late-onset alcoholism, whilst multifactorial genetic factors may also alter responsivity to pharmacological agents. Furthermore, experience of alcohol withdrawal may play a role in future drinking in a way that may distinguish alcoholism from other forms of addiction.

Additionally, our neurobiological models, based largely upon results from rodent studies, may not mimic specific aspects of the human condition and may reflect different underlying phenomena and biological processes from the clinical pattern. As a result, potential treatments may be targeting inappropriate aspects of alcohol-related behaviours. Instead, we suggest a more profitable approach is (a) to identify well-defined intermediate behavioural phenotypes in human experimental models that reflect defined aspects of the human clinical disorder and (b) to develop animal models that are homologous with those phenotypes in terms of psychological processes and underlying neurobiological mechanisms.

This review describes an array of animal models currently used in the addiction field and what they tell us about alcoholism. We will then examine how established pharmacological agents have been developed using only a limited number of these models, before describing some alternative novel approaches to achieving homology between animal and human experimental measures.

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Alcoholism

The term alcoholism has been defined as 'a primary, chronic disease characterized by impaired control over drinking, preoccupation with the drug alcohol, use of alcohol despite adverse consequences, and distortions in thinking' (Morse and Flavin, 1992). For the purpose of this paper, the term is used as synonymous with alcohol addiction. This definition has much in common with both the Diagnostic and Statistical Manual 4th Edition (DSM-IV) (American Psychiatric Association, 1994) and International Classification of Diseases, 10th edition (WHO, 1973) descriptions of substance dependence that emphasize tolerance, withdrawal, taking the substance in larger amounts than intended, desire to reduce intake, excessive time taken in obtaining the drug or recovering from its effects, diversion of effort from previously important activities and persistent use despite knowledge of harm. Within this description, one can identify the main aspects of addiction: on the one hand, physical dependence and tolerance, and on the other, criteria that reflect an overarching phenomenon, loss of control of drug taking. In the case of alcoholism, continued drinking despite serious family, health or legal problems; taking alcohol in larger amounts or over a longer period than was intended; occurrence of a persistent desire for alcohol; or unsuccessful efforts to cut down or control its use, and spending excessive time in activities necessary to obtain alcohol,

consume it, or recover from its effects. This latter group of criteria, when they occur without evidence of dependence, tolerance or compulsive alcohol-related behaviour, are also referred to in DSM-IV as alcohol abuse. While the term 'dependence' is theoretically neutral (adaptive changes that result in adequate function only in the presence of the drug), loss of control may arise from several underlying causes, to which different theories lend different weights.

Although such descriptors characterize the clinical features of alcoholism, they are not intended to provide an account of how such phenomena arise and certainly do not attempt to provide a theoretical account of the ontogeny of alcoholism, or a means of treating it. At best, they point to those aspects of the disorder that require addressing by potential treatments. Even if it proves possible for alcoholics to achieve abstention from drinking, maintaining abstinence is difficult. This inability to maintain reduced levels of alcohol use is often referred to as relapse and consists of a process by which an abstaining individual slips back into old behavioural patterns and substance use. Relapse is often initiated by the abstaining alcoholic encountering 'reminders' of the drug (exposure to drug-related cues), for example being in the presence of drugs or alcohol, drug or alcohol users, or places where drugs are bought or used. Another precipitating factor can be negative affect – experiencing depressed or anxious mood, or exposure to stressful situations. Relapse prevention has been a major target in the development of pharmacological treatments for drug abuse. Nevertheless, despite considerable progress in understanding the underlying behavioural indices of alcoholism, as well as molecular and cellular mechanisms of sensitization (increased sensitivity to drug effects), tolerance (decreased sensitivity to drug effects), dependence (adaptive changes that result in adequate function only in the presence of the drug) and withdrawal (the experience of disturbed function when the drug is no longer present), there is still a large amount of work to be done in understanding the behavioural and neural substrates of compulsive drug use.

Alongside alcoholism, there are several aspects of alcohol abuse that fail to meet DSM-IV criteria but which nevertheless pose problems for the individual and society. Health and regulatory authorities use a number of ways to define heavy drinking; for example, in many countries, it is illegal to drive with blood alcohol levels exceeding 50 or 80 mg·dL^{-1}. In the UK, government recommendations indicate that consumption in excess of 4 units of alcohol per day for a man, or 3 units for a woman, is likely to result in health problems (one UK unit is defined as 10 mL of pure ethanol; note that other countries have other definitions). Binge drinking is a particular pattern of alcohol consumption where individuals consume excessive amounts of alcohol over a limited period of time. This leads to a rapid increase in blood alcohol concentrations and results in drunkenness. In the UK, government guidelines define binge drinking as consumption of twice the daily benchmark allowance (http://www.parliament.uk/documents/post/postpn244.pdf). Other common definitions of binge drinking refer to blood alcohol levels in excess of 80 mg·dL^{-1} on a given drinking occasion (Lange and Voas, 2000; NIAAA, 2004). Some alcoholic patients reach and maintain blood alcohol levels in excess of these levels for protracted periods of time.

Several pharmacological medications have been developed for supporting abstinence from excess alcohol intake and are currently available by prescription. Drugs currently prescribed in the UK include acamprosate, naltrexone and disulfiram. However, the effectiveness of these treatments is not universal across alcoholic patients (Egli, 2005; Heilig and Egli, 2006; Johnson, 2008; Johnson, 2010), suggesting that a single treatment for all forms of alcoholism may not be possible. For instance, only 20–30% of patients respond to either naltrexone or acamprosate. Addictive behaviour is likely to be influenced by both genetic and epigenetic factors, as well as the consequence of long-term exposure to alcohol and withdrawal (Spanagel and Kiefer, 2008), and such a complex interaction between genes and the environment may well account for the clinical heterogeneity. A number of attempts have been made to classify different forms of alcoholism that are likely to have different aetiologies. One familiar example is that of Cloninger (1987) who described two forms of alcoholism, type 1 that arises in mid-life, may be related to anxiety disorders, and is only weakly familial, and type 2, that appears to be largely hereditary, found usually in males, of early onset, and characterized by violent behaviour. Inasmuch as different forms of alcoholism may have quite different genetic bases, it seems possible that they will respond to different pharmacotherapies. Current developments suggest that predicting treatment response to at least one current treatment (naltrexone) may be possible through the discovery of a range of biomarkers, including genetic markers, and endophenotypes.

Thus, the development of an array of pharmacological relapse treatments, which can be tailored for these individual differences, may be required. Animal models may be used to screen potential new medications and to identify aetiology but are inevitably limited as no single model can capture all features of alcoholism, or types of alcoholism. However, certain features of the human disorder can perhaps be captured in a model. This review will consider factors that have been suggested to lead to alcohol addiction. It will then examine a range of animal models that have been developed to address some of these different factors. Finally, the review will look at current and potential treatments for alcoholism and how they perform in different animal models.

Theories behind why people become alcoholics

We do not yet have a universally accepted theory of addiction, and it may well be that no single theory can adequately account for such a complex and multifactorial phenomenon. Many individuals happily consume alcohol, even to excessive levels on occasion, with few long-term harmful effects. For others, alcohol consumes their lives.

Factors that predict an individual's vulnerability to alcoholism have been studied in length including family history, genetics, behavioural traits and social–economic background. Psychological traits such as impulsiveness, low self-esteem and a need for approval can prompt inappropriate drinking, whilst others drink to cope with emotional problems. Social and environmental factors, including the availability of alcohol, can also play key roles. Once a cycle of excessive drinking is established, the problem can perpetuate itself,

with heavy drinking leading to psychological and physiological changes that contribute to further drinking.

These multiple aspects of alcoholism have led to the development of many theoretical models as to why people become addicted to alcohol. Whilst these models often disagree about the key psychological processes underlying the aetiology of substance abuse and addiction, they often agree on the involvement of a number of recognizable subcomponents (see Stephens *et al*., 2010 for a brief overview). In very basic terms, the 'motivation' to consume alcohol can reflect both the seeking of the rewarding aspects of drug and the avoidance of the negative aspects of drug withdrawal. Within the clinic, it is accepted that certain individuals drink for the euphoric effects of alcohol, whilst others drink to alleviate anxious moods (Booth and Hasking, 2009; Goldsmith *et al*., 2009). Ray *et al*. (2009) developed these ideas further and proposed a three-factor model, capturing the dimensions (1) stimulation and other pleasant effects, (2) sedative and unpleasant effects and (3) alleviation of tension and negative mood.

