CNS Drugs (2014) 28:343–360
DOI 10.1007/s40263-014-0149-3

REVIEW ARTICLE

Pharmacological Approaches to Reducing Craving in Patients with Alcohol Use Disorders

Carolina L. Haass-Koffler · Lorenzo Leggio · George A. Kenna

Published online: 27 February 2014

Abstract Research on the concept of craving may lead to better understanding of the biobehavioural circuitries that contribute to the complexity of alcohol use disorders (AUDs). The experiences described as craving or desire to drink are often associated with physical responses such as increased salivation and heart rate, and alteration of stress hormones, as well as psychological responses such as anxiety and depression. Greater craving has been associated with an increased probability of alcohol relapse. Reversal of craving, which is understood as a symptom of protracted abstinence, offers the possibility of preventing relapses and treating alcoholism. Various medications have been studied to establish whether they are able to reduce craving; however, the results obtained from clinical studies have been inconsistent. Here, we review the interdisciplinary models developed to evaluate craving, then the different approaches used to assess and measure craving and, finally, the medications utilized and tested to lessen craving in patients suffering from AUDs.

Key Points

Now recognized by the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) as an important diagnostic assessment for alcoholism, craving is an ever-changing subjective concept, which is difficult to express and accurately assess across the heterogeneous population of alcoholics.

Though related to alcohol relapse, reductions in craving seen with pharmacotherapy have not consistently been associated with reductions in drinking.

Better understanding of craving is needed to help advance the successful treatment of alcoholism.

1 Background

As a subjective experience, craving is a difficult phenomenon to define, but this concept is used by patients, clinicians and researchers to describe a strong desire to drink alcohol. It was first recognized as a component of alcoholism in 1955 [1]. The term 'craving', however, was acknowledged later in the scientific and clinical communities [2] and investigated for its association with alcohol withdrawal and relapse [3–5]. The experience of craving has been identified as being on a continuum, rather than being an on-and-off symptom. Craving is also positively

C. L. Haass-Koffler · L. Leggio · G. A. Kenna (✉)
Center for Alcohol and Addiction Studies, Brown University, Box G-S121-5, Providence, RI 02812, USA
e-mail: george_kenna@brown.edu

L. Leggio
Section on Clinical Psychoneuroendocrinology and Neuropsychopharmacology, Laboratory of Clinical and Translational Studies (LCTS), National Institute on Alcohol Abuse and Alcoholism (NIAAA), National Institutes of Health (NIH), Bethesda, MD, USA

L. Leggio
Intramural Research Program, National Institute on Drug Abuse (NIDA), National Institutes of Health (NIH), Baltimore, MD, USA

G. A. Kenna
Department of Psychiatry and Human Behavior, Brown University, Providence, RI, USA

correlated with negative emotions [6, 7], stress and anxiety [8–10], and is negatively correlated with the duration of alcohol abstinence [11].

Researchers have used different definitions of craving. For example, craving has been described by some as 'desire and urge', while others have defined it as only the 'desire' to experience the effects of a drug, while using the term 'urge' to describe the behavioural intention to use the drug [4]. Additionally, in clinical practice, craving is a difficult symptom to assess because patients may deny experiencing it [2]. Moreover, they may be unable to recognize it because of the overwhelming emotional experience that occurs during abstinence and withdrawal [12], or simply because they do not remember having experienced craving before a relapse occurred [13]. Proposing a uniform definition of craving has been challenging because of the lack of a valid method to measure psychological, behavioural and brain functions of subjective experiences [14, 15]. Furthermore, because of the lack of a standardized definition, operationalizing valid and reliable preclinical models that can be used as predictors of human craving is especially challenging [16].

The understanding of craving has evolved considerably because of progress in many cross-interdisciplinary studies. For example, elucidating neurobiological circuitries [17, 18], developing preclinical models [19–21] and evolving cue-elicitation investigation in human studies [22] are several approaches that researchers have investigated to understand the role of craving in Alcohol Use Disorder (AUD). In addition, cognitive psychology [23], advanced neuroimaging techniques [24–26] and pharmacological studies [27–29] have inferred that overlapping neurochemical systems contribute to alcohol craving.

While craving is actively discussed as a symptom in addictive behaviour disorders [30–33], it is called "a strong desire or sense of compulsion to take the substance" in the *International Statistical Classification of Diseases and Related Health Problems 10th Revision* (ICD-10) [34]. The inclusion of a 'craving' criterion in the newly released *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) was predicted to bring an improvement in application of the diagnostic criteria used to assess alcohol problems [35]. In addition to the merger of the two diagnoses of Alcohol Abuse and Alcohol Dependence into a monothetic diagnosis of AUD, recent research evaluated the addition of the proposed 'craving' criterion to the DSM-5 diagnosis of AUD [36, 37]. Empirically, while the AUD coalesced criterion in the DSM-5 includes individuals who are less severely affected than those meeting only DSM-IV criteria, the consequences of adding the craving criterion could not be fully evaluated, because of the lack of relevant comparative data regarding craving [36].

The hypothesis that an ideal pharmacotherapy to treat alcoholism should target a decrease in alcohol craving was first suggested in the 1990s [38]. While many behavioural and pharmacotherapy approaches targeting craving have been shown to reduce alcohol consumption in randomized controlled trials (RCTs) [12], they have not consistently been associated with reduced alcohol relapse [4, 39–43]. Moreover, pharmacological approaches alone or combined with behavioural interventions that reduce drinking by attenuating craving have not always improved drinking outcomes [4, 44].

2 Alcohol Craving: Models and Neurobiology

Several clinical and preclinical models and approaches have been proposed to assess craving and relapse. One of the first approaches to establish a comprehensive definition of alcohol craving was derived from the hypothesis that numerous mechanisms were responsible for the urge to drink, and therefore a multidisciplinary approach was necessary to elucidate the basis of alcohol craving [45].

Psychological approaches to assess craving include study of conditioning (alcohol-related cues, i.e. the association of experiences with alcohol ingestion, which become conditioned stimuli) and cognitive models (cognitive processes that dictate the response to alcohol and alcohol-related cues during abstinence). Further, alcohol cue-exposure techniques have been utilized to evaluate cognitive changes in alcoholics [46]. According to the conditioning model, relapse situations originate from neutral stimuli that produce conditioned craving after repeated pairing of environmental stimuli and withdrawal. Many human studies targeting experimental approaches have used the cue-exposure paradigm to test pharmacotherapies for potential alcohol anti-craving properties [47]. Cue-reactivity models developed in laboratory studies allow assessment of potential risk factors for alcohol relapse. In addition, cue-reactivity sessions provide a platform to evaluate potential medications for protracted abstinence, as an alternative to laboratory methods involving alcohol administration [48, 49]. Because of the simplicity of the model adopted in original studies, craving has not always predicted alcohol relapses. The dynamics of craving (tonic, phasic, pulsatile, continuous, discontinuous) [50] and integration of neurochemical circuitry in the three-pathway psychobiological model (reward, relief and obsessive craving) offered the opportunity to simultaneously evaluate multiple psychoneural networks in AUD [51]. From the dual-process model [23], craving was conceptualized as the result of an imbalance between reflective and reflexive systems. Alcohol may increase hyper-excitability in reflexive brain areas (the prefrontal cortex) and reduce

reflective circuitries (in the amygdala). Later experimental psychology approaches corroborated the idea that drugs (as well as alcohol) have the ability to trigger specific inner mechanisms (from the locus of the emotions, such as the amygdala), which modulate, or even take over, individual cognitive resources that are needed for exercising willpower to resist drugs [52].

Reaching for alcohol, rather than trying to avoid it, is a more common behaviour in heavy-drinking alcohol-dependent individuals. It is hypothesized that this harmful behaviour is related to cue-induced craving [53]. Attention bias has also been associated with subjective craving [54]; however, 'substance seeking' is not always a conscious experience [55]. Finally, lack of self-control, impulsivity and suppression of unwanted affects are also attributed to 'resource depletion', which may trigger urges and craving [56].

Preclinical models have generated many hypotheses to explain the neurobiological mechanisms associated with anticipatory states, which have significant relevance for studies on the neurobiology of craving [57] and relapse [58]. Dysregulation of brain reward processing produced by alterations in mesolimbic dopamine (DA), glutamate, γ-aminobutyric acid (GABA) and stress circuitries may be responsible for compulsive drug use and loss of control over drug taking [59]. This neuroadaptive model of craving was based on the theory that hyper-sensitization to drugs (including alcohol) and drug-associated stimuli converts ordinary 'wanting' into craving, and prolonged abstinence may prompt reward memory, thereby inducing craving [55].

The effects of alcohol in the development of craving have been hypothesized to directly affect the mesolimbic DA pathway [60]. The implication of the limbic system in mediation of craving and loss of control is described as the incentive sensitization model. The acquisition and sensitization of craving for alcohol (and other addictive drugs) may develop by repeated exposure and release of DA in response to cues [55, 61, 62]. Additionally, the dopamine receptor subtypes described as D_1-like (D_1 and D_5) and D_2-like (D_{2-4}) are expressed in brain structures such as the amygdala and hippocampus, both of which have been implicated in human and preclinical models of addiction [55, 63–65]. The mesolimbic DA pathway projecting from the ventral tegmental area to the nucleus accumbens has been recognized as a site for the reinforcing actions of ethanol and other addictive drugs in preclinical models (Fig. 1) [66–68]. In addition, glutamatergic neurotransmission projecting from the prefrontal cortex, amygdala and hippocampus to the nucleus accumbens and ventral tegmental area are associated with relapse (Fig. 1) [69]. Alcohol is shown to modulate mesolimbic pathways and induce the urge to drink and loss of control [55].

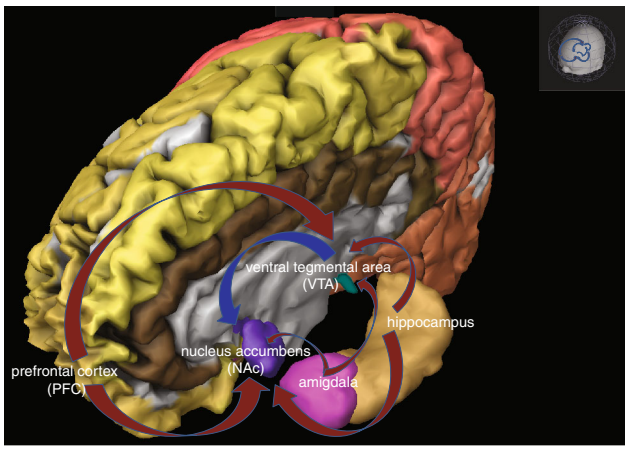

Fig. 1 Involvement of the limbic system in the mediation of craving. Mesolimbic dopamine pathways that project from the ventral tegmental area (VTA) to the nucleus accumbens (NAc) are recognized as sites for the reinforcing actions of ethanol and other addictive drugs (*blue arrow*); glutamatergic projections from the prefrontal cortex (PFC), amygdala and hippocampus to the NAc and VTA are associated with relapse (*red arrows*). [Image created using Brain Explore2, Allen Human Brain Atlas, available for download from http://human.brain-map.org/static/brainexplorer 9/12/2013]

Loss of control, with the manifestation of withdrawal symptoms [51], may be due to alterations in the increased dopaminergic and glutamatergic action and a decrease in GABAergic neurotransmission [25, 70, 71]. Modulation of serotonin (5-HT, or 5-hydroxytryptamine)-mediated signal transmission has been linked to increased alcohol consumption [72, 73] and to obsessive–compulsive behaviour in alcohol craving [74, 75]. Serotonergic neurons, located in the raphe nucleus, project to the amygdala, ventral tegmental area, hippocampus and nucleus accumbens. Serotonin traverses the synaptic clefts, tightly regulated by transporters, and binds to a discrete group of 5-HT-subtype receptors, which can selectively affect behaviours and mood states. Furthermore, the serotonergic system interacts with other neurotransmitters such as GABA in the hippocampal formation (influencing cognition and judgment) and with DA in the ventral tegmental area (mediating rewarding effects).

Alcohol alters the serotonergic system in both acute and chronic exposure. Single alcohol ingestion may increase central 5-HT levels [72] and activate 5-HT_3 receptors [76], which are widely distributed in the brain. Chronic alcohol exposure may be responsible for 5-HT_2 receptor adaptive changes resulting from the effort to compensate for continuous alcohol-induced alterations (such as increasing receptor numbers) [77]. Augmented activation of 5-HT_3 receptors in GABAergic neurons results in increased neuronal inhibition, and the increase in mesolimbic DA activity contributes to enhancement of alcohol rewarding effects. This dual mechanism has been described as the

two-stage process of craving [55, 78, 79]. Moreover, the deleterious neuroadaptations of the 5-HT_2 receptor in the effort to re-establish normal homeostasis functions may be responsible for the individual's anxiety [80] and withdrawal symptoms [81], mood dysregulation and obsessive alcohol-seeking behaviours [51], which may result in development of craving. A deficiency of serotonergic function at any level of this highly structured system may contribute to craving and increase vulnerability to development of AUD [78]. The role of serotonergic neurotransmission in alcohol craving has been evaluated using several methodologies, including interventions favouring serotonergic neurotransmission, stabilization of mood, and reduction of obsessional thinking [51].

Extensive preclinical data have demonstrated an essential role for the endogenous opioid system in stimulation of DA release by ethanol in the nucleus accumbens [82]. More recently, positron emission tomography (PET) studies have shown a correlation between alcohol craving and μ-opioid receptors in alcoholic individuals during abstinence [24, 83]. Under physiological conditions, the action of the endogenous opioid system is very subtle. Acute alcohol exposure stimulates release of brain β-endorphins, which may interact with brain regions that affect many neurobiological and behavioural effects of alcohol, either by opioid-receptor binding in the mesolimbic region or by distant action such as activation of the hypothalamic–pituitary axis (HPA). As we noted previously for other neurobiological systems affected by alcohol ingestion, chronic alcohol exposure induces adaptive changes to maintain normal homeostatic levels to overcome the effects of alcohol deprivation. Therefore, the decrease in β-endorphin activity during alcohol abstinence may favour alcohol consumption through the mechanisms of negative reinforcement, inducing craving and promoting relapses. Interventions in both direct and endocrine-like functions of the endogenous opioid system may alter mood and motivation, and may modify drinking behaviours, control alcohol craving and prevent relapses in individuals suffering from AUD [84].

In summary, human and animal models have been developed to elucidate the underlying mechanism of craving at the psychological, neurobiological, behavioural, cellular and molecular levels. However, the subjective, self-reported cognition of a state obtained in human laboratory studies is not feasible to measure in a preclinical setting [16]. Paradigms such as stress-induced techniques, conditioning, extinction and self-operant chambers are utilized to evaluate alcohol consumption and deprivation prior to drinking or during protracted abstinence [85]. More recently, others have developed novel preclinical paradigms to test tolerance during intoxication following withdrawal periods [86].

Future craving research should incorporate a large array of interdisciplinary theories, since little is known of craving in the naturalistic environment. Our current research is based mostly on assessing craving under detoxification (withdrawal craving) or in laboratory sessions (cue-reactivity craving) [50]. From a neurobiological perspective, addictive drugs produce incremental neuroadaptations, which may encompass many systems and consequent behavioural and psychological effects. To facilitate the translation of these findings into the clinical setting, neuroadaptive mechanisms entail an integration of basic neuroscience with psychology, including genetics. Neuroadaptations may be increased in subjects who have inherited a genetic predisposition [87–89] or because they have acquired susceptibility through repeated experience of intense stress [90, 91].

3 Measuring Craving

Because there is no uniformly accepted definition of craving [15], a measure that captures both the psychological and neurobiological aspects of urge and desire has been elusive [14]. The different types of craving, such as physical craving (with manifestation of withdrawal symptoms) or impulsive craving (excitability triggered by cues) [50], are not experienced by all alcohol-dependent individuals, or they may be experienced at different times during alcohol abstinence. Craving variability may be due to the individual salience of drinking, tolerance, intensity of withdrawal symptoms and subjective awareness of a compulsion to drink alcohol [16]. Measurement error in assessing craving has limited selection and monitoring of pharmacotherapies that target the desire and urge to drink during abstinence.

The major problem with assessing and measuring craving is that it is a self-reported event, and validation of subjective craving is a major issue in measuring craving in alcoholic individuals. In clinical research studies, craving assessments have included both subjective approaches (questionnaires and drinking behaviours) and objective parameters (measures of autonomic responses such as heart rate changes and salivary output). Physical responses, however, do not provide assurance that craving measurements are precise. Autonomic responses can be triggered by numerous homeostatic imbalances (thermoregulation, circadian rhythm, baroreceptors), which are very common in patients during withdrawal or in those suffering from other comorbidities. The retrospective nature of the self-reported measurement of subjective experiences by patients is widely accepted both in research and in clinical settings to assess alcohol urge and desire, despite the lack of an absolute scale for craving [92]. Measurement of craving

should include a series of items that have common meaning for the participants and the researchers. Craving is a continuous experience and cannot be exclusively restricted to a specific point during an episode of craving [93].

A commonly used measure of alcohol craving is a single-item measure that assesses craving in terms of frequency or intensity on a continuous scale (i.e. a Likert scale or visual analogue scale) [94]. This approach is easy to implement but focuses only on the current state and does not provide robust prediction over time [95, 96]. A more robust measurement of alcohol craving is the multiple-item Penn Alcohol Craving Scale. It comprises five items, which assess the frequency, intensity and duration of craving [97], and is widely used and accepted in RCTs [14]. The Yale–Brown Obsessive Compulsive Scale for heavy drinking is based the theory that craving is similar to obsessive–compulsive disorder behaviours [74, 98]. Its modified version, the Obsessive Compulsive Drinking Scale (OCDS) [2, 3, 99, 100], is regarded as one of the better-performing multi-item measures for alcohol craving [14]. The Questionnaire of Alcohol Urges, Alcohol Urge Questionnaire [101] and Alcohol Craving Questionnaire (ACQ) were derived from the 32-item Questionnaire for Smoking Urges [13]. Desire to drink is also a fluctuating experience assessed during abstinence [102], and the Desires for Alcohol Questionnaire [103] attempts to capture this subjective experience as well. These questions seek to assess the desire, pleasure, reinforcement and control over drinking. Currently, it is impossible to assess if one questionnaire is more suitable than another in assessing alcohol craving. Factors affecting self-reported measures of craving are extensive and, because of the individual differences in the severity of alcohol dependence, they are conceptually complex and have challenged researchers to develop additional questionnaires such as the Jellinek Craving Questionnaire [96] and the Alcohol Craving Experience Questionnaire [94, 103, 104].

Craving may also result from an affective state; therefore, analysis of facial expressions has been utilized to measure craving in clinical studies. Facial muscle activity, measured by facial electromyography, has been used to effectively assess global positive and negative facial expressions [105] and has previously been utilized in measuring craving in smoking studies [106]. Measurement of craving though imaging studies showing specific craving manipulation has been widely used to determine the participation of isolated brain structures. For example, using PET [107] and functional magnetic resonance imaging (fMRI) [108], it has been possible to assess craving in real time (as measured on a visual analogue scale) during alcohol cue-induced activation. Using these approaches, it was possible to visualize the involvement of specific neuroanatomical regions such as the amygdala (the emotional locus), the hippocampus (the cognitive nucleus) and the ventral striatum (with the nucleus accumbens being one of the primary neural substrates mediating addiction) specifically at the moment when patients were experiencing craving.

In summary, several tools and questionnaires are available to measure craving, but no single approach available today represents a state-of-the-art instrument to measure and capture craving from the psychological and neurobiological perspectives [14].

4 Current Pharmacotherapy Treatments to Reduce Craving for Alcohol

Specifically targeting the psychological aspects associated with the three-pathway psychological model of alcohol craving [51], experimental approaches to evaluate pharmacotherapies to reduce craving have been based on a theory of dysregulation of neurobiological mechanisms of craving associated with clinical symptoms in alcoholic individuals. First, targeting of reward pathways, which involve the stimulating effects of alcohol, may result from DA and/or opioid dysregulation. Therefore, opioid receptor antagonists (e.g. naltrexone) and DA receptor antagonists (e.g. atypical antipsychotics) have been evaluated as anti-craving medications. Another possible approach targets obsessive mechanisms. The second pathway affects the dysregulation of the 5-HT system, resulting in intrusive thoughts about drinking with impaired social functioning. As such, 5-HT_3 antagonists (e.g. ondansetron) and selective serotonin reuptake inhibitor (SSRIs; e.g. sertraline) have been tested extensively. Finally, the dysregulation of relief circuitry, resulting from GABAergic and glutamatergic activity, which is hypothesized to be responsible for several withdrawal symptoms (anxiety, tension, and arousal), was evaluated with pharmacological treatments (e.g. baclofen, gabapentin, topiramate). Table 1 lists the medications discussed in this section and their mechanisms of action.