Factors influencing motivation to consume alcohol

A classical view of alcohol abuse is that alcohol is taken because it has rewarding effects. However, the nature of these effects is not clearly defined and indeed may vary across individuals. In practice, reward value probably represents an aggregate measure resulting from the experience of 'euphoria' and 'feelings of high', as well as those more related to relaxation, satisfaction and fulfilment, relief from tension and craving. Measures of reward value can differ substantially among individual subjects (Schuckit, 1984; Schuckit, 1994) and may represent a heritable trait (Viken *et al*., 2003). However, even within these subcategories of reward, additional factors such as dose and pharmacokinetic time course may influence the drug experience. Thus, the euphorigenic effects of alcohol are often associated with rising blood alcohol levels (e.g. (Martin *et al*., 1993; Erblich *et al*., 2003), while declining levels are more likely accompanied by sedation (Earleywine, 1994a; Earleywine, 1994b; Erblich *et al*., 2003). Additionally, these measures often rely upon subjective self-assessment (self-report) of mood states, assessed using questionnaire-type tools, for example the Profile of Mood States (POMS; McNair *et al*., 1971). However, even within the human literature, the results obtained from application of different rating scales are not entirely consistent (Ray *et al*., 2010), and there is long-standing evidence to indicate that human subjects have poor conscious access to and/or cannot reliably report to us about their affective states (Nisbet and Wilson, 1977). This fundamental problem is even more evident when researchers have to rely on retrospective reports as even brief delays between the actual experience and reporting produce pronounced biases (Schwarz, 2007). For these reasons, animal models that seek to mirror rewarding effects of alcohol in humans, whether social drinkers or clinically dependent individuals, are difficult to interpret and generalize to the human.

The role of conditioning

Despite difficulties in defining the nature of alcohol 'reward', a view common to several accounts of addictive processes emphasizes the role of environmental events (cues) that have become conditioned to the 'rewarding' effects of drug (including alcohol) ingestion in initiating future alcohol seeking and drinking. Some of these theories are outlined briefly below:

Positive-incentive (sensitization) theories of addiction

According to Stewart *et al*. (1984b), learned Pavlovian associations between drug-induced positive effects (e.g. hedonia) and stimuli in the environment (simple and/or contextual stimuli) that predict them endow these drug cues with the ability to directly access the mental representations of the drug and, like the drug itself, make them attractive, 'wanted' and able to trigger appetitive drug-directed responses. Such a conditioned incentive account does not in itself distinguish between processes that lead to 'normal' seeking for rewards such as food and those that contribute to drug addiction, but an addition to the theory, proposed by Robinson and Berridge, 1993, holds that, unlike 'natural' rewards, drugs, including alcohol, additionally sensitize the brain mechanisms that underlie incentive behaviours, so that cues associated with drug taking come to have greater effects on incentive for drug than do cues associated with 'natural' rewards (Stewart *et al*., 1984a; Robinson and Berridge, 1993).

Transition to habit

Many addictions are described informally as 'drug habits', but this term also has a specific meaning within theoretical accounts of drug taking. Within psychology, 'habit' has a well-characterized meaning and refers to the increasing automatization of behaviours that are repeated frequently, so that they may be initiated without conscious thought, or even awareness (Atkinson and Shiffrin, 1971). Tiffany (1990) described the transition in drug-taking behaviour from a state of drug seeking, where behaviour is driven by the outcome of the drug-taking behaviour (i.e. reward, or relief from aversive withdrawal states), to a state of automated habit, where the behaviour is insensitive to the consequences of drug taking as individuals report becoming increasing 'unaware' of their drug-seeking and drug-taking behaviour (see Tiffany, 1990). This shift in behaviour away from conscious control of the kind described by Stewart *et al*. (1984b), to an automatic process initiated by encountering the drug cue, may be associated with a shift in the neurobiological mechanisms that underlie the two processes from circuits including the ventral striatum to those involving dorsal striatum (Everitt *et al*., 2008). A contributing factor to this shift in behavioural control may additionally involve cognitive decision-making and/or inhibitory control processes critically dependent on prefrontal cortical function (Duka *et al*., 2004; Stephens *et al*., 2010), resulting in behavioural inflexibility (e.g. inability to withhold a drug-elicited response, or failure to integrate novel factors into control of behaviour) and/or insensitivity to changes in outcome value (devaluation).

Factors influencing the drive to avoid the negative aspects of alcohol withdrawal

In contrast to hypotheses that view alcohol abuse as being driven by the positive effects of the drug, a number of hypotheses view drug and, especially, alcohol addiction as resulting from the negative consequences in the dependent individual of not taking drug. Long-term consumption of large amounts of alcohol results in biological adaptations to the presence of the drug that result in the development of tolerance and dependence, revealed as withdrawal signs and symptoms on cessation of use. Withdrawal episodes themselves result in long-term neurobiological changes that impact on brain function, with the types of repeated patterns of alcohol intoxication and withdrawal seen in binge drinking causing the most severe damage to neurobiological processing. Initial symptoms of alcohol withdrawal include dysphoria, insomnia, anxiety, nausea and irritability. More severe symptoms are seen in individuals with previous episodes of withdrawal and include seizures and delirium. The long-term nature of many of these withdrawal symptoms and the ability to trigger withdrawal-like effects on exposure to cues associated with drug taking or withdrawal are associated with relapse potential. Two theories that focus on the withdrawal prevention aspects of alcohol relapse are outlined below.

Opponent process-type theories

The opponent process theory (Solomon and Corbit, 1974) focuses on the ability of drug-associated stimuli to trigger physiological and psychological experiences of drug withdrawal, which drive drug-seeking behaviours in order to resolve the aversive state. In a variation of the theory (the Allostasis model), Koob and Le Moal (2008) propose that prolonged cycles of drug taking and withdrawal lead to a general state of anhedonia, so that only very powerful rewards (such as drugs) would be capable of overcoming this state (Koob, 1992). Such an account allows an understanding of why, after long-term drug use, and in the absence of drug-induced positive effect, drug seeking nevertheless takes place. Additionally, the theory clearly predicts that addiction is associated with both decreased ability to experience 'reward' and increased motivation to obtain it. In keeping with this theory, abstinent alcoholic patients report increased negative mood and also show attentional biases to words with negative emotional meaning (Duka *et al.*, 2002). They also show exaggerated brain responses to negative affective stimuli and reduced or eliminated responses to positive stimuli (Gilman and Hommer, 2008).

However, this theory would also predict that addicts would be less sensitive to the rewarding properties of the drug, yet we are unaware of specific evidence in support of this phenomenon, and indeed, occasional studies have reported an increase in drug liking with increasing drug experience (e.g. Willner *et al.*, 2005).

Loss of control

In recent years, an additional component has been added to explanations of addiction as it has become recognized that drug taking (and, at least in the case of ethanol, also withdrawal) leads to changes in function of prefrontal cortical mechanisms that exert 'top-down' control over drug taking. Such mechanisms are normally involved in monitoring appropriateness of ongoing behaviours and may act normally to prevent events such as reward-conditioned cues from initiating reward seeking and taking. Loss of such mechanisms will lead to loss of control over behaviours initiated by such cues, especially if they have become powerful as a result of the events described in the preceding paragraphs. Such top-down processes can be seen as increased impulsivity in decision making (doing without thinking) and control of drug taking. There is increasing evidence that drug addicts may show deficits in such control mechanisms, either premorbidly, or as a consequence of long-term drugs use and/or of repeated experiences of withdrawal from the drug (Volkow *et al.*, 2003; Stephens and Duka, 2008; Duka *et al.*, 2011).

Animal models

Considering the broad range of theories to account for the initiation and maintenance of drug-taking behaviour, it is hardly surprising that the definitive animal model of 'alcoholism' does not exist. Research scientists repeatedly claim to have developed models that mimic particular aspects of alcoholism, but a true model where the animal consumes alcohol in a similar drinking pattern and quantity seen in humans, that escalates in drinking to compulsive levels and that results in repeated bouts of drinking despite intense adverse effects, including withdrawal, has not been established. Animals do not develop alcoholism; neither do they abuse alcohol. Thus, an approach that attempts to directly model either of these human disorders in animals is doomed.

Animal models can therefore vary in the 'degree of validity' with which they mimic the human condition. Models with *predictive validity* allow the identification of treatments on the basis that drugs that have been found to be useful in the treatment of alcoholism also have an effect in the animal model. This does not necessarily show that the measured behaviour directly contributes to addiction processes. Animal models that have *face validity* include behaviours that have some resemblance to, or postulated role in, the addiction process, though the attribution of 'face similarity' must remain subjective. Drugs that change such behaviours have also been shown to be useful in the treatment of alcoholism, but, as will be discussed below, there are a number of cases in which treatments have been active in such models but have not been found to be effective in the clinic. For that reason, a more sensible approach may be to identify aspects of behaviour that are fundamental to the addiction process (biomarkers or intermediate behavioural phenotypes) (Duka *et al.*, 2010) and to establish animal models that are homologous with these processes. These markers must contribute to addictive behaviour, and the animal model needs to be homologous with a human laboratory model.

It should also be remembered that rodents and humans differ markedly in their ability to metabolize alcohol, so that attempts at equalizing consumption (say on a body weight basis) simply do not allow parallels in blood alcohol concentrations over a 24 h time period. Creative ways of inducing

high blood alcohol levels in rodents have had to be developed to mimic alcohol consumption akin to binges and blackouts in humans. The extent to which these result in behavioural and neurobiological consequences that parallel the consequences of alcohol abuse in human is not clear and probably varies across method, though some are surprisingly accurate in their ability to mimic or even predict the consequences of alcohol abuse in humans. Thus, for example, our method of repeated episodes of withdrawal from a chronic ethanol diet in the rat, gives rise to impaired fear conditioning (Stephens *et al.*, 2001), a phenomenon that was subsequently sought for and confirmed in alcoholic patients who had undergone repeated detoxifications (Stephens and Duka, 2008); the same rat model identified a cognitive deficit in the negative patterning test (Borlikova *et al.*, 2006) that we have subsequently found to occur in repeatedly detoxified alcoholic patients, and which we have identified as resulting from withdrawal-associated loss of grey matter in ventromedial prefrontal cortex, and superior frontal gyrus (Duka *et al.* 2011).

Consumption models

Three basic animal models of ethanol consumption and seeking have been described: (1) free-choice (voluntary) consumption; (2) operant self-administration; and (3) a relapse model in which reinstatement of ethanol seeking follows a period of extinction of operant self-administration. Small changes in experimental paradigm, such as duration of access and ethanol concentration, and genetic influences can dramatically alter behaviour in these models. A history of dependence has been shown to enhance ethanol intake in each of these models (see Leeman *et al.*, 2010 for review).

(1) Voluntary consumption models

The most commonly employed model for studying reward value in laboratory animal alcohol research is the simple measure of consumption. Such models fall into two main categories, the two bottle free choice paradigm and drinking in the dark (Roehrs and Samson, 1981; 1982; Grant and Samson, 1985; Samson, 1986; Tolliver *et al.*, 1988; Rhodes *et al.*, 2005).

Two-bottle choice paradigm. With the exception of a few selective inbred strains, rodents have an inherent dislike of the taste of alcohol and will usually avoid consuming it. However, they can be trained to drink relatively large volumes of alcohol using a sucrose-fading technique, which resembles the typical pattern of human alcohol use often beginning with sweetened cocktails (alcopops) or cider, before progressing to more 'adult' unsweetened drinks. In the two-bottle choice paradigm, animals have access to two bottles; one contains an ethanol solution, and the other contains a non-ethanol beverage (usually water). Access to alcohol can be presented on either a limited or *ad libitum* basis. This technique provides a relatively course measure on consumption (Heilig and Koob, 2007) and is viewed as not useful as a measure of the motivational component of behaviour (Tabakoff and Hoffman, 2000), because the effort required to obtain ethanol is so minimal that it cannot differentiate different levels of willingness to work for the reward.

Although rats have been most frequently used in this model, a limited number of studies have employed mice, and such models have been frequently used to study both genetic influences on alcohol self-consumption (e.g. Stephens *et al.*, 2005) and to test the potential of novel pharmacological approaches to treating alcohol abuse (e.g. Middaugh *et al.*, 2000).

C57BL/6 mice drink considerable amounts of alcohol, typically 10–15 $g \cdot kg^{-1}$ ethanol per day in the 24 h two-bottle choice test. Even when water is freely available, these mice will take all their daily fluid from a bottle containing 10% ethanol. C3H/He mice drink much less alcohol under the same conditions (Wahlsten *et al.*, 2006). Such genetic models provide a useful simple model for assessing the effects of novel agents on ethanol consumption. Similar approaches use rat strains selectively bred for high and low alcohol consumption. Note that from such data, we cannot interpret the degree to which a treatment alters the 'reward' value of alcohol. We could conclude that increased alcohol consumption reflects an effect of the drug in reducing reward, so the animals drink more, but equally, reducing the reward value may result in reduced drinking.

It should also be noted that differences in consumption might also reflect differences in sensitivity to aversive effects. In fact, a recent review of the genetics of conditioned taste aversion (CTA) suggests a strong genetic relationship between sensitivity to the CTA-inducing effects of ethanol and ethanol intake/preference in rodents (Cunningham *et al.*, 2008).

Additionally, in 24 h two-bottle choice experiments, alcohol-'preferring' strains such as C57BL/6J mice drink sporadically over the 24 h period, leading to relatively low blood alcohol levels, rarely sufficient to induce motor impairments (Dole and Gentry, 1984). Therefore, this test fails to model one of the main characteristic features of human alcoholism, repeated excessive ethanol consumption to the point of intoxication.

Drinking-in-the-dark (DID). A recently developed procedure in mice, drinking-in-the-dark (DID), has aimed to overcome this problem. In this procedure, mice are given access to ethanol for a short period of time during the early phase of the dark period (Rhodes *et al.*, 2005). Using this method, C57BL/6J mice reliably drink to behavioural intoxication, reaching blood ethanol levels above 1 $mg \cdot mL^{-1}$ (Kamdar *et al.*, 2007; Rhodes *et al.*, 2007). A similar approach, and similar success in achieving high blood alcohol concentrations, is taken with other limited access models using alcohol-preferring strains (Grahame and Grose, 2003). However, it should be noted that in both these models, mice are given limited access to ethanol, whereas humans control the availability of their alcohol. Furthermore, it is not known whether the mechanisms underlying drinking in these models resemble those underlying high alcohol intake in alcoholics. Therefore, drug treatments that are effective in reducing alcohol intake in these rodent models can only provide us with limited information as regards their likely effectiveness in human alcoholism.

As human alcohol consumption is strongly influenced by social factors, it seems highly unlikely that the factors controlling consumption in humans and experimental animals

are homologous. While there is an extensive literature on alcohol effects on rodent and primate social behaviour, especially aggression, on the whole, this literature has not concerned itself with investigating potential treatments for alcohol abuse. The extent to which such rodent models are homologous with social stresses in humans and how these might relate to control over alcohol intake is thus a question for further work.

(2) Operant self-administration

In operant models, the animal must perform an arbitrary response, often in the form of lever presses or nose poking into a small detection hole, in order to obtain ethanol. By definition, the ethanol is acting as a 'reinforcer' of the arbitrary behaviour. Rates of responding for the reinforcer provide an index of the animal's motivation to obtain the drug. Motivational (desire, wanting) rather than consummatory (taking) components of self-administration behaviour can therefore be measured (Tabakoff and Hoffman, 2000).

By varying the schedule of reinforcement, it is possible to measure different aspects of motivation. One commonly used schedule used to investigate the effects of drug on motivation to drink is the progressive ratio (PR) schedule, in which the instrumental response requirement to obtain an ethanol reinforcer is progressively increased until the animal ceases to respond (breakpoint) (Brown *et al.*, 1998). However, this schedule is highly influenced by drug effects on locomotor activity, with break points for ethanol reinforcement being lower than those with psychostimulant reinforcement (Brown and Stephens, 2002).

(3) Relapse models

Environmental stimuli that have become associated with the subjective effects of ethanol are thought to play a critical factor in the relapsing nature of alcohol addiction. Exposure to these cues, stress or a small priming dose of alcohol can lead to an increase in the urge to drink, which can result in relapse in detoxified alcoholics (Ludwig and Stark, 1974; McCusker and Brown, 1990; 1991; Staiger and White, 1991; Monti *et al.*, 1993). This relapse-like drinking behaviour can be modelled in the animal laboratory. Le and Shaham (2002) highlighted two relapse models in the rat: reinstatement and alcohol deprivation. In the operant reinstatement model, the animal must press a lever to obtain ethanol. Delivery of the reinforcer is paired with a conditioning cue (e.g. a light or a tone). Once established, the reinforced behaviour, lever pressing, is extinguished by omitting ethanol delivery. In the final test phase, the ability of ethanol, the conditioning cue or a foot-shock stressor to reinstate lever pressing for ethanol is recorded. The extent of the reinstatement of responding is taken as a measure of motivation to seek ethanol (Le and Shaham, 2002). This model has been pharmacologically validated with drugs that reduce alcohol craving and relapse in alcohol-dependent patients (Katner *et al.*, 1999; Bachteler *et al.*, 2005) and has some face validity (though note that the means of reducing ethanol seeking is quite different from that in the addicted human).

In the alcohol deprivation model, a period of ethanol exposure (either voluntary intake or operant self-administration) is followed by a period of ethanol deprivation. When ethanol is reintroduced, there is a temporary increase in ethanol intake (Khisti *et al.*, 2006). This increase in consumption is referred to as the alcohol deprivation effect (ADE) (Spanagel and Holter, 2000). This effect has been demonstrated in rats selectively bred for high ethanol drinking (HAD-1, HAD-2), with a twofold increase in consumption levels after four cycles of ethanol deprivation (Rodd *et al.*, 2009). This model also has predictive validity as has been pharmacologically validated with anti-relapse drugs (Spanagel and Zieglgansberger, 1997).

Conditioned place preference (CPP)

One of the most commonly used tasks to study the 'rewarding' effects of drugs is the place conditioning procedure. In this model, animals are exposed repeatedly to alcohol in one distinctive environment and to placebo in an alternative environment. During the test phase, the non-drugged animal will tend to spend proportionally more time in the drug-paired environment than in the placebo-paired environment if that drug was rewarding and vice versa if the drug was aversive (see Tzschentke, 1998; Bardo and Bevins, 2000; Cunningham *et al.*, 2006 for reviews).