4.1 Pharmacological Interventions That Target the Reward Pathway

4.1.1 Opioid Receptor Antagonists

The opioid-receptor antagonist naltrexone is approved by the US Food and Drug Administration (FDA) for treatment of alcoholism. In the last 20 years, many RCTs evaluating naltrexone for alcoholism have included craving as an outcome. Randomized clinical trial data have shown that naltrexone-treated patients drink less (in terms of both quantity and frequency) than placebo-treated subjects [109] and crave alcohol less than acamprosate-treated subjects [15]. Naltrexone, at a dose of 50 mg/day in combination

Table 1 Medications used to reduce craving in alcohol-dependent individuals, their mechanism of actions and their receptor selectivity

Medication	Receptor selectivity and other mechanisms of action	System
Naltrexone	μ, κ and δ competitive antagonist	Opioid
Nalmefene	μ, κ and δ competitive antagonist	
Haloperidol	D_2 antagonist	Dopamine
Aripiprazole	D_2 and 5-$HT_{1A/2C}$ partial agonist	
	5-HT_{2A} antagonist	
Quetiapine	D_{1-2} antagonist	
	5-HT_{1A} partial agonist	
	5-HT_{2A} antagonist	
	Adrenergic α_{1-2} antagonist	
Olanzapine	$D_{2,4}$ and 5-HT_2 antagonist	
Ondansetron	5-HT_3 antagonist	Serotonin
Fluoxetine	SSRI	
Topiramate	AMPA/kainate glutamate antagonist	Inhibition
	$GABA_A$ agonist	
	Carbonic anhydrase enzyme antagonist	
Lamotrigine	Sodium channel blocker	
Levetiracetam	Not fully elucidated, but it has been found to target high-voltage, N-type calcium channels, SV2A	
Zonisamide	Modulation of voltage-gated ion channels, enhancement of synaptic inhibition and inhibition of synaptic excitation	
Baclofen	$GABA_B$ agonist	
GHB	$GABA_B$ agonist	
	GHB agonist	
Memantine	NMDA antagonist	Glutamate
Acamprosate	NMDA antagonist	
	mGluR5 antagonist	
Disulfiram	Acetaldehyde dehydrogenase inhibitor	Alcohol metabolism
Varenicline	$\alpha_4\beta_2$ partial agonist	Adrenergic
Prazosin	α_1 antagonist	

5-HT serotonin, *AMPA* α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor, *GABA* γ-aminobutyric acid, *GHB* gamma-hydroxybutyric acid, *mGluR5* metabotropic glutamate receptor 5, *NMDA* N-methyl-D-aspartate, *SSRI* selective serotonin reuptake inhibitor, *SV2A* synaptic vesicle protein 2A

with behavioural therapy, decreases alcohol relapse and has been associated with a reduction in craving [110]. More recent clinical studies have shown that naltrexone is more effective in heavy-drinking alcoholics [111] and in patients with a strong family history of alcoholism [112]. Heavy-drinking early-onset alcoholics, defined as type B alcoholics, tend to crave alcohol more intensely than moderate-drinking late-onset (or type A) alcoholics [113]. These data support the usefulness of using a craving measurement as a clinical guide in assessing relapse risk in heavy-drinking alcoholics; however, the role of craving in treatment outcomes and as a predictor of drinking in moderate-drinking alcoholics remains unclear.

The fact that naltrexone, compared with placebo or acamprosate, was effective in reducing overall alcohol consumption in heavy-drinking alcoholics brought about the possibility of a feedback loop between craving and the amount of drinking in the COMBINE (Combined Pharmacotherapies and Behavioral Interventions for Alcohol Dependence) study [44]. Interestingly, it was demonstrated that naltrexone was more successful in reducing relapse when patients experienced a high level of alcohol craving at study randomization [38, 114–116]. This observation suggests that naltrexone may represent a pharmacotherapy to help patients at the initial state of recovery, when craving is at its most intense.

To establish whether opioid antagonists may be an effective anti-craving pharmacotherapy, clinical researchers have used different approaches. For example, a study was designed to administer naltrexone 'as needed' in anticipation of high-risk drinking, when triggers were expected or when drinking was felt to be imminent [117]. Compared with patients in the placebo group, patients in the naltrexone intervention group reported less craving and showed reduced drinking after 12 weeks. This approach targeted two important aspects: (1) craving intensity, which addresses the primary impact on relapse issues when the craving experience is acute [14]; and (2) craving frequency and duration, which addresses the concept of the time of maximum desire [50, 94]. A subsequent trial corroborated the targeted naltrexone data, showing that naltrexone (compared with placebo) taken only when craving occurred was effective in maintaining alcohol reduction by heavy-drinking alcoholics [118]. The efficacy of 'as needed' modification of the opioid system to reduce alcohol consumption in patients suffering from AUD has also been used with nalmefene, an opioid antagonist with a longer half-life, greater oral bioavailability and no observed dose-dependent liver toxicity, compared with naltrexone [119]. The European Medicines Agency recently approved nalmefene as a treatment for alcoholism, for use 'as needed'.

Researchers have adopted the use of a combination of pharmaceutical and behavioural therapies, and have evaluated the results, compared with monotherapies [44, 120–124]. The COMBINE study investigators demonstrated that naltrexone alone, not in combination with combined behavioural intervention (CBI), improved alcohol drinking outcomes [125]. However, both naltrexone and CBI were shown to reduce craving; yet naltrexone's anti-craving effects were visible after only 4 weeks of treatment, while CBI required 12 weeks of intervention before it reduced craving episodes [44].

The anti-craving effect of naltrexone has also been evaluated in longer studies. A 12-month open-label study in India compared the efficacy of naltrexone and disulfiram in preventing alcohol relapses in conditions similar to those seen in routine clinical practice [126]. That study demonstrated that naltrexone was superior to disulfiram in reducing craving [126]. The study supported the beneficial anti-craving effect of naltrexone that was observed in another long-term (12-month), randomized, single-blind study comparing the effects of naltrexone and acamprosate [15]. While the mean time to the 'first drink' was similar in the naltrexone group (44 days) and the acamprosate group (39 days), the time to the 'first relapse' (five or more drinks) was longer in the naltrexone group (63 days) than in the acamprosate group (42 days). At the end of treatment, participants in the naltrexone group experienced less craving than those in the acamprosate group. Conversely, despite the positive results in reducing craving when compared with other medications, naltrexone failed to be effective in reducing relapse in chronic heavy-drinking alcoholics in another study [127].

Largely as a result of genetic heritability, alcoholic individuals with a family history of alcoholism appear to have greater benefits with naltrexone therapy than those with no family history [128]. The effect of naltrexone as an anti-craving medication may be moderated by variations in the *OPRM1* (opioid receptor, mu 1) gene [89, 129, 130]. The A118G single nucleotide polymorphism (SNP) of the *OPRM1* gene was tested in a double-blind, placebo-controlled laboratory trial of naltrexone in heavy-drinking alcoholics [88]. Individuals with at least one copy of the G allele reported lower alcohol craving and a higher alcohol-induced 'high' than patients with the A homozygous allele. In other words, naltrexone attenuated alcohol craving and an alcohol-induced 'high', with a stronger effect among patients with the heterozygous G allele [88]. The efficacy of naltrexone in reducing relapses, however, was not confirmed by a study of polymorphic variants of each of the three opioid receptor genes, *OPRM1*, *OPRK1* (opioid receptor, kappa 1) and *OPRD1* (opioid receptor, delta 1) [131]. The study specifically focused on the *OPRM1* Asn40Asp variant, which was previously identified as a predictor of response to naltrexone [51, 89, 129, 130]. The moderating effects of the Asn40Asp variant on the relation between craving, alcohol consumption and the attenuating effects of naltrexone was, however, confirmed by a recent 12-week RCT [132]. In summary, naltrexone is one of the most evaluated medications in clinical research for reducing craving. It has been shown to be superior to placebo in lessening craving, preventing relapses into heavy drinking, and in increasing the percentage of abstinent days. The results obtained from numerous studies are consistent with evidence that naltrexone may reduce craving, compared with other medications (acamprosate and disulfiram); however, it has not been effective in reducing alcohol drinking as a long-term clinical outcome.

4.1.2 Dopamine Receptor Antagonists

The involvement of the dopaminergic limbic system [133] and the 'incentive sensitization' model of craving [55, 62] suggest that dopamine antagonists may counteract the DA-moderated effects of alcohol intoxication [134]. An RCT investigating the effect of the D_2 antagonist haloperidol in alcohol-dependent individuals showed that pre-treatment with haloperidol significantly reduced alcohol craving and the amount of alcohol ingested, and reduced impulsivity [134]. The detrimental consequences associated with the first generation of antipsychotics, such as extrapyramidal effects involving motor control (akathisia) and involuntary movement disorder (tardive dyskinesia), limited their use both in research and in clinical applications in treating AUD [135–137]. It was subsequently hypothesized that if first-generation antipsychotics were proved to block alcohol cue elicitation and blunt craving experiences, newer atypical antipsychotics might reduce craving symptoms without the substantial adverse effect profile associated with the first-generation antipsychotics [138]. Ultimately, use of atypical antipsychotics was shown to provide some benefit in patients suffering from AUD and those with concomitant psychiatric illness [139–143].

Aripiprazole is an atypical antipsychotic, which acts as a partial agonist both at D_2 and at 5-HT_{1A} receptors. Like other atypical antipsychotics, it also displays an antagonist profile at 5-HT_{2A} receptors. Aripiprazole, which was first proposed for use in alcoholism in 2003 [144], also antagonizes 5-HT_7 receptors and acts as a partial agonist at 5-HT_{2C} receptors. Aripiprazole was subsequently tested in a multi-site RCT but failed to achieve its primary outcomes [145]. In another double-blind comparison trial, aripiprazole was shown to reduce craving [146] but to a lesser extent than naltrexone [147].

Quetiapine, which binds to $D_{1–2}$, 5-$HT_{1A–2A}$ and adrenergic $\alpha_{1–2}$ receptors, has been shown to improve abstinence, possibly by addressing sleep disturbances in alcohol-dependent patients [148, 149]. Furthermore, quetiapine has also been shown to provide benefits in reducing craving in patients suffering from the more complicated type B alcoholism [139]. In a case study of alcoholics with mood disorder comorbidity and persistent craving after withdrawal, eight of nine individuals who received quetiapine remained abstinent during a 2- to 7-month period [150]. In a later open-label study, quetiapine was used as the sole therapy for patients suffering from alcohol dependence with a comorbid diagnosis of bipolar disorder, schizophrenia or other borderline personality disorder [151]. In this study of alcoholic patients with a concurrent axis I disorder, quetiapine not

only reduced overall alcohol consumption and psychiatric symptom intensity but also reduced craving [151]. The extended-release formulation of quetiapine was also evaluated in a larger multi-site trial but was no better than placebo in reducing heavy drinking in alcoholic patients, and also failed to improve craving [152].

Olanzapine, an atypical $D_{2,4}$ and 5-HT_2 antagonist, was investigated in a placebo-controlled RCT where participants were exposed to both the control and alcohol cues in each session [138]. The results demonstrated that a single dose of olanzapine was capable of reducing the urge to drink alcohol and loss of control, without affecting the alcohol reward mechanism [138]. Because olanzapine possesses high affinity for the D_4 receptor, clinical researchers continue to investigate whether the *DRD4* (dopamine receptor D4) gene may influence the effect of a priming dose of alcohol on craving in alcohol-dependent patients. This pharmacogenomic approach targets the effect of craving in heavy-drinking alcoholics with different variable numbers of tandem repeat (VNTR) polymorphisms of the DRD4 gene (*DRD4* VNTR). Olanzapine was capable of reducing craving exclusively in patients who possessed a long sequence of *DRD4* VNTR repeat alleles after exposure to alcohol cues [87]. A follow-up 12-week study using olanzapine showed that individuals with the *DRD4* 7-repeat allele or greater reported reductions in cue-elicited alcohol craving and consumption, while olanzapine did not attenuate alcohol craving in subjects with less than the *DRD4* 7-repeat allele [153].

Researchers reporting the results of a recent study, which evaluated the genetic influences of the dopaminergic pathways involving DA receptor genes ($DRD_{1–4}$), and the gene that encodes the DA transporter, *SLC6A3* [solute carrier family 6 (neurotransmitter reporter), member 3], concluded that despite the large sample size ($n = 3{,}976$), it was not possible to identify a strong enough genetic influence of DA to moderate craving with the severity of alcohol dependence [154].

In summary, pharmacological interventions that target the antagonist effect at the limbic system by counteracting the dopaminergic effects of alcohol intoxication with the intent of mediating craving have not provided consistent results, although they have provided some benefit in patients suffering from AUD and those with concomitant psychiatric illness.