Although seemingly simple in concept, and technically easy to carry out, CPP is in fact a procedure whose theoretical underpinnings are poorly understood. Furthermore, ethanol-induced CPP is particularly sensitive to methodological procedure, and it may also differ across species (Cunningham *et al.*, 1993). Minor variations are likely to bias the test to assess different psychological processes including Pavlovian approach (sign tracking), conditioned approach to positive incentives (Cunningham and Patel, 2007; Mead *et al.*, 2005), anxiolytic effects of the drug, or effects on learning.

Such considerations make the results of place conditioning experiments difficult to interpret. For example, C57BL/6J mice that show high rates of ethanol consumption in a free choice paradigm do not show high rewarding effects in the CPP task (Cunningham, 1995). One possibility is that development of place 'preference' in CPP reflects a balance of the aversive and rewarding effects of ethanol, so that variations in sensitivity to aversiveness may interfere with assessment of reward (Cunningham and Henderson, 2000; Cunningham *et al.*, 2003).

Conditioned reward and Pavlovian approach

Both conditioned reward and Pavlovian approach may contribute to the behavioural outcome in a CPP task. Conditioned reward refers to the ability of environmental cues associated with rewards such as alcohol to acquire reinforcing properties in their own right. Hence, the animal might approach the drug-associated environment as it is 'seeking' a conditioned reward. This type of conditioning phenomenon is often measured in operant paradigms in which animals acquire a novel instrumental response to gain access to a discrete stimulus previously associated with a conventional reward (conditioned reinforcement task) (Robbins, 1978).

On the other hand, Pavlovian approach refers to a situation where animals spontaneously approach environmental stimuli that are predictive of reward. This phenomenon results in sign-tracking behaviour where animals interact with reward-predictive stimuli, even though the animal's behaviour has no consequences for reward availability (Brown and Jenkins, 1968). CPP could therefore represent nothing more than a simple reflex approach to reward-predictive cues.

Conditioned reward implies that the animal attributes positive incentive value to the cues associated with the primary reinforcer and will thus perform flexible or voluntary responses to obtain access to such cues (Robbins, 1978). In contrast, Pavlovian approach is less flexible, and the form of the behaviour is determined by the nature of the cue, rather than its acquired rewarding properties (Gallagher *et al.*, 1990). These two aspects of cue–reward association appear to be mediated by different neural systems (Parkinson *et al.*, 2000). In a modified version of the CPP task, Cunningham and Patel (2007) demonstrated that mice will show Pavlovian approach, seen as approach to a discrete cue associated with alcohol administration. Additionally, we have recently demonstrated that binge exposure to ethanol enhances sign-tracking behaviour for a sucrose reward in C57BL/6J mice (Ripley, unpubl. obs.). These results would suggest that neuronal circuitry underlying Pavlovian approach behaviour is activated, and possibly sensitized, by repeated exposure to alcohol.

A human laboratory task analogous to animal Pavlovian approach behaviour consists of orientating responses to cues predictive of reward (Buzsaki, 1982). In addicts, this is seen as an allocation of attention to a stimulus associated with their drug of abuse over alternative competing stimuli, and importantly it has been shown that the more the attentional bias to drug cues, the poorer the treatment outcome. This relationship has been found especially for attentional bias measured by the Stroop interference effect and has been demonstrated for alcohol (Cox *et al.*, 2002). The existence of homologous measures in animal and human models based on well-established processes contributing to addictive behaviour offers a potential that is seldom realized in animal models.

Pavlovian-instrumental transfer

Cues that have been associated with reward during Pavlovian training sessions can facilitate instrumental responding for that or other rewards. This phenomenon is known as Pavlovian-instrumental transfer (PIT) (see (O'Connor *et al.*, 2010). Depending on training conditions, the cue may facilitate responding for a particular reward (outcome-specific PIT) or generalize to a range of rewards (generalized form of PIT). Although most work in the animal laboratory has used food rewards to establish the cue–reward association, two reports indicate that cues previously associated with ethanol delivery are capable of increasing instrumental responding for ethanol, consistent with ethanol-related cues facilitating ethanol-seeking behaviour (Glasner *et al.*, 2005; Corbit and Janak, 2007).

In contrast to the sign-tracking experiment described above, rats that were chronically exposed to ethanol prior to Pavlovian and instrumental training failed to show PIT to a cue associated with a food reward (Ripley *et al.*, 2004). Thus, while ethanol reward supports the development of PIT, ethanol dependence may impair the subsequent development of PIT.

Encouragingly, the PIT phenomenon is readily reproduced in the human laboratory (Paredes-Olay *et al.*, 2002; Hogarth *et al.*, 2007), but, to our knowledge, no human studies have investigated PIT using ethanol rewards.

Impulsivity

The term impulsivity is used to describe a number of behavioural distinct phenomena. Animal tasks can be divided into those that measure the inability to withhold a response ('impulsive disinhibition'), or intolerance to delay of reward or perseveration of a nonrewarded response ('impulsive decision making'). Although several tasks fall within these descriptors, two tasks have become increasingly popular, the five-choice serial reaction time task (5-CSRTT) (Robbins, 2002) that measures response inhibition (i.e. waiting) and delay discounting tasks where animals must choose between an immediate small reward and a larger delayed reward (e.g. Richards *et al.*, 1997). Although not encompassing all types of impulsivity, these tasks give a reasonable assessment of the two basic concepts of 'impulsive action' and 'impulsive choice'.

In the case of the 5-CSRTT, acute alcohol did not increase the number of premature (impulsive) responses in the standard, over-trained form of 5-CSRTT in mice (Oliver *et al.*, 2009) or rats (Bizarro *et al.*, 2003). However, when premature responding was provoked during probe trials by increasing the inter-trial interval, Oliver *et al.* (2009) found 1 $g \cdot kg^{-1}$ ethanol increased impulsivity. This result may suggest that actions that are performed habitually can be insensitive to effects of ethanol, while non-habitual situations, in which the subject is required to adapt its behaviour and respond accordingly to new requirements, is susceptible to the effects of alcohol on impulsivity.

These findings are supported by results from studies using different paradigms of impulsivity in rats, including the delay of reinforcement paradigm, where ethanol increased impulsive behaviour (Poulos *et al.*, 1998; Tomie *et al.*, 1998; Evenden and Ryan, 1999; Olmstead *et al.*, 2006), suggesting that alcohol given acutely increases both impulsive choice and impulsive action.

In human studies, in measures of response inhibition, when the subject is required to withhold an already initiated response (stop signal tasks), alcohol increases impulsivity in moderate drinkers and in college students (Mulvihill *et al.*, 1997; Dougherty *et al.*, 1999; Dougherty *et al.*, 2000). Thus, in a number of laboratory tasks designed to tease out specific aspects of impulsive behaviour, there appears to be good consistency between animal and human laboratory tasks in the acute effects of alcohol, offering the possibility of testing potential pharmacotherapies in animals with a high chance that finding will be replicated in the human studies.

Anhedonia

Lowered hedonic experience has been proposed as an explanation both of the tendency of some individuals to take

drugs, while others do not (e.g. Blum *et al.*, 1996; Volkow *et al.*, 1999) and as an account of relapse to drug taking following abstention. Thus, Koob and Le Moal (2001) hypothesized that repeated cycles of drug taking and withdrawal would induce a progressive dysregulation of the brain reward system, leading to allostasis (a resetting of the hedonic setpoint) and anhedonia. Such allostasis would drive further drug-seeking behaviour, moving an individual from a pattern of drug taking to compulsive drug use.

Two well-established techniques, intracranial self stimulation (ICSS) and reactivity to pleasantness, can measure anhedonia. ICSS provides a measure of brain reward thresholds, which has been shown to be elevated in animals undergoing withdrawal from several drug of abuse including ethanol (Schulteis *et al.*, 1995). These data are interpreted to indicate that in withdrawal, regulatory systems are increasingly displaced from the hedonic homeostatic set point, inducing increased desire for drug and hence relapse. However, it should be noted that in animal experimental studies, the effects of drug withdrawal on ICSS thresholds are rather short-lasting and thus would not provide an account of relapse following an interval of abstention.

Alternatively, reactivity to a pleasant taste, such as dilute sucrose, has also been used to measure anhedonia in human subjects (Papp *et al.*, 1991; Phillips *et al.*, 1991). In a rodent model of hedonic response, which appears homologous to human responses, when a taste is introduced into the mouth, a rat emits a series of behaviours that are organized along ingestive/hedonic or aversive dimensions. Consumption behaviour, seen as tongue protrusions and paw licks, follows the introduction of a sweet sucrose solution, whilst a bitter quinine solution will results in aversive behaviours aimed at expelling the solution (e.g. head shaking, gaping). These taste patterns vary as a function of motivational state, substance palatability and associative learning (taste aversion learning) (Berridge, 2000). Therefore, according to the Allostasis theory of Koob, rodents in a low hedonic state (anhedonia) during drug withdrawal should show decreased taste reactivity. Koob and Le Moal hypothesized that these animals would also more readily consume drugs of abuse. Thus, in agreement with Blum *et al.* (1996), a high motivation for alcohol might be expected to be associated with anhedonia and a low preference for sweet fluids. However, rat lines bred to exhibit high alcohol preference, including preferring (P) and high alcohol drinking (HAD) strains, show a stronger preference for sweet tastes than the corresponding low alcohol-preference strains, non-preferring (NP) and low alcohol drinking (LAD) rats, which argues against this idea (Bice and Kiefer, 1990; Woods *et al.*, 2003).

Drugs used in treatment of alcoholism

Alcohol dependence is, to an extent, a treatable disorder utilizing both pharmacological and psychosocial treatment regimes. While animal models including some of those described above have contributed to our understanding of neurobiological processes underpinning the rewarding properties of alcohol, opening doors for new therapeutic targets, few drugs have been tested in the more sophisticated models. Instead, research has focussed on the simpler voluntary intake and reinstatement models, and therefore, this review will be primarily limited to these models.

It is known that some alcoholics possess a biological predisposition to the disease. Tailor-made pharmacological treatment regimes for these individuals can target specific underlying abnormalities in neurobiological functioning. Here we will focus mainly on drugs where there is clinical evidence for a decrease in the desire to drink and/or promote abstinence.

To date, successful treatment of alcohol craving and relapse remains a problem, although advances have been made with the μ-opioid antagonist naltrexone and the glutamatergic compound acamprosate (calcium bis-*n*-acetyl homotaurinate, Campral®). Serotonergic compounds also show potential in the treatment of alcohol dependence, though they are not licensed for this purpose. More recently tested potential treatments, including the mGluR5 metabotropic glutamate antagonist MPEP, antagonists of corticotropin-releasing hormone and cannabinoids, may hold future promise.

Detoxification

The first important step in the treatment of substance abuse is detoxification. It has three main goals: to initiate abstinence, to reduce withdrawal symptoms and to retain the patient on the treatment. This process is not without risk, and may result in withdrawal symptoms including anxiety and development of seizures. For this reason, it is considered unethical to initiate an alcohol detoxification programme without concurrent therapy to control these life-threatening events. Typically, alcohol-dependent individuals are given a benzodiazepine (e.g. chlordiazepoxide, diazepam or lorazepam) or other CNS depressant such as chlormethiazol, or anticonvulsants such as carbamazepine, during the initial withdrawal phase, followed by tapering out of these treatments over several days (Kosten and O'Connor, 2003). Withdrawal-associated hyper-vigilance and aspects of anxiety may be treated with α-adrenergic agonists (e.g. clonidine).

Such treatments are usually successful in treating the withdrawal symptoms, including seizures, and may also contribute to avoiding immediate relapse as the patient seeks to control withdrawal-induced anxieties. However, an insidious feature of alcohol detoxification, which may distinguish alcohol from other drug dependencies, is that the severity of certain withdrawal symptoms, especially seizure sensitivity, increases with successive withdrawals, a phenomenon that has been likened to epileptic kindling (Ballenger and Post, 1978). Such withdrawal sensitization has been shown to result in long-term deficits in cognitive and emotional processing that may contribute to further loss of control over drinking, as well as to difficulties in adequate social functioning (Stephens and Duka, 2008). Current evidence suggests that pharmacological intervention that is successful in controlling signs and symptoms of acute withdrawal may not be effective in preventing withdrawal-sensitization (Gonzalez *et al.*, 2001).

Relapse prevention

The next stage, and one of the major challenges in addiction treatment, is how to prevent relapse when an abstinent

patient is exposed to alcohol or an alcohol-related stimulus (Skinner and Aubin, 2010). The brief account of theories of addiction outlined above indicates that such exposures may induce relapse in different ways, by triggering incentive processes, with or without awareness (i.e. craving) (Robinson and Berridge, 2000), or habitual responses (Tiffany, 1990; Everitt *et al.*, 2008) or by triggering conditioned opponent processes (Solomon and Corbit, 1974; Koob and Le Moal, 2008). In each case (with the possible exception of habit theory), a plausible treatment would be for the addict to learn that alcohol drinking is now associated with punishment.

Disulfiram (Antabuse®) was the first medicine approved for the treatment of alcohol abuse and alcohol dependence by the U.S. Food and Drug Administration (FDA). This drug inhibits acetaldehyde dehydrogenase preventing complete alcohol metabolism and leading to a build-up of acetaldehyde, a toxic substance that causes hangover-like symptoms. A recent report (Schroeder *et al.*, 2010) suggests that disulfiram may additionally inhibit dopamine β-–hydroxylase, thus decreasing noradrenaline availability, and disulfiram's effects on at least cocaine seeking are mimicked by another drug with a selective action in blocking dopamine β-–hydroxylase.

Although disufiram has been used to treat alcohol dependence since the 1940s, the evidence for its effectiveness is weak. In general, it is felt that disulfiram has no effect on craving for alcohol (Johnson, 2008), although some clinical trials have shown a decrease in craving in patients (De Sousa, 2004; de Sousa, 2005; Petrakis *et al.*, 2005; De Sousa *et al.*, 2008) and an increase the duration of abstinence (Chick *et al.*, 1992; Fuller and Gordis, 2004; Diehl *et al.*, 2010; Mutschler *et al.*, 2010). The main problem with studies with oral disulfiram is in patient compliance, with high drop-out rates of up to 46%. Newer compounds, such as naltrexone and acamprosate, have been shown to have a greater effect on alcohol craving.

In animal studies, disulfiram has been shown to decrease free choice consumption for ethanol by 50% in C57BL/6J mice (He *et al.*, 1997), an effect that could be attributed to the unpleasant side effects associated with ethanol consumption. Of more interest when considering the rewarding properties of ethanol is that disulfiram blocked the development of behavioural sensitization induced by 2 $g \cdot kg^{-1}$ ethanol (Kim and Souza-Formigoni, 2010).

The alternative approach has been to reduce the rewarding effects of ethanol, or the effectiveness of alcohol-related cues. Two pharmacotherapies (Naltrexone, Acamprosate) are available that use this general approach.

Drugs affecting the opioid system: Naltrexone, Nalmefene

The endogenous opioid system has been shown to play a key role in the expression of the reinforcing effects of ethanol, either directly or through its effect on other neurotransmitter systems including dopamine. Via actions at μ- and κ-opioid receptor, opiates may exert opposing effects on forebrain DA release (Spanagel *et al.*, 1992; Margolis *et al.*, 2006).

Naltrexone, which has been approved for use in the treatment of alcohol dependence in conjunction with psychosocial interventions, works primarily through its antagonism of μ-opioid receptors, although it has some affinity for the κ-opioid receptor (Raynor *et al.*, 1994). Naltrexone is reported to reduce the rewarding effects of alcohol in humans, leading to decreased feelings of intoxication and fewer cravings. In subjects with a history of alcohol abuse, naltrexone has been shown to reduce alcohol consumption, craving and relapse (O'Brien *et al.*, 1996; Anton *et al.*, 1999; Davidson *et al.*, 1999; Heidbreder and Hagan, 2005). It is particularly effective at reducing short-term relapse rates but has shown less promising effects in longer studies (O'Malley *et al.*, 1992). Similar conclusions have been reached from more recent meta-analysis studies (e.g. (Bouza *et al.*, 2004)), whilst other studies have failed to show a significant effect of naltrexone unless high compliance rates are reached (Litten and Allen, 1998).

In human laboratory studies, naltrexone has been reported to increase the latency to consume alcohol and to reduce alcohol-induced positive subjective mood (Swift *et al.*, 1994; Davidson *et al.*, 1996), though other studies have failed to replicate these findings (Doty and de Wit, 1995).

Since μ-opioid receptors have been hypothesized to mediate ethanol reward, naltrexone may reduce drinking by decreasing the rewarding effect of alcohol (Swift *et al.*, 1994; Volpicelli *et al.*, 1995; Sinclair, 2001). Nevertheless, the mechanism underlying naltrexone's efficacy in reducing alcohol intake in humans is still incompletely understood. An alternative account holds that that naltrexone reduces drinking by generating ethanol-induced aversive side effects, such as nausea (e.g. Davidson *et al.*, 1999), suggesting an action whose end effect is similar to that of disulfiram (although by distinct pharmacological mechanisms). However, naltrexone significantly reduces alcohol craving during abstinence (Monti *et al.*, 1999; O'Malley *et al.*, 2002) and can enhance an individual's ability to resist urges to drink and behaviours associated with drinking (Anton *et al.*, 1999), findings that are clearly incompatible with the nausea hypothesis, but also difficult to understand in terms of naltrexone effects on primary reward processes (though compatible with effects on conditioned incentive effects).