4.2 Pharmacological Interventions That Target Obsessive Mechanisms

4.2.1 The Serotonin System: 5-HT Receptor Antagonists and SSRIs

The role of the serotonergic system in alcohol craving has focused mainly on the participation of impulse-control processes as meditators of addictive behaviours [78], targeting both antagonism at the widely expressed 5-HT_3 receptor and inhibitory action of SSRIs. Ondansetron is a 5-HT_3 receptor antagonist used as an antiemetic for post-operative nausea and has been shown to have beneficial effects in reducing drinking behaviour in early-onset drinkers [155, 156]. An fMRI study, which targeted the ventral striatum—an area of the brain identified as being cue stimulated with release of alcohol-induced DA output [157]—demonstrated that naltrexone and ondansetron, alone or in combination, decreased alcohol cue-induced activation [108].

The serotonergic system has also been identified as a critical component of the craving experience [78]. In an early placebo-controlled trial, the SSRI fluoxetine reduced craving for alcohol [158]. However, in a subsequent trial, while it was reported that craving was reduced, there were no differences in alcohol drinking outcomes [159]. Despite the intensive research dedicated to understanding the effects of alcohol on the serotonergic system, RCTs utilizing SSRIs have reported conflicting results [160–162]. The lack of clinical consensus regarding beneficial outcomes from use of SSRIs may be due to the complexity of the serotonergic system, since distinct 5-HT receptor subtypes act on several neural mechanisms associated with alcohol consumption [163, 164]. In addition, different genetic variations in the 5-HT system suggest that the diverse populations previously discussed, such as type A and type B alcoholics [113], may respond differentially to SSRI treatment [165–167] or may even benefit from treatment using specific 5-HT_3-receptor antagonists [155, 168–170]. The type B group may benefit from a pharmacotherapy that offers more than blocking 5-HT reuptake [139].

Genetic influences may be responsible for some of the conflicting results in the study of the relationship between 5-HT and alcohol dependence. For example, the gene that encodes the 5-HT transporter, *SLC6A4* [solute carrier family 6 (neurotransmitter transporter), member 4] contains a SNP (rs1042173) that may be a genetic marker for cue-induced alcohol craving among alcoholics [171]. More specifically, these data support the hypothesis that an underlying neurobiological mechanism associated with the rs1042173-TT genotype may trigger disproportionate craving in response to alcohol consumption [171].

4.3 Pharmacological Interventions That Target a Relief Mechanism

4.3.1 The Inhibition System

Topiramate is an FDA-approved antiepileptic drug with multiple mechanisms of action, including antagonism of α-

amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA)/kainate glutamate receptors, potentiation of GABA, enhancement of $GABA_A$ receptor function and inhibition of the carbonic anhydrase enzyme. Topiramate, at 300 mg/day (after titration), was evaluated as a possible treatment to reduce drinking days, with positive outcomes, compared with placebo, in reducing the percentage of heavy drinking days from baseline and overall drinking days [172]. It was also suggested that topiramate may attenuate drinking consumption by lessening alcohol craving [173]. A laboratory study evaluated a lower dose of topiramate (200 mg/day) in an alcohol-cue reactivity paradigm, showing that topiramate reduced drinking during the titration period, as compared with placebo, but did not alter craving [43]. The results from this study suggested that topiramate might reduce drinking at lower doses than those previously tested, and that the reduced drinking may not be linked to the reduction of craving. A pharmacogenetic investigation also reported that a SNP (rs2832407) of the *GRIK1* (glutamate receptor, ionotropic, kainite 1) gene was associated with serum levels of topiramate, affecting the severity of topiramate-induced side effects on the basis of genotype [174].

Lamotrigine, levetiracetam and zonisamide are other anti-epileptic medications that have a broad combination of mechanisms of action [175–177] and have been evaluated for treating alcohol craving or urge. Lamotrigine is a sodium channel blocker with many indeterminate mechanisms of action. Lamotrigine has reduced craving both in preclinical models [178] and in human trials [142]. In combination with clozapine, lamotrigine was shown to reduce craving among patients suffering from schizophrenia and comorbid alcohol dependence [142]. Levetiracetam has been shown to reduce alcohol craving in open-label studies [179]; however, in a double-blind, placebo-controlled RCT, levetiracetam did not show beneficial effects on alcohol consumption in patients suffering from severe AUD [180]. In an open-label study of alcohol-dependent patients, zonisamide reduced craving, weekly drinking and urge [181]. Zonisamide also reduced heavy drinking, overall drinking and urge in a double-blind RCT, compared with placebo [182].

Baclofen, a $GABA_B$ receptor agonist approved by the FDA to control muscular spasticity, has been used with beneficial effects in treating AUD [183–185]. On the basis of its limited liver metabolism, baclofen was hypothesized as a pharmacotherapy intervention suitable for alcoholic patients with cirrhosis [186], including those with hepatitis C virus infection [187], and effective in suppressing alcohol withdrawal [183, 185, 188]. The positive outcomes, measured as lessening of craving in alcoholics [189–192], were suggested by the effects of baclofen in reducing anxiety [190, 193], which is a frequent comorbid condition in alcoholics [194]. It was also demonstrated that despite the previous positive drinking outcomes and the reduction of anxiety, baclofen was not superior to placebo in the treatment of alcohol dependence [195]. In addition to the difference in the severity of alcohol dependence [196] and a large placebo effect [197], a reason for these conflicting results might be the large variability of baclofen's pharmacokinetic profile in alcoholics [198]. Finally, a recent pilot laboratory study provided preliminary evidence that baclofen may not reduce cue-induced craving, and suggested that baclofen's ability to reduce alcohol drinking might be secondary to its ability to alter alcohol-related biphasic effects [199].

Gamma-hydroxybutyric acid (GHB), which is approved in Italy and Austria as a treatment for alcohol dependence, has been investigated as an anti-craving medication for alcohol dependence [200]. GHB is a naturally occurring substance and is approved by the FDA for restricted use in treating narcolepsy. GHB has also been used as a general anaesthetic and to treat conditions such as insomnia, clinical depression and alcoholism in Europe. It is also used as an illegal intoxicant or as a date-rape drug [200]. The transient beneficial effect of GHB in reducing craving, compared with placebo [201, 202], may be due to the short half-life of the drug [203]. In one study, patients receiving the same dose of GHB (50 mg/kg) from three to six times daily reported less craving than at baseline [204]. Despite the encouraging results from investigations of GHB in lessening craving, the clinical application of a drug that requires administration six times daily in patients suffering from AUD (who often have other comorbidities)—and that is itself an addicting substance—is difficult to justify. Nonetheless, GHB is widely used in some European countries, but it is distributed under very strict medical monitoring [205].

4.3.2 The Glutamate System: NMDA Receptor Antagonists

Glutamate, the major excitatory neurotransmitter in the brain, utilizes both inotropic and metabotropic receptors to transduce excitatory signals. *N*-methyl-D-aspartate (NMDA) receptors are gated by membrane potentials and provide binding sites simultaneously for both glycine and glutamate. NMDA receptors represent one of the highest-affinity ethanol targets in the central nervous system (CNS) [206–209]). Specifically, ethanol inhibits responses to NMDA in distinct regional variants in NMDA receptor subunit composition. Preclinical glutamatergic studies have therefore dedicated intensive research to exploring novel pharmacotherapies for alcoholism [210, 211]. In clinical studies, NMDA receptor antagonists have been used to produce a state of intoxication that resembles ethanol's effects [212]. Therefore, pharmacotherapies that could

counteract this effect by acting on NMDA receptors have been investigated in alcohol-dependent patients [213]. Moreover, the potential benefits of NMDA receptor antagonists as treatments for craving in alcohol-dependent patients have also been investigated in preclinical trials [214] and in clinical trials [215].

Human studies using memantine, an NMDA receptor antagonist, show that NMDA receptor neurotransmission may be involved in both alcohol craving and alcohol-induced subjective dissociative effects [215, 216]. While a human laboratory study reported that pre-treatment with memantine—but not treatment of post-alcohol consumption—lessened craving [215], memantine had no effect on drinking in a placebo-controlled trial [217].

Though acamprosate (*N*-acetyl homotaurine) has been approved in Europe since 1989, it was only approved in the USA for treatment of alcohol dependence in 2004. In vitro studies have shown that acamprosate may attenuate excessive glutamatergic activity by blocking the toxicity produced by abrupt ethanol withdrawal [218]. The action of acamprosate on metabotropic glutamate receptor 5 (mGluR5) has been shown both in preclinical models [219] and in clinical findings [220]. The inclusion of acamprosate as an adjunctive pharmacotherapy to psychotherapy was shown to be successful in reducing the incidence of relapse [221] and maintaining abstinence in alcohol-dependent patients [222, 223]. A double-blind RCT, which administered acamprosate for 21 days, demonstrated that acamprosate-treated patients showed significantly reduced craving, compared with placebo-treated patients [224].

The effective acamprosate response in alcohol-dependent subjects may be influenced by genetically controlled variations in NMDA receptors and mGluR5 [219]. Pharmacogenetically relevant variants in alcohol-dependent patients were explored in a genome-wide association study, which included a follow-up study of relapse behaviour and pharmacological treatment response in patients suffering from AUD [225]. This double-blind, placebo-controlled RCT with acamprosate and naltrexone reported that the intronic SNP rs13273672, which is encoded by the *GATA4* (GATA binding protein 4) gene, was associated with a relapse in the acamprosate-treated arm only, and was a potential predictor of response to acamprosate among alcoholic individuals. However, the genetically moderated response to acamprosate was not associated with craving.

4.4 Pharmacological Interventions That Target Other Mechanisms

4.4.1 Alcohol Metabolism

Disulfiram was the first medication that received an FDA indication to treat alcoholism. It produces aversive effects by interfering with alcohol metabolism and increasing acetaldehyde concentration [226]. In RCTs, disulfiram has demonstrated inconsistent results as a pharmacotherapy to increase abstinence in alcoholics by reducing craving. As an adjunctive therapy, disulfiram has facilitated clinical benefits in reducing alcohol craving by providing additional psychological support [227]. An 8-month study comparing disulfiram with acamprosate demonstrated that although disulfiram showed more beneficial effects in preventing relapses in alcoholics, the acamprosate group reported lower craving [228].

Another study testing disulfiram in patients with a concurrent axis I psychiatric disorder and alcohol dependence suggested that disulfiram might have some benefits in reducing alcohol craving [229]. This effect may be attributed to disulfiram interfering with the metabolism of DA [230] and therefore potentially influencing development of craving. Additionally, subjects with post-traumatic stress disorder (PTSD) had better alcohol outcomes with disulfiram than with naltrexone and placebo [231]. Patients diagnosed with PTSD receiving disulfiram responded better than non-PTSD patients, possibly because of disulfiram inhibition of DA beta-hydroxylase in the CNS, potentially resulting in an excess of DA and decreased synthesis of norepinephrine [232]. The beneficial effect of disulfiram has been limited to trials where the drug was administered under supervision [233], and these trials have not provided enough evidence to support its use to treat AUD or to reduce craving in the clinical setting [234].