Genetics may play an important role in the effectiveness of naltrexone with individuals with a positive family history for alcoholism being more responsive to naltrexone than a family history-negative control group (Krishnan-Sarin *et al.* 2007). Indeed, people with the A118G μ-receptor polymorphism show reduced μ-receptor expression (Zhang *et al.*, 2005) and more effective naltrexone-mediated abstinence from alcohol (Oslin *et al.*, 2003).

Recent evidence from human studies (Mitchell *et al.*, 2007; Boettiger *et al.*, 2009) suggests that naltrexone helps control impulsive choice (choosing to obtain an immediate reward rather than wait for a larger or normally preferred outcome), an effect that was related to the degree of κ-receptor-mediated effect relative to μ-receptor-mediated effect in genetically heterogeneous subjects.

Thus, although there is now evidence that naltrexone may be an effective agent in some individuals in controlling drinking, the mechanism whereby such effects are achieved remains unclear.

The importance of the endogenous opioid system in alcohol dependence has been studied in depth in animal

models. First, mice lacking μ-opioid receptors fail to self-administer ethanol in either the two-bottle choice paradigm or in operant self-administration tasks (Roberts *et al.*, 2000). Second, opioid receptor densities are higher in ethanol-preferring rodent strains in brain regions thought to mediate the rewarding effects of drugs of abuse. For example, alcohol-preferring AA rats have significantly higher μ-receptor densities in the nucleus accumbens and ventral tegmental area than their non-preferring ANA counterparts (de Waele *et al.*, 1995; Soini *et al.*, 1999). Additionally, alcohol-preferring inbred strains, such as C57BL/6J mice, show higher levels of μ-receptors in the amygdala than the alcohol-avoiding DBA/2J mice (de Waele and Gianoulakis, 1997). Complementary studies have shown that naltrexone reduces ethanol ingestion in a range of high-drinking alcohol-preferring rat strains (Froehlich *et al.*, 1990; Hyytia and Sinclair, 1993; Badia-Elder and Kiefer, 1999).

In low-drinking strains, the precise pattern of availability of ethanol may be important in predicting the efficacy of naltrexone. Thus, naltrexone was shown to be more effective in reducing intakes when access to ethanol was limited, either using scheduled access, operant self-administration paradigms or drinking-in-the-dark procedures (Stromberg *et al.*, 1998a; Stromberg *et al.*, 1998b; Stromberg *et al.*, 2002; Kamdar *et al.*, 2007). Continuous ethanol access models were less sensitive to naltrexone's effects (Goodwin *et al.*, 2001). Animal studies using repeated administration of naltrexone have produced inconsistent results; with some reporting loss of efficacy (e.g. Gardell *et al.*, 1997; Overstreet *et al.*, 1999), whilst others reported a progressive decrease in alcohol drinking across the treatment period (Stromberg *et al.*, 1998b; Bienkowski *et al.*, 1999).

In the ADE model, naltrexone given acutely was found to be more effective in reducing elevated levels of drinking following periods of withdrawal, than initial baseline drinking (Holter and Spanagel, 1999), whilst chronic naltrexone administered during the withdrawal period blocked the elevated alcohol drinking following reinstatement (Heyser *et al.*, 2003). A promising finding in the reinstatement model showed that naltrexone protected against ethanol-induced reinstatement triggered by either priming injections of ethanol or ethanol-associated cues, but not by stress (Bienkowski *et al.*, 1999; Katner *et al.*, 1999; Ciccocioppo *et al.*, 2002). These studies suggest naltrexone to be effective in a broad range of animal models, perhaps by interfering with aspects of reward signalling, whether conditioned or unconditioned.

In contrast, there is little evidence from animal studies that naltrexone affects top-down processes leading to increased control over-drinking. Thus, for instance, in the delayed discounting test for impulsivity, naltrexone did not affect impulsivity at doses that selectively decreased alcohol intake (Oberlin *et al.*, 2010). These observations appear to stand in contradiction to human data from an apparently homologous task (Mitchell *et al.*, 2007; Boettiger *et al.*, 2009), though it should be noted that while the animal studies use 'real' rewards, the human studies require the subject to imagine the reward value. These subtle differences may contribute to the apparently different findings.

Recent interest in kappa opioid receptor systems has led to studies on μ/κ-opioid receptor antagonists in the treatment of alcoholism. Nalmefene, which has higher affinity for κ-opioid receptors than naltrexone, was shown to be significantly more effective at reducing ethanol-intake in ethanol-dependent animals when compared with naltrexone (Walker and Koob, 2008). However, mixed results have been seen with the κ-receptor antagonist norbinaltrophimine. This compound decreased ethanol consumption in dependent, but not non-dependent animals (Walker and Koob, 2008), and failed to reduce the ADE in animal studies (Holter *et al.*, 2000b). It has also been shown to decrease stress-induced increases in ethanol consumption and conditioned place preference (Sperling *et al.*, 2010). The κ-opioid receptor agonist U50 488 has been shown to decrease ethanol conditioned place preference (Logrip *et al.*, 2009).

These findings in animals predict that kappa agonists are potentially useful drugs for the treatment of alcoholism, and preliminary studies in the clinic support this view. In alcohol-dependent patients receiving weekly CBT sessions, nalmefene significantly reduced relapse to heavy drinking (Mason *et al.*, 1999). Patients receiving nalmefene had a 37% relapse rate compared with 59% in the placebo group. However, these two groups did not differ in the total number of days abstinent, in the number of drinks consumed on a drinking day or in self-reported craving ratings.

Drugs affecting the glutamate system: Acamprosate, Neramexane

Acamprosate (calcium homotaurinate) is a taurine derivative whose precise mechanism of action is still unclear, though interaction with glutamatergic systems is likely, with interactions with *N*-methyl-D-aspartate (NMDA) receptors, and the metabotropic-5 glutamate receptors (mGlur5) (Zeise *et al.*, 1993; Spanagel and Zieglgansberger, 1997; Harris *et al.*, 2002; Blednov and Harris, 2008) proposed. Littleton and Zieglgansberger (2003) suggest that modulations of the NMDA receptor may be the primary method of action. However, acamprosate's action at NMDA receptors appears complex, acting as a partial co-agonist, facilitating functioning at low levels of endogenous activators and inhibiting at high levels (Naassila *et al.*, 1998). During alcohol withdrawal, increased calcium influx through NMDA receptors would lead to neuronal hyperexcitability associated with physical symptoms of withdrawal, and this may contribute to relapse. By inhibiting calcium influx associated with high levels of activity, acamprosate might reverse such adaptations. Thus, according to this reasoning, acamprosate may ameliorate aversive effects of withdrawal (De Witte *et al.*, 2005), which opponent process theories postulate are responsible for driving addictive behaviour (Koob and Le Moal, 2008). Alternative molecular actions of acamprosate may be modulation of glutamatergic neurotransmission at metabotropic-mGluR5 (Harris *et al.*, 2002). Other suggestions include an action to decrease activity at voltage-gated calcium channels (see Johnson, 2008 for review).

Acamprosate has been shown to reduce short-term and long-term relapse rates in patients with alcohol dependence when combined with psychosocial treatments, seen as fewer patients returning to drinking and a higher percentage of days of total abstinence (Mason, 2001; Mann *et al.*, 2004).

It has been suggested that acamprosate may ameliorate aversive effects of withdrawal (De Witte *et al.*, 2005), by attenuating conditioned opponent processes associated with exposure to alcohol related cues (Littleton, 1995; Cole *et al.*, 2000). Such an account has been used to explain the drug's ability to reduce risk of relapse even following the resolution of acute withdrawal symptoms, though an ability to reduce the rewarding effects of alcohol (Cano-Cebrian *et al.*, 2003; McGeehan and Olive, 2003) might also account for this property.

The effect of acamprosate in animal models has recently been reviewed (Mann *et al.*, 2008). Like naltrexone, acamprosate, showed greater efficacy in reducing alcohol drinking under schedules of limited access (Olive *et al.*, 2002) than under continuous access conditions (Stromberg *et al.*, 2001). Acamprosate was less effective in studies where ethanol intake was low (Rimondini *et al.*, 2002), with minimal effect in operant self-administration studies with low-preference strains with limited history of alcohol exposure (Stromberg *et al.*, 2001; Heyser *et al.*, 2003). In ethanol-preferring strains, acute acamprosate has been shown to reduce voluntary alcohol drinking, operant self-administration and drinking-in-the-dark paradigms (Cowen *et al.*, 2005; Gupta *et al.*, 2008). In animals chronically exposed to ethanol, acamprosate has a similar effect, significantly reducing voluntary consumption whether the acamprosate was given during the initial chronic ethanol phase or during the withdrawal period (Le Magnen *et al.*, 1987; Gewiss *et al.*, 1991; Rimondini *et al.*, 2002).

In the ADE test, acamprosate prevented elevated alcohol drinking following reinstatement (Heyser *et al.*, 1998), whilst repeated acamprosate administration during the first 48 h of reinstatement reduced drinking in a dose-dependent manner (Spanagel *et al.*, 1996a).