4.4.2 The Adrenergic System: Nicotinic Receptor Antagonists

Because both nicotine and ethanol increase DA release in the reward pathway, it has been hypothesized that they may play a synergistic role when administered simultaneously [235]. In addition, some of the effects of ethanol in the brain seem to be mediated by the activation of neuronal nicotinic acetylcholine receptors (nAChRs) [236]. Varenicline is an FDA-approved treatment for smoking cessation, which targets nAChRs and has been investigated both in preclinical studies [237–239] and in clinical settings [240, 241] as a medication to reduce alcohol consumption. Varenicline has been shown to have beneficial effects in preclinical craving models in reducing cue-induced ethanol relapses but not nicotine seeking in self-administration-reinstatement models [242]. A double-blind, placebo-controlled study examined the effect of varenicline following a priming alcohol drink and showed that varenicline attenuated alcohol craving and reduced subjective reinforcing alcohol effects [243]. Furthermore, a randomized, double-blind, 16-week study in heavy-drinking smokers, which was designed to determine the effects of varenicline on

alcohol craving, revealed that patients allocated to the varenicline arm reported less craving than the placebo group [240]. In a recent pilot study, the effects of varenicline in term of drinking outcomes were not significantly greater than the placebo effect [244]; however, a multi-site 13-week RCT, which assessed varenicline in alcohol-dependent patients (both smokers and nonsmokers), showed that the varenicline group reported significantly lower alcohol craving than the placebo control group [245].

Prazosin, an FDA-approved α_1 receptor antagonist medication approved for treatment of blood pressure and benign prostatic hyperplasia, was demonstrated to be efficacious in stress-induced alcohol reinstatement in preclinical models [246–248]. The rationale for utilization of prazosin to treat AUD was based on the potential to antagonize postsynaptic α_1 activity involved in stress-induced reinstatement of alcohol seeking and to modulate craving experiences. A preliminary clinical study performed during early recovery from alcoholism reported a favourable outcome in reducing alcohol craving, anxiety and negative emotion following stress exposure in patients taking prazosin [249]. In a second study using 16 mg/day of prazosin compared with placebo, among the 20 completers, the prazosin group reported fewer drinking days per week than the placebo group during the final 3 weeks of the study [250].

5 Conclusion

The challenges associated with the understanding of alcohol craving and its role in AUD has been a difficult task to operationalize in both the research and clinical settings. Researchers have developed interdisciplinary craving models to reduce the knowledge gap in an attempt to explain the brain circuitry pathways and the central behavioural feature of addiction. Clinicians have assessed and measured craving to monitor the efficacy of pharmacotherapies in patients suffering from AUD. However, given the relatively rudimentary understanding of the subjective nature of craving, it is not yet possible to accurately assess what experiencing craving means to both the patient and the clinician. Scientists, though, continue to strive to find medications that can reduce drinking and craving, with the assumption that treating both will result in better outcomes. As a result, many drugs have been studied, with mixed results.

Naltrexone, a medication evaluated extensively in clinical research, was shown to be superior to placebo and other interventions (CBI, disulfiram and acamprosate) in lessening craving; however, it was not effective in reducing alcohol drinking as a long-term clinical outcome. Pharmacological interventions that target the antagonist effect at the limbic system (antipsychotics) have not provided consistent results, although they have demonstrated benefit in patients with concomitant psychiatric illness. RCTs utilizing SSRIs have reported inconclusive results on their therapeutic effect in preventing relapses and lessening craving for alcohol. Varenicline, which utilizes the similar craving aspects and the synergistic effects of smoking and alcohol, has been shown to reduce craving and smoking in both smokers and nonsmokers; however, it has not always been associated with reducing alcohol consumption. A better understanding of the neurobiology associated with AUD and more comprehensive methods to measure and assess craving may favour more effective pharmacological interventions that will lead to beneficial clinical outcomes.

The development of alternative approaches that aim to reduce craving has yielded interesting interventions that require further evaluation. For example, by easing stress-induced alcohol seeking, it may be possible to reduce craving experiences, diminish the risk of relapses and facilitate the formation of memories with less deleterious behavioural consequences [251]. There are no current medications that target stress-induced craving at the extrahypothalamic brain level in order to reduce compulsive alcohol seeking, although non-peptidic, blood–brain barrier-penetrating corticotropin releasing factor (CRF) receptor 1 antagonists have shown efficacy in animal models of alcoholism treatment [252, 253]. A pharmacological intervention that targets stress-induced alcohol craving may be more suitable for patients who suffer anxiety or are prone to stress-triggered situations such as cue-induced relapses [254]. CRF antagonists that target the effect of stress on alcohol consumption, despite evidence that stress increases the risk of relapses and induces alcohol craving, have demonstrated in clinical investigations that not all alcoholics experience anxiety during abstinence, thereby limiting CRF antagonists to patients who are prone to stress-triggered situations such as cue-induced relapses. Craving is dictated by intertwined mechanisms that affect adjacent neuronal or distant physiologic systems. Current research on evaluating medications that target multi-systems may lead to new pharmacological approaches to treat AUDs.

Acknowledgements Drs Haass-Koffler, Leggio and Kenna have no conflicts of interest that are directly relevant to the content of this review. The authors would like to express their thanks for the 5T32AA007459-28 training grant from the National Institute on Alcohol Abuse and Alcoholism (NIAAA), which supports the work of Dr Haass-Koffler. Dr Leggio's current work is supported by the Division of Intramural Clinical and Biological Research of the National Institute on Alcohol Abuse and Alcoholism (NIAAA) and the Intramural Research Program of the National Institute on Drug Abuse (NIDA). Dr Kenna has received funding from the National Institute on Alcohol Abuse and Alcoholism for the following drugs: R01-AA016079 (ondansetron and sertraline), R03AA020169

(baclofen), R21AA019709 (ghrelin), R01 AA015753 (aripiprazole and topiramate), R21AA019994 (doxazosin) and R21AA021128 (metadoxine); and has received a consultancy fee from CT San Remo (GET73).

References

1. Jellinek EM. The craving for alcohol. Q J Stud Alcohol. 1955;16(1):35–8.
2. Anton RF. What is craving? Models and implications for treatment. Alcohol Res Health. 1999;23(3):165–73.
3. Anton RF, Moak DH, Latham PK. The Obsessive Compulsive Drinking Scale: a new method of assessing outcome in alcoholism treatment studies. Arch Gen Psychiatry. 1996;53(3):225–31.
4. Swift RM. Medications and alcohol craving. Alcohol Res Health. 1999;23(3):207–13.
5. Kenna GA, Swift RM, Hillemacher T, Leggio L. The relationship of appetitive, reproductive and posterior pituitary hormones to alcoholism and craving in humans. Neuropsychol Rev. 2012;22(3):211–28.
6. Litt MD, Cooney NL, Kadden RM, Gaupp L. Reactivity to alcohol cues and induced moods in alcoholics. Addict Behav. 1990;15(2):137–46.
7. Cooney NL, Litt MD, Morse PA, Bauer LO, Gaupp L. Alcohol cue reactivity, negative-mood reactivity, and relapse in treated alcoholic men. J Abnorm Psychol. 1997;106(2):243–50.
8. Fox HC, Bergquist KL, Hong KI, Sinha R. Stress-induced and alcohol cue-induced craving in recently abstinent alcohol-dependent individuals. Alcohol Clin Exp Res. 2007;31(3):395–403.
9. Breese GR, Chu K, Dayas CV, Funk D, Knapp DJ, Koob GF, et al. Stress enhancement of craving during sobriety: a risk for relapse. Alcohol Clin Exp Res. 2005;29(2):185–95.
10. Sinha R, Fox HC, Hong KA, Bergquist K, Bhagwagar Z, Siedlarz KM. Enhanced negative emotion and alcohol craving, and altered physiological responses following stress and cue exposure in alcohol dependent individuals. Neuropsychopharmacology. 2009;34(5):1198–208.
11. Mathew RJ, Claghorn JL, Largen J. Craving for alcohol in sober alcoholics. Am J Psychiatry. 1979;136(4B):603–6.
12. Monti PM, Rohsenow DJ, Rubonis AV, Niaura RS, Sirota AD, Colby SM, et al. Cue exposure with coping skills treatment for male alcoholics: a preliminary investigation. J Consult Clin Psychol. 1993;61(6):1011–9.
13. Tiffany ST. A cognitive model of drug urges and drug-use behavior: role of automatic and nonautomatic processes. Psychol Rev. 1990;97(2):147–68.
14. Kavanagh DJ, Statham DJ, Feeney GF, Young RM, May J, Andrade J, et al. Measurement of alcohol craving. Addict Behav. 2013;38(2):1572–84.
15. Rubio G, Jimenez-Arriero MA, Ponce G, Palomo T. Naltrexone versus acamprosate: one year follow-up of alcohol dependence treatment. Alcohol Alcohol. 2001;36(5):419–25.
16. Li TK. Clinical perspectives for the study of craving and relapse in animal models. Addiction. 2000;95(Suppl 2):S55–60.
17. Childress AR, Mozley PD, McElgin W, Fitzgerald J, Reivich M, O'Brien CP. Limbic activation during cue-induced cocaine craving. Am J Psychiatry. 1999;156(1):11–8.
18. Kalivas PW, O'Brien C. Drug addiction as a pathology of staged neuroplasticity. Neuropsychopharmacology. 2008;33(1):166–80.
19. Shaham Y, Shalev U, Lu L, De Wit H, Stewart J. The reinstatement model of drug relapse: history, methodology and major findings. Psychopharmacology (Berl). 2003;168(1–2):3–20.
20. Katz JL, Higgins ST. The validity of the reinstatement model of craving and relapse to drug use. Psychopharmacology (Berl). 2003;168(1–2):21–30.
21. Fuchs RA, Tran-Nguyen LT, Specio SE, Groff RS, Neisewander JL. Predictive validity of the extinction/reinstatement model of drug craving. Psychopharmacology (Berl). 1998;135(2):151–60.
22. Monti PM, Rohsenow DJ, Hutchison KE, Swift RM, Mueller TI, Colby SM, et al. Naltrexone's effect on cue-elicited craving among alcoholics in treatment. Alcohol Clin Exp Res. 1999;23(8):1386–94.
23. Tiffany ST. Cognitive concepts of craving. Alcohol Res Health. 1999;23(3):215–24.
24. Bencherif B, Wand GS, McCaul ME, Kim YK, Ilgin N, Dannals RF, et al. Mu-opioid receptor binding measured by [11C]carfentanil positron emission tomography is related to craving and mood in alcohol dependence. Biol Psychiatry. 2004;55(3):255–62.
25. Heinz A, Beck A, Grusser SM, Grace AA, Wrase J. Identifying the neural circuitry of alcohol craving and relapse vulnerability. Addict Biol. 2009;14(1):108–18.
26. Sinha R, Li CS. Imaging stress- and cue-induced drug and alcohol craving: association with relapse and clinical implications. Drug Alcohol Rev. 2007;26(1):25–31.
27. Anton RF, Moak DH, Waid LR, Latham PK, Malcolm RJ, Dias JK. Naltrexone and cognitive behavioral therapy for the treatment of outpatient alcoholics: results of a placebo-controlled trial. Am J Psychiatry. 1999;156(11):1758–64.
28. Volpicelli JR, Alterman AI, Hayashida M, O'Brien CP. Naltrexone in the treatment of alcohol dependence. Arch Gen Psychiatry. 1992;49(11):876–80.
29. O'Malley SS, Jaffe AJ, Chang G, Schottenfeld RS, Meyer RE, Rounsaville B. Naltrexone and coping skills therapy for alcohol dependence. A controlled study. Arch Gen Psychiatry. 1992;49(11):881–7.
30. Casey M, Adamson G, Shevlin M, McKinney A. The role of craving in AUDs: dimensionality and differential functioning in the DSM-5. Drug Alcohol Depend. 2012;125(1–2):75–80.
31. Keyes KM, Krueger RF, Grant BF, Hasin DS. Alcohol craving and the dimensionality of alcohol disorders. Psychol Med. 2011;41(3):629–40.
32. Cherpitel CJ, Borges G, Ye Y, Bond J, Cremonte M, Moskalewicz J, et al. Performance of a craving criterion in DSM alcohol use disorders. J Stud Alcohol Drugs. 2010;71(5):674–84.
33. Mewton L, Slade T, McBride O, Grove R, Teesson M. An evaluation of the proposed DSM-5 alcohol use disorder criteria using Australian national data. Addiction. 2011;106(5):941–50.
34. Janca A, Ustun TB, Early TS, Sartorius N. The ICD-10 symptom checklist: a companion to the ICD-10 classification of mental and behavioural disorders. Soc Psychiatry Psychiatr Epidemiol. 1993;28(5):239–42.
35. Kupfer DJ, Regier DA. Neuroscience, clinical evidence, and the future of psychiatric classification in DSM-5. Am J Psychiatry. 2011;168(7):672–4.
36. Edwards AC, Gillespie NA, Aggen SH, Kendler KS. Assessment of a modified DSM-5 diagnosis of alcohol use disorder in a genetically informative population. Alcohol Clin Exp Res. 2013;37(3):443–51.
37. Haass-Koffler CL, Kenna GA. Bacchus by Caravaggio as the visual diagnosis of alcohol use disorder from the Fifth Edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). Front Psychiatry. 2013;4:86.
38. Volpicelli JR, Alterman AI, Hayashida M, O'Brien CP. Naltrexone in the treatment of alcohol dependence. Arch Gen Psychiatry. 1992;49(11):876–80.