Using a modified version of operant self-administration (Samson *et al.*, 1998), which allowed separate measurement of motivational and consumatory phases of ethanol self-administration, Czachowski *et al.* (2001) showed that acamprosate significantly reduced consumption of ethanol without decreasing motivation measured as lever pressing to obtain access to the ethanol solution. A similar result has been seen with naltrexone (Sharpe and Samson, 2001). This would suggest that acamprosate does not directly reduce incentive motivation (craving) for alcohol.

However, in reinstatement models that test the ability of cues associated with alcohol to reinstate alcohol-seeking behaviour, thought to reflect cue-induced relapse, acamprosate significantly reduced alcohol seeking (Bachteler *et al.*, 2005). This effect may be due to a decrease in arousal following exposure to alcohol-related cues rather than a direct effect on craving (Ooteman *et al.*, 2007).

Acamprosate dose-dependently decreased the development of ethanol CPP without producing conditioned place preference or aversion when tested alone (McGeehan and Olive, 2003). As acamprosate does not impair memory at these doses (Okulicz-Kozaryn *et al.*, 2001; Mikolajczak *et al.*, 2002), these results suggest that acamprosate can have a selective action on suppression of the conditioned rewarding effects of ethanol.

Other NMDA receptor antagonists have also been tested for their ability to decrease alcohol drinking. Neramexane is a low-affinity, non-competitive NMDA receptor antagonist. It has been shown to prevent the increase of ethanol intake seen following withdrawal periods in the ADE task (Holter *et al.*, 2000a). However, in the reinstatement model, it had no effect on cue-induced reinstatement (Bachteler *et al.*, 2005).

Due to the action of acamprosate on mGluR5 receptors, it may be promising to pursue this site as a potential therapeutic target for the treatment of alcoholism. The mGlur5 receptor antagonist MPEP has been tested in animal models. In rat models, MPEP was shown to have efficacy on alcohol withdrawal (Spanagel *et al.*, 1996b; Schroeder *et al.*, 2005), relapse (Backstrom *et al.*, 2004; Bachteler *et al.*, 2005) and reinforcement (Besheer *et al.*, 2008). Of particular value is the fact that tolerance to MPEP does not develop, meaning that it can be repeatedly used across multiple treatment cycles. Additionally, activation of presynaptic metabotropic-2 glutamate receptors (mGluR2) decreased both cue-induced and stress-induced reinstatement (Zhao *et al.*, 2006), probably as a result of decreasing glutamatergic tone.

An alternative way to modulate glutamatergic tone is through DL-α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors. Blockade of these receptors also results in a dose-dependent decrease in cue-induced reinstatement and in heightened alcohol drinking during the ADE task (Sanchis-Segura *et al.*, 2006). In keeping with these findings, the anticonvulsant topiramate, which antagonizes both AMPA and kainate receptors, has also been shown to reduce craving and relapse rates in alcohol-dependent patients, including a reduction in self-reported drinks per day, drinks per drinking day and heavy drinking days (for review, see Kenna *et al.*, 2009).

Drugs affecting the endocannabinoid system

Using animal models, researchers have begun to investigate a wider range of potential therapeutic targets for the treatment of alcoholism. The cannabinoid system, and in particular the CB1 receptor, has been implicated in having a role in drug abuse due to its location in brain reward pathways. CB1 receptors are found in high density in the hippocampus, cerebellum, cortex and striatum (Howlett, 2002). The main active ingredient in marijuana, Δ^9-tetrahydrocannabinol (Δ^9-THC), acts at the CB1 receptor to produce its rewarding effects (Wilson and Nicoll, 2002), possibly by producing elevated dopamine levels in the nucleus accumbens (Chen *et al.*, 1990).

Recent studies have suggested that activation of the endocannabinoid system may be responsible for some of the rewarding properties of alcohol (Hungund *et al.*, 2002). Lower CB1 receptor binding densities have been reported in alcohol preferring mouse strains (Hungund and Basavarajappa, 2000), whilst stimulation of these receptors with the agonist CP-55 940 greatly increased ethanol consumption in both mice and rats (Colombo *et al.*, 2002; Vinod *et al.*, 2008). Conversely, genetic deletion of the CB1 receptor or pharmacological antagonism using compounds such as SR141716A significantly reduced ethanol preference (Lallemand *et al.*, 2001; Colombo *et al.*, 2004; Naassila *et al.*, 2004; Vinod *et al.*,

2008). CB1 knockout mice also fail to show CPP for ethanol (Houchi *et al.*, 2005; Thanos *et al.*, 2005) and show minimal signs of withdrawal after discontinuation of alcohol when compared with wild-type animals (Racz *et al.*, 2003). Similarly, the CB1 receptor antagonist rimonabant significantly reduced preference for alcohol, craving and/or intake in different species or strains of rodents (Arnone *et al.*, 1997; Freedland *et al.*, 2001; Lallemand *et al.*, 2001; Serra *et al.*, 2001; Wang *et al.*, 2003) and blocked elevated alcohol consumption effects in the alcohol deprivation task, indicating a potential role in preventing relapse (Serra *et al.*, 2002). These findings might suggest a role for CB1 receptor antagonists in the treatment of alcohol withdrawal.

In human studies, a sub-population of alcoholic patients, who show severe withdrawal symptoms, also show a greater frequency in the occurrence of CB1 receptor polymorphisms (Schmidt *et al.*, 2002). Nevertheless, a moderately sized study of remonabant in alcoholic patients in a double blind, placebo-controlled trial (258 patients exposed to medication) found no statistical evidence of reduced rates of relapse (Soyka *et al.*, 2008).

Drugs affecting the serotonergic system

There has been some speculation that selective serotonin reuptake inhibitors (SSRIs) may be effective in the treatment of patients with alcohol dependence, though research has provided inconsistent results. In a recent review, Kenna (2010) provides a useful summary. In brief, fluoxetine (Prozac) and other SSRIs have been shown to be more effective in treating alcoholics with major depression than those without, as measured by fewer drinks, fewer drinking days and fewer heavy drinking days than those receiving placebo. The $5HT_{1A}$ partial agonist, buspirone, also decreased alcohol consumption, though, when baseline levels of anxiety were taken into account, it was no more effective than placebo for alcoholic patients.

From animal studies, alcohol appears to potentiate serotonergic transmission through activation of $5HT_3$ receptors (Lovinger and Zhou, 1994). Hence, low transmission through these systems may act as a potential biomarker for alcoholism. High alcohol-preferring rat stains show low levels of 5HT when compared with their non-preferring controls (McBride and Li, 1998), an effect also seen in human alcoholics (Kenna, 2010). However, the picture is complicated as $5HT_3$ antagonists have been shown to decrease voluntary alcohol consumption (Rodd-Henricks *et al.*, 2000), whilst overexpression of $5HT_3$ receptors lead to a reduction in alcohol self-administration (Engel *et al.*, 1998). Such observations might indicate that a balance in the serotinergic system is required for controlling alcohol intake, and this may require tailor-made treatment for each patient. 5HT3 antagonists have been shown to block reinstatement of responding for ethanol induced by an intermittent foot shock (Le *et al.*, 1999b; Le *et al.*, 2006).

Clinical studies (Sellers *et al.*, 1994; Kenna, 2010) have found that patients with early-onset alcoholism responded well to the $5HT_3$ antagonist ondansetron (Zofran) as seen by a significant reduction in self-reported drinking when combined with cognitive behaviour therapy. These patients reported having fewer drinks per day, a greater percentage of days of abstinence and a greater total number of days abstinent when compared with a placebo control group. Nevertheless, drugs from this class are not yet licensed for the treatment of alcoholism.

Drugs affecting the stress system

Repeated cycles of alcohol exposure followed by periods of abstinence are known to lead to long-lasting neuroadaptation. One of the key characteristics known to occur following these repeated cycles of intoxication and withdrawal is an increase reactivity to stressors (Sommer *et al.*, 2008), which could increase relapse potential (Brownell *et al.*, 1986; Shaham *et al.*, 2003). In ethanol-dependent animals, with a prolonged history of alcohol consumption, stress leads to an extended increase in consumption (Sommer *et al.*, 2008).

Receptors for corticotrophin-releasing hormone (CRH) are found in the central nucleus of the amygdala and the bed nucleus of the stria terminalis, where they are thought to mediate behavioural responses to stress. Repeated cycles of alcohol intoxication and withdrawal can lead to a sensitization of this system. Changes in the release of CRH in the amygdala during the initial phase of withdrawal results in long-term elevated levels post-withdrawal (Zorrilla *et al.*, 2001), and up-regulation of CRH_1 receptor expression (see Heilig *et al.*, 2010 for review).

Alcohol-dependent rats and alcohol-preferring Marchigian–Sardinian Preferring rats show elevated levels of CRH_1 receptors (Ciccocioppo *et al.*, 2006; Sommer *et al.*, 2008) and, in keeping with this finding, CRH_1 antagonists reduce alcohol self-administration in alcohol-dependent animals during either the acute or prolonged withdrawal phase. They also block stress-induced reinstatement of alcohol seeking, although they are not effective in blocking cue-induced reinstatement (Valdez *et al.*, 2002; Gehlert *et al.*, 2007).