39. Drummond DC, Glautier S. A controlled trial of cue exposure treatment in alcohol dependence. J Consult Clin Psychol. 1994;62(4):809–17.
40. Grusser SM, Wrase J, Klein S, Hermann D, Smolka MN, Ruf M, et al. Cue-induced activation of the striatum and medial prefrontal cortex is associated with subsequent relapse in abstinent alcoholics. Psychopharmacology (Berl). 2004;175(3):296–302.
41. Litt MD, Cooney NL, Morse P. Reactivity to alcohol-related stimuli in the laboratory and in the field: predictors of craving in treated alcoholics. Addiction. 2000;95(6):889–900.
42. Verheul R, van den Brink W, Geerlings P. A three-pathway psychobiological model of craving for alcohol. Alcohol Alcohol. 1999;34(2):197–222.
43. Miranda R Jr, MacKillop J, Monti PM, Rohsenow DJ, Tidey J, Gwaltney C, et al. Effects of topiramate on urge to drink and the subjective effects of alcohol: a preliminary laboratory study. Alcohol Clin Exp Res. 2008;32(3):489–97.
44. Subbaraman MS, Lendle S, van der Laan M, Kaskutas LA, Ahern J. Cravings as a mediator and moderator of drinking outcomes in the COMBINE study. Addiction. 2013;14.
45. Singleton EG, Gorelick DA. Mechanisms of alcohol craving and their clinical implications. Recent Dev Alcohol. 1998;14:177–95.
46. Cooney NL, Gillespie RA, Baker LH, Kaplan RF. Cognitive changes after alcohol cue exposure. J Consult Clin Psychol. 1987;55(2):150–5.
47. Monti PM, Rohsenow DJ, Hutchison KE. Toward bridging the gap between biological, psychobiological and psychosocial models of alcohol craving. Addiction. 2000;95(Suppl 2):S229–36.
48. Mason BJ, Light JM, Williams LD, Drobes DJ. Proof-of-concept human laboratory study for protracted abstinence in alcohol dependence: effects of gabapentin. Addict Biol. 2009;14(1):73–83.
49. Miranda R, Ray L, Blanchard A, Reynolds EK, Monti PM, Chun T, et al. Effects of naltrexone on adolescent alcohol cue reactivity and sensitivity: an initial randomized trial. Addict Biol. 2013. doi:10.1111/adb.12050.
50. Drummond DC, Litten RZ, Lowman C, Hunt WA. Craving research: future directions. Addiction. 2000;95(Suppl 2):S247–55.
51. Verheul R, van den Brink W, Geerlings P. A three-pathway psychobiological model of craving for alcohol. Alcohol Alcohol. 1999;34(2):197–222.
52. Noel X, Van Der Linden M, Bechara A. The neurocognitive mechanisms of decision-making, impulse control, and loss of willpower to resist drugs. Psychiatry (Edgmont). 2006;3(5):30–41.
53. Stacy AW, Wiers RW. Implicit cognition and addiction: a tool for explaining paradoxical behavior. Annu Rev Clin Psychol. 2010;6:551–75.
54. Field M, Munafo MR, Franken IH. A meta-analytic investigation of the relationship between attentional bias and subjective craving in substance abuse. Psychol Bull. 2009;135(4):589–607.
55. Robinson TE, Berridge KC. The neural basis of drug craving: an incentive-sensitization theory of addiction. Brain Res Brain Res Rev. 1993;18(3):247–91.
56. Hofmann W, Schmeichel BJ, Baddeley AD. Executive functions and self-regulation. Trends Cogn Sci. 2012;16(3):174–80.
57. Meyer RE. Craving: what can be done to bring the insights of neuroscience, behavioral science and clinical science into synchrony. Addiction. 2000;95 Suppl 2:S219–27.
58. Simms JA, Haass-Koffler CL, Bito-Onon J, Li R, Bartlett SE. Mifepristone in the central nucleus of the amygdala reduces yohimbine stress-induced reinstatement of ethanol-seeking. Neuropsychopharmacology. 2012;37(4):906–18.
59. Koob GF, Le Moal M. Drug abuse: hedonic homeostatic dysregulation. Science. 1997;278(5335):52–8.
60. Modell JG, Mountz JM. Focal cerebral blood flow change during craving for alcohol measured by SPECT. J Neuropsychiatry Clin Neurosci. 1995;7(1):15–22.
61. Berridge KC, Robinson TE. What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? Brain Res Brain Res Rev. 1998;28(3):309–69.
62. Wise RA. The neurobiology of craving: implications for the understanding and treatment of addiction. J Abnorm Psychol. 1988;97(2):118–32.
63. Oak JN, Oldenhof J, Van Tol HH. The dopamine D(4) receptor: one decade of research. Eur J Pharmacol. 2000;405(1–3):303–27.
64. Asghari V, Sanyal S, Buchwaldt S, Paterson A, Jovanovic V, Van Tol HH. Modulation of intracellular cyclic AMP levels by different human dopamine D4 receptor variants. J Neurochem. 1995;65(3):1157–65.
65. Noain D, Avale ME, Wedemeyer C, Calvo D, Peper M, Rubinstein M. Identification of brain neurons expressing the dopamine D4 receptor gene using BAC transgenic mice. Eur J Neurosci. 2006;24(9):2429–38.
66. Katner SN, Weiss F. Neurochemical characteristics associated with ethanol preference in selected alcohol-preferring and -nonpreferring rats: a quantitative microdialysis study. Alcohol Clin Exp Res. 2001;25(2):198–205.
67. Koob GF. Neural mechanisms of drug reinforcement. Ann N Y Acad Sci. 1992;654:171–91.
68. Melendez RI, Rodd-Henricks ZA, Engleman EA, Li TK, McBride WJ, Murphy JM. Microdialysis of dopamine in the nucleus accumbens of alcohol-preferring (P) rats during anticipation and operant self-administration of ethanol. Alcohol Clin Exp Res. 2002;26(3):318–25.
69. Kalivas PW, Volkow N, Seamans J. Unmanageable motivation in addiction: a pathology in prefrontal-accumbens glutamate transmission. Neuron. 2005;45(5):647–50.
70. Heinz A, Siessmeier T, Wrase J, Hermann D, Klein S, Grusser SM, et al. Correlation between dopamine D(2) receptors in the ventral striatum and central processing of alcohol cues and craving. Am J Psychiatry. 2004;161(10):1783–9.
71. Heinz A, Lober S, Georgi A, Wrase J, Hermann D, Rey ER, et al. Reward craving and withdrawal relief craving: assessment of different motivational pathways to alcohol intake. Alcohol Alcohol. 2003;38(1):35–9.
72. LeMarquand D, Pihl RO, Benkelfat C. Serotonin and alcohol intake, abuse, and dependence: clinical evidence. Biol Psychiatry. 1994;36(5):326–37.
73. Johnson BA. Serotonergic agents and alcoholism treatment: rebirth of the subtype concept—an hypothesis. Alcohol Clin Exp Res. 2000;24(10):1597–601.
74. Modell JG, Glaser FB, Cyr L, Mountz JM. Obsessive and compulsive characteristics of craving for alcohol in alcohol abuse and dependence. Alcohol Clin Exp Res. 1992;16(2):272–4.
75. Roberts JS, Anton RF, Latham PK, Moak DH. Factor structure and predictive validity of the Obsessive Compulsive Drinking Scale. Alcohol Clin Exp Res. 1999;23(9):1484–91.
76. Lovinger DM, Zhou Q. Alcohols potentiate ion current mediated by recombinant 5-HT3RA receptors expressed in a mammalian cell line. Neuropharmacology. 1994;33(12):1567–72.
77. Pandey SC, Davis JM, Pandey GN. Phosphoinositide system-linked serotonin receptor subtypes and their pharmacological properties and clinical correlates. J Psychiatry Neurosci. 1995;20(3):215–25.
78. Ciccocioppo R. The role of serotonin in craving: from basic research to human studies. Alcohol Alcohol. 1999;34(2):244–53.
79. Di Chiara G. A motivational learning hypothesis of the role of mesolimbic dopamine in compulsive drug use. J Psychopharmacol. 1998;12(1):54–67.

80. Lal H, Prather PL, Rezazadeh SM. Potential role of 5HT1C and/or 5HT2 receptors in the mianserin-induced prevention of anxiogenic behaviors occurring during ethanol withdrawal. Alcohol Clin Exp Res. 1993;17(2):411–7.
81. Lovinger DM. 5-HT3 receptors and the neural actions of alcohols: an increasingly exciting topic. Neurochem Int. 1999;35(2):125–30.
82. Di Chiara G, Imperato A. Ethanol preferentially stimulates dopamine release in the nucleus accumbens of freely moving rats. Eur J Pharmacol. 1985;115(1):131–2.
83. Heinz A, Reimold M, Wrase J, Hermann D, Croissant B, Mundle G, et al. Correlation of stable elevations in striatal mu-opioid receptor availability in detoxified alcoholic patients with alcohol craving: a positron emission tomography study using carbon 11-labeled carfentanil. Arch Gen Psychiatry. 2005;62(1):57–64.
84. Gianoulakis C. Influence of the endogenous opioid system on high alcohol consumption and genetic predisposition to alcoholism. J Psychiatry Neurosci. 2001;26(4):304–18.
85. Koob GF, Weiss F, Tiffany ST, Zieglgansberger W, Spanagel R. Animal models of craving: a roundtable discussion. Alcohol Res Health. 1999;23(3):233–6.
86. Rhodes JS, Best K, Belknap JK, Finn DA, Crabbe JC. Evaluation of a simple model of ethanol drinking to intoxication in C57BL/6J mice. Physiol Behav. 2005;84(1):53–63.
87. Hutchison KE, Wooden A, Swift RM, Smolen A, McGeary J, Adler L, et al. Olanzapine reduces craving for alcohol: a DRD4 VNTR polymorphism by pharmacotherapy interaction. Neuropsychopharmacology. 2003;28(10):1882–8.
88. Ray LA, Hutchison KE. Effects of naltrexone on alcohol sensitivity and genetic moderators of medication response: a double-blind placebo-controlled study. Arch Gen Psychiatry. 2007;64(9):1069–77.
89. Oslin DW, Berrettini W, Kranzler HR, Pettinati H, Gelernter J, Volpicelli JR, et al. A functional polymorphism of the mu-opioid receptor gene is associated with naltrexone response in alcohol-dependent patients. Neuropsychopharmacology. 2003;28(8):1546–52.
90. Brown SA, Vik PW, McQuaid JR, Patterson TL, Irwin MR, Grant I. Severity of psychosocial stress and outcome of alcoholism treatment. J Abnorm Psychol. 1990;99(4):344–8.
91. Breese GR, Knapp DJ, Overstreet DH. Stress sensitization of ethanol withdrawal-induced reduction in social interaction: inhibition by CRF-1 and benzodiazepine receptor antagonists and a 5-HT1A-receptor agonist. Neuropsychopharmacology. 2004;29(3):470–82.
92. Sloan JA, Aaronson N, Cappelleri JC, Fairclough DL, Varricchio C. Assessing the clinical significance of single items relative to summated scores. Mayo Clin Proc. 2002;77(5):479–87.
93. Sitharthan T, McGrath D, Sitharthan G, Saunders JB. Meaning of craving in research on addiction. Psychol Rep. 1992;71(3 Pt 1):823–6.
94. Drobes DJ, Thomas SE. Assessing craving for alcohol. Alcohol Res Health. 1999;23(3):179–86.
95. Ooteman W, Koeter MW, Vserheul R, Schippers GM, van den Brink W. Measuring craving: an attempt to connect subjective craving with cue reactivity. Alcohol Clin Exp Res. 2006;30(1):57–69.
96. Connor JP, Feeney GF, Young RM. A comparison of the Yale–Brown Obsessive Compulsive Scale for "heavy drinking" with a single item craving measure: construct validity and clinical utility. Subst Use Misuse. 2005;40(4):551–61.
97. Flannery BA, Volpicelli JR, Pettinati HM. Psychometric properties of the Penn Alcohol Craving Scale. Alcohol Clin Exp Res. 1999;23(8):1289–95.
98. Modell JG, Glaser FB, Mountz JM, Schmaltz S, Cyr L. Obsessive and compulsive characteristics of alcohol abuse and dependence: quantification by a newly developed questionnaire. Alcohol Clin Exp Res. 1992;16(2):266–71.
99. Anton RF, Moak DH, Latham P. The Obsessive Compulsive Drinking Scale: a self-rated instrument for the quantification of thoughts about alcohol and drinking behavior. Alcohol Clin Exp Res. 1995;19(1):92–9.
100. Anton RF. Obsessive–compulsive aspects of craving: development of the Obsessive Compulsive Drinking Scale. Addiction. 2000;95(Suppl 2):S211–7.
101. Bohn MJ, Krahn DD, Staehler BA. Development and initial validation of a measure of drinking urges in abstinent alcoholics. Alcohol Clin Exp Res. 1995;19(3):600–6.
102. Kavanagh DJ, Andrade J, May J. Imaginary relish and exquisite torture: the elaborated intrusion theory of desire. Psychol Rev. 2005;112(2):446–67.
103. Kavanagh DJ, May J, Andrade J. Tests of the elaborated intrusion theory of craving and desire: features of alcohol craving during treatment for an alcohol disorder. Br J Clin Psychol. 2009;48(Pt 3):241–54.
104. Statham DJ, Connor JP, Kavanagh DJ, Feeney GF, Young RM, May J, et al. Measuring alcohol craving: development of the Alcohol Craving Experience questionnaire. Addiction. 2011;106(7):1230–8.
105. Cacioppo JT, Martzke JS, Petty RE, Tassinary LG. Specific forms of facial EMG response index emotions during an interview: from Darwin to the continuous flow hypothesis affect-laden information processing. J Pers Soc Psychol. 1988;54(4):592–604.
106. Drobes DJ, Tiffany ST. Induction of smoking urge through imaginal and in vivo procedures: physiological and self-report manifestations. J Abnorm Psychol. 1997;106(1):15–25.
107. Everitt B. Craving cocaine cues: cognitive neuroscience meets drug addiction research. Trends Cogn Sci. 1997;1(1):1–2.
108. Myrick H, Anton RF, Li X, Henderson S, Randall PK, Voronin K. Effect of naltrexone and ondansetron on alcohol cue-induced activation of the ventral striatum in alcohol-dependent people. Arch Gen Psychiatry. 2008;65(4):466–75.
109. Chick J, Anton R, Checinski K, Croop R, Drummond DC, Farmer R, et al. A multicentre, randomized, double-blind, placebo-controlled trial of naltrexone in the treatment of alcohol dependence or abuse. Alcohol Alcohol. 2000;35(6):587–93.
110. O'Malley SS, Krishnan-Sarin S, Farren C, Sinha R, Kreek MJ. Naltrexone decreases craving and alcohol self-administration in alcohol-dependent subjects and activates the hypothalamo–pituitary–adrenocortical axis. Psychopharmacology (Berl). 2002;160(1):19–29.
111. Davidson D, Palfai T, Bird C, Swift R. Effects of naltrexone on alcohol self-administration in heavy drinkers. Alcohol Clin Exp Res. 1999;23(2):195–203.
112. Monterosso JR, Flannery BA, Pettinati HM, Oslin DW, Rukstalis M, O'Brien CP, et al. Predicting treatment response to naltrexone: the influence of craving and family history. Am J Addict. 2001;10(3):258–68.
113. Babor TF, Hofmann M, DelBoca FK, Hesselbrock V, Meyer RE, Dolinsky ZS, et al. Types of alcoholics, I. Evidence for an empirically derived typology based on indicators of vulnerability and severity. Arch Gen Psychiatry. 1992;49(8):599–608.
114. Jaffe AJ, Rounsaville B, Chang G, Schottenfeld RS, Meyer RE, O'Malley SS. Naltrexone, relapse prevention, and supportive therapy with alcoholics: an analysis of patient treatment matching. J Consult Clin Psychol. 1996;64(5):1044–53.
115. O'Malley SS, Jaffe AJ, Chang G, Schottenfeld RS, Meyer RE, Rounsaville B. Naltrexone and coping skills therapy for alcohol

dependence: a controlled study. Arch Gen Psychiatry. 1992;49(11):881–7.
116. Volpicelli JR, Clay KL, Watson NT, O'Brien CP. Naltrexone in the treatment of alcoholism: predicting response to naltrexone. J Clin Psychiatry. 1995;56(Suppl 7):39–44.
117. Kranzler HR, Tennen H, Penta C, Bohn MJ. Targeted naltrexone treatment of early problem drinkers. Addict Behav. 1997;22(3):431–6.
118. Heinala P, Alho H, Kiianmaa K, Lonnqvist J, Kuoppasalmi K, Sinclair JD. Targeted use of naltrexone without prior detoxification in the treatment of alcohol dependence: a factorial double-blind, placebo-controlled trial. J Clin Psychopharmacol. 2001;21(3):287–92.
119. Mann K, Bladstrom A, Torup L, Gual A, van den Brink W. Extending the treatment options in alcohol dependence: a randomized controlled study of as-needed nalmefene. Biol Psychiatry. 2013;73(8):706–13.
120. Anton RF, Moak DH, Latham P, Waid LR, Myrick H, Voronin K, et al. Naltrexone combined with either cognitive behavioral or motivational enhancement therapy for alcohol dependence. J Clin Psychopharmacol. 2005;25(4):349–57.
121. Anton RF, Moak DH, Latham PK, Waid LR, Malcolm RJ, Dias JK, et al. Posttreatment results of combining naltrexone with cognitive–behavior therapy for the treatment of alcoholism. J Clin Psychopharmacol. 2001;21(1):72–7.
122. Anton RF, Moak DH, Waid LR, Latham PK, Malcolm RJ, Dias JK. Naltrexone and cognitive behavioral therapy for the treatment of outpatient alcoholics: results of a placebo-controlled trial. Am J Psychiatry. 1999;156(11):1758–64.
123. Heilig M, Egli M. Pharmacological treatment of alcohol dependence: target symptoms and target mechanisms. Pharmacol Ther. 2006;111(3):855–76.
124. Weiss RD, Kueppenbender KD. Combining psychosocial treatment with pharmacotherapy for alcohol dependence. J Clin Psychopharmacol. 2006;26(Suppl 1):S37–42.
125. Anton RF, O'Malley SS, Ciraulo DA, Cisler RA, Couper D, Donovan DM, et al. Combined pharmacotherapies and behavioral interventions for alcohol dependence: the COMBINE study. A randomized controlled trial. JAMA. 2006;295(17):2003–17.
126. De Sousa A. A one-year pragmatic trial of naltrexone vs disulfiram in the treatment of alcohol dependence. Alcohol Alcohol. 2004;39(6):528–31.
127. Krystal JH, Cramer JA, Krol WF, Kirk GF, Rosenheck RA. Naltrexone in the treatment of alcohol dependence. N Engl J Med. 2001;345(24):1734–9.
128. Krishnan-Sarin S, Krystal JH, Shi J, Pittman B, O'Malley SS. Family history of alcoholism influences naltrexone-induced reduction in alcohol drinking. Biol Psychiatry. 2007;62(6):694–7.
129. McGeary JE, Monti PM, Rohsenow DJ, Tidey J, Swift R, Miranda R Jr. Genetic moderators of naltrexone's effects on alcohol cue reactivity. Alcohol Clin Exp Res. 2006;30(8):1288–96.
130. Anton RF, Oroszi G, O'Malley S, Couper D, Swift R, Pettinati H, et al. An evaluation of mu-opioid receptor (OPRM1) as a predictor of naltrexone response in the treatment of alcohol dependence: results from the Combined Pharmacotherapies and Behavioral Interventions for Alcohol Dependence (COMBINE) study. Arch Gen Psychiatry. 2008;65(2):135–44.
131. Gelernter J, Gueorguieva R, Kranzler HR, Zhang H, Cramer J, Rosenheck R, et al. Opioid receptor gene (OPRM1, OPRK1, and OPRD1) variants and response to naltrexone treatment for alcohol dependence: results from the VA Cooperative Study. Alcohol Clin Exp Res. 2007;31(4):555–63.
132. Kranzler HR, Armeli S, Covault J, Tennen H. Variation in OPRM1 moderates the effect of desire to drink on subsequent drinking and its attenuation by naltrexone treatment. Addict Biol. 2013;18(1):193–201.
133. Modell JG, Mountz JM, Beresford TP. Basal ganglia/limbic striatal and thalamocortical involvement in craving and loss of control in alcoholism. J Neuropsychiatry Clin Neurosci. 1990;2(2):123–44.
134. Modell JG, Mountz JM, Glaser FB, Lee JY. Effect of haloperidol on measures of craving and impaired control in alcoholic subjects. Alcohol Clin Exp Res. 1993;17(2):234–40.
135. Sussman N. The implications of weight changes with antipsychotic treatment. J Clin Psychopharmacol. 2003;23(3 Suppl 1):S21–6.
136. Osser DN, Najarian DM, Dufresne RL. Olanzapine increases weight and serum triglyceride levels. J Clin Psychiatry. 1999;60(11):767–70.
137. Heiskanen T, Niskanen L, Lyytikainen R, Saarinen PI, Hintikka J. Metabolic syndrome in patients with schizophrenia. J Clin Psychiatry. 2003;64(5):575–9.
138. Hutchison KE, Swift R, Rohsenow DJ, Monti PM, Davidson D, Almeida A. Olanzapine reduces urge to drink after drinking cues and a priming dose of alcohol. Psychopharmacology (Berl). 2001;155(1):27–34.
139. Kampman KM, Pettinati HM, Lynch KG, Whittingham T, Macfadden W, Dackis C, et al. A double-blind, placebo-controlled pilot trial of quetiapine for the treatment of type A and type B alcoholism. J Clin Psychopharmacol. 2007;27(4):344–51.
140. Scheller-Gilkey G, Woolwine BJ, Cooper I, Gay O, Moynes KA, Miller AH. Relationship of clinical symptoms and substance use in schizophrenia patients on conventional versus atypical antipsychotics. Am J Drug Alcohol Abuse. 2003;29(3):553–66.
141. Green AI, Burgess ES, Dawson R, Zimmet SV, Strous RD. Alcohol and cannabis use in schizophrenia: effects of clozapine vs. risperidone. Schizophr Res. 2003;60(1):81–5.
142. Kalyoncu A, Mirsal H, Pektas O, Unsalan N, Tan D, Beyazyurek M. Use of lamotrigine to augment clozapine in patients with resistant schizophrenia and comorbid alcohol dependence: a potent anti-craving effect? J Psychopharmacol. 2005;19(3):301–5.
143. Drake RE, Xie H, McHugo GJ, Green AI. The effects of clozapine on alcohol and drug use disorders among patients with schizophrenia. Schizophr Bull. 2000;26(2):441–9.
144. Kenna GA. Rationale for use of aripiprazole for alcohol dependence treatment. Drugs Future. 2003;28(12):1227–35.
145. Anton RF, Kranzler H, Breder C, Marcus RN, Carson WH, Han J. A randomized, multicenter, double-blind, placebo-controlled study of the efficacy and safety of aripiprazole for the treatment of alcohol dependence. J Clin Psychopharmacol. 2008;28(1):5–12.
146. Martinotti G, Di Nicola M, Janiri L. Efficacy and safety of aripiprazole in alcohol dependence. Am J Drug Alcohol Abuse. 2007;33(3):393–401.
147. Martinotti G, Di Nicola M, Di Giannantonio M, Janiri L. Aripiprazole in the treatment of patients with alcohol dependence: a double-blind, comparison trial vs. naltrexone. J Psychopharmacol. 2009;23(2):123–9.
148. Monnelly EP, Ciraulo DA, Knapp C, LoCastro J, Sepulveda I. Quetiapine for treatment of alcohol dependence. J Clin Psychopharmacol. 2004;24(5):532–5.
149. Landolt HP, Gillin JC. Sleep abnormalities during abstinence in alcohol-dependent patients: aetiology and management. CNS Drugs. 2001;15(5):413–25.

150. Croissant B, Klein O, Gehrlein L, Kniest A, Hermann D, Diehl A, et al. Quetiapine in relapse prevention in alcoholics suffering from craving and affective symptoms: a case series. Eur Psychiatry. 2006;21(8):570–3.
151. Martinotti G, Andreoli S, Di Nicola M, Di Giannantonio M, Sarchiapone M, Janiri L. Quetiapine decreases alcohol consumption, craving, and psychiatric symptoms in dually diagnosed alcoholics. Hum Psychopharmacol. 2008;23(5):417–24.
152. Litten RZ, Fertig JB, Falk DE, Ryan ML, Mattson ME, Collins JF, et al. A double-blind, placebo-controlled trial to assess the efficacy of quetiapine fumarate XR in very heavy-drinking alcohol-dependent patients. Alcohol Clin Exp Res. 2012;36(3):406–16.
153. Hutchison KE, Ray L, Sandman E, Rutter MC, Peters A, Davidson D, et al. The effect of olanzapine on craving and alcohol consumption. Neuropsychopharmacology. 2006;31(6):1310–7.
154. Agrawal A, Wetherill L, Bucholz KK, Kramer J, Kuperman S, Lynskey MT, et al. Genetic influences on craving for alcohol. Addict Behav. 2013;38(2):1501–8.
155. Johnson BA, Roache JD, Javors MA, DiClemente CC, Cloninger CR, Prihoda TJ, et al. Ondansetron for reduction of drinking among biologically predisposed alcoholic patients: a randomized controlled trial. JAMA. 2000;284(8):963–71.
156. Johnson BA, Roache JD, Ait-Daoud N, Zanca NA, Velazquez M. Ondansetron reduces the craving of biologically predisposed alcoholics. Psychopharmacology (Berl). 2002;160(4):408–13.
157. Myrick H, Anton RF, Li X, Henderson S, Drobes D, Voronin K, et al. Differential brain activity in alcoholics and social drinkers to alcohol cues: relationship to craving. Neuropsychopharmacology. 2004;29(2):393–402.
158. Naranjo CA, Poulos CX, Bremner KE, Lanctot KL. Fluoxetine attenuates alcohol intake and desire to drink. Int Clin Psychopharmacol. 1994;9(3):163–72.
159. Kabel DI, Petty F. A placebo-controlled, double-blind study of fluoxetine in severe alcohol dependence: adjunctive pharmacotherapy during and after inpatient treatment. Alcohol Clin Exp Res. 1996;20(4):780–4.
160. Pettinati HM. The use of selective serotonin reuptake inhibitors in treating alcoholic subtypes. J Clin Psychiatry. 2001;62(Suppl 20):26–31.
161. Pettinati HM, Volpicelli JR, Luck G, Kranzler HR, Rukstalis MR, Cnaan A. Double-blind clinical trial of sertraline treatment for alcohol dependence. J Clin Psychopharmacol. 2001;21(2):143–53.
162. Kranzler HR, Burleson JA, Brown J, Babor TF. Fluoxetine treatment seems to reduce the beneficial effects of cognitive–behavioral therapy in type B alcoholics. Alcohol Clin Exp Res. 1996;20(9):1534–41.
163. Lovinger DM. Serotonin's role in alcohol's effects on the brain. Alcohol Health Res World. 1997;21(2):114–20.
164. Kenna GA, McGeary JE, Swift RM. Pharmacotherapy, pharmacogenomics, and the future of alcohol dependence treatment, part 2. Am J Health Syst Pharm. 2004;61(22):2380–8.
165. Pettinati HM, Volpicelli JR, Kranzler HR, Luck G, Rukstalis MR, Cnaan A. Sertraline treatment for alcohol dependence: interactive effects of medication and alcoholic subtype. Alcohol Clin Exp Res. 2000;24(7):1041–9.
166. Johnson BA. The role of serotonergic agents as treatments for alcoholism. Drugs Today (Barc). 2003;39(9):665–72.
167. Johnson BA, Seneviratne C, Wang XQ, Ait-Daoud N, Li MD. Determination of genotype combinations that can predict the outcome of the treatment of alcohol dependence using the 5-HT(3) antagonist ondansetron. Am J Psychiatry. 2013;170(9):1020–31.
168. Johnson BA, Ait-Daoud N, Ma JZ, Wang Y. Ondansetron reduces mood disturbance among biologically predisposed, alcohol-dependent individuals. Alcohol Clin Exp Res. 2003;27(11):1773–9.
169. Kenna GA, Zywiak WH, McGeary JE, Leggio L, McGeary C, Wang S, et al. A within-group design of nontreatment seeking 5-HTTLPR genotyped alcohol-dependent subjects receiving ondansetron and sertraline. Alcohol Clin Exp Res. 2009;33(2):315–23.
170. Kranzler HR, Armeli S, Tennen H, Covault J, Feinn R, Arias AJ, et al. A double-blind, randomized trial of sertraline for alcohol dependence: moderation by age of onset [corrected] and 5-hydroxytryptamine transporter-linked promoter region genotype. J Clin Psychopharmacol. 2011;31(1):22–30.
171. Ait-Daoud N, Seneviratne C, Smith JB, Roache JD, Dawes MA, Liu L, et al. Preliminary evidence for cue-induced alcohol craving modulated by serotonin transporter gene polymorphism rs1042173. Front Psychiatry. 2012;3:6.
172. Johnson BA, Rosenthal N, Capece JA, Wiegand F, Mao L, Beyers K, et al. Topiramate for treating alcohol dependence: a randomized controlled trial. JAMA. 2007;298(14):1641–51.
173. Johnson BA, Ait-Daoud N, Bowden CL, DiClemente CC, Roache JD, Lawson K, et al. Oral topiramate for treatment of alcohol dependence: a randomised controlled trial. Lancet. 2003;361(9370):1677–85.
174. Ray LA, Miranda R Jr, MacKillop J, McGeary J, Tidey JW, Rohsenow DJ, et al. A preliminary pharmacogenetic investigation of adverse events from topiramate in heavy drinkers. Exp Clin Psychopharmacol. 2009;17(2):122–9.
175. Biton V. Clinical pharmacology and mechanism of action of zonisamide. Clin Neuropharmacol. 2007;30(4):230–40.
176. Ulloa CM, Towfigh A, Safdieh J. Review of levetiracetam, with a focus on the extended release formulation, as adjuvant therapy in controlling partial-onset seizures. Neuropsychiatr Dis Treat. 2009;5:467–76.
177. Coulter DA. Antiepileptic drug cellular mechanisms of action: where does lamotrigine fit in? J Child Neurol. 1997;12(Suppl 1):S2–9.
178. Vengeliene V, Heidbreder CA, Spanagel R. The effects of lamotrigine on alcohol seeking and relapse. Neuropharmacology. 2007;53(8):951–7.
179. Sarid-Segal O, Piechniczek-Buczek J, Knapp C, Afshar M, Devine E, Sickles L, et al. The effects of levetiracetam on alcohol consumption in alcohol-dependent subjects: an open label study. Am J Drug Alcohol Abuse. 2008;34(4):441–7.
180. Fertig JB, Ryan ML, Falk DE, Litten RZ, Mattson ME, Ransom J, et al. A double-blind, placebo-controlled trial assessing the efficacy of levetiracetam extended-release in very heavy drinking alcohol-dependent patients. Alcohol Clin Exp Res. 2012;36(8):1421–30.
181. Rubio G, Lopez-Munoz F, Ferre F, Martinez-Gras I, Ponce G, Pascual JM, et al. Effects of zonisamide in the treatment of alcohol dependence. Clin Neuropharmacol. 2010;33(5):250–3.
182. Arias AJ, Feinn R, Oncken C, Covault