Drugs affecting substance P

A novel treatment approach for alcoholism has focused on substance P (SP) and its receptor, neurokinin 1 receptor (NK1). These receptors are highly expressed in brain areas involved in stress responses, including the hypothalamus and the amygdala (Nakaya *et al.*, 1994). They are believed to play a role in regulation of affect, with $NK1^{-/-}$ mice showing an anxiolytic behavioural profile (see Heilig *et al.*, 2010 for review). $NK1^{-/-}$ mice, backcrossed on a C57BL/6J alcohol-preferring strain, also showed a significant decrease in ethanol consumption when compared with wild-type controls, an effect that was mimicked by the NK1 receptor antagonist L-703606. $NK1^{-/-}$ mice also failed to show the increase in alcohol consumption in the ADE paradigm and failed to show conditioned place preference for alcohol (Heilig *et al.*, 2010). These findings would suggest a potential role of NK1 antagonists in the treatment of alcohol dependence.

In a hospitalized clinical population, the NK1 receptor antagonist LY686017 significantly decreased both spontaneous and stress-induced alcohol cravings. When exposed to positive versus negative affect stimuli, the LY686017 group showed normalisation of brain activity when compared with a placebo-treated patient group (Heilig *et al.*, 2010). This result indicated a shift in the balance of negative and positive emotionality that may contribute to the subjective improvement shown in clinical rating scales.

Clinically ineffective medications

The studies outlined above paint a rosy picture of the ability of animal models to predict the utility of pharmacological treatments of alcohol abuse. On the whole, there is good agreement between their effects in animal tests, especially those purporting to measure aspects of reward, and in reducing drinking and desire for alcohol in clinical studies. This empirical data set thus contradicts to an extent our critical review of such animal models in the first part of this article. Nevertheless, the predictive worth of the models is not complete. Notably, although acamprosate has been found active in a range of animal models and has been reported to be effective in a number of clinical trials, a recent, large, well-controlled trial in the USA (Anton *et al.*, 2006) did not find evidence for efficacy. Furthermore, there are a number of compounds that, despite showing initial promise in animal models of alcohol dependence, have been shown to be clinically ineffective in the treatment of alcoholism. A few of these compounds are described below.

As mentioned above, SSRIs showed initial promise in animal tests. Fluoxetine decreased ethanol drinking and self-administration in both preferring and non-preferring strains (Murphy *et al.*, 1985; Maurel *et al.*, 1999a; Maurel *et al.*, 1999b; Rezvani *et al.*, 2000). Fluoxetine was also able to block stress-induced reinstatement while having less consistent effects on alcohol-induced reinstatement (Le *et al.*, 1999a). SSRIs do not affect place conditioning to ethanol (Risinger, 1997). However, within the clinic, SSRIs have largely found to be ineffective, though they may have some effect in treating a sub-population of alcoholics with major depression.

The $5HT_2$ antagonist ritanserin has also been shown to decrease ethanol drinking in rats (Meert *et al.*, 1991; Panocka and Massi, 1992; Lin and Hubbard, 1994), though other studies report no effect of ritanserin on ethanol preference or consumption (e.g. Svensson *et al.*, 1993). In the clinic, ritanserin has not proved to be an efficacious treatment for alcohol dependence and in a 12 week, multi-centre clinical trial did not show any greater effect on improving drinking outcomes placebo (Johnson *et al.*, 1996).

A number of dopamine receptor agonists have been claimed to reduce ethanol reward. For instance, the dopamine D_2 receptor agonist bromocriptine caused a reduction in ethanol drinking and preference in C57BL/6J mice (Ng and George, 1994; Ng *et al.*, 1994) and selectively reduced operant ethanol self-administration in Wistar and alcohol-preferring P rats (Weiss *et al.*, 1990). Nevertheless, clinical studies have failed to find an effect of bromocriptine on alcohol drinking or related behaviours (see Johnson, 2008).

These examples of false positives in animal tests reveal that they are limited in their ability to discriminate effective from ineffective substances. One might argue that the number of experiments with clinically effective agents outweighs the smaller number of false-positive tests with ineffective agents, but in making this argument, it should be borne in mind that many of the animal tests with acamprosate and naltrexone were carried out after the drugs had been introduced into the clinic (respectively, 1996 in Europe and 2004 in the USA, and 1988 in Europe and 1994 in the USA). Furthermore, and disappointingly, less than one-third of patients respond to either naltrexone or acamprosate, so that one may ask why they consistently give rise to positive findings in animal models.

Additionally, there is a range of other compounds from different pharmacological classes, some of which have been mentioned above, that have shown promise in animal models, but which have failed to show efficacy in treatment of alcohol abuse. These include the glutamatergic compound memantine (Evans *et al.*, 2007), the cannabinoid receptor 1 blocker rimonabant (Soyka *et al.*, 2008; George *et al.*, 2010), the cholinergic drug galantamine (Mann *et al.*, 2006) and several anticonvulsant drugs (De Sousa, 2010). However, the causes of the failed clinical efficacy are rarely established (Becker and Greig, 2010), and thus, whether the failure to find therapeutic effects represents weaknesses in the study designs or technical ability to carry them through adequately, use of subpopulations that are insensitive to the particular treatment used, or (most relevant to the present article) the failures in the predictive ability of the animal models remain unclear.

Individually tailor-made pharmacotherapies in the treatment of alcoholism

It is well known that genetic disposition plays a significant role in alcoholism. Emerging evidence suggest that responsiveness to drugs prescribed to treat alcohol abuse may also be dependent on genetic makeup. Recent research has begun to look at the heterogeneity of responses to different pharmacological treatments for alcohol dependence and has revealed the need to characterize genetic and protein markers, and endophenotypes for the development of individual pharmacotherapy (Spanagel and Kiefer, 2008). Ideas of how to initially screen patients for best therapeutic options are underway but may include a range of both genetic and behavioural measures.

Identification of specific gene polymorphisms

O'Brien and colleagues were the first to report that alcoholics carrying a functional variant of the μ-opioid receptor gene (OPRM1*A118G) show greater naltrexone efficacy (Oslin *et al.*, 2003; Anton *et al.*, 2008). These findings offer a potential explanation for why drugs like naltrexone are effective in only subpopulations of alcoholics.

However, if these potentially exciting findings are correct, they raise the issue of why naltrexone is effective in a wide

range of animal models using different strains. One possibility, of course, is that rodent strains chosen for studies of the effectiveness of alcohol treatments are themselves models of the human alcoholics bearing the OPRM1*A118G variation (though not necessarily themselves carrying this variation). Thus, in alcohol-preferring P rats, acute administration of ethanol led to an increase pro-opiomelanocortin (POMC) mRNA in the pituitary (Krishnan-Sarin *et al.*, 1998) and preproenkephalin (PPENK) mRNA in the nucleus accumbens, when compared with non-preferring NP rats (Li *et al.*, 1998). In mice, ethanol produces a larger and longer release of β-endorphin from the hypothalamus of alcohol-preferring C57BL/6 mice than in non-preferring DBA/2 mice (de Waele and Gianoulakis, 1993). Perhaps these high-drinking strains are particularly susceptible to the actions of naltrexone at μ- and κ-receptors.

The notion that certain drugs are most effective in individuals carrying a particular gene variant raises the question of whether the type of alcoholism expressed by individuals bearing that variant differs from other types. Thus, for instance, the OPRM1*A118G variation influences the striatal dopamine response to alcohol (Ramchandani *et al.*, 2010), potentially influencing alcohol incentive mechanisms. Other subtypes of alcoholism may relate to susceptibility to stress. Thus, a potentially important factor in determining effective treatments for alcoholism is to establish the major psychological factors underlying a particular individual's abuse. It might then be possible to tailor pharmacotherapy to the underlying neurobiological deficit.

A corollary of this approach would be to identify animal tests capable of modelling the underlying deficit. To the extent that current animal models do not attempt to distinguish between different forms of alcoholism, it is surprising that they are effective in identifying clinically active compounds.

Conclusion

Alcohol dependence and abuse appear to have a number of overlapping causes, so that rational treatments will need to take into account differential diagnoses and aetiologies. Currently approved treatments (disulfiram, acamprosate, naltrexone) have limited effectiveness across the entire population of alcoholic patients, possibly because they address different aspects and/or forms of alcoholism. Animal models in current use make little attempt to differentiate different aspects of alcoholism, and all three approved treatments appear to be effective across a broad range of models. However, the same models have been used to predict efficacy of other approaches that have not been found useful in clinical trials; other potential treatments identified in animal models have not yet been fully evaluated in the clinic. Until we have a better grasp of the processes underlying drug abuse, the rational development of novel agents by screening in animal models will be difficult. We make some suggestions as to how we might apply current knowledge of the psychological and neurobiological processes that contribute to alcohol abuse to develop novel, more rigorous animal models.

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Conflict of interest

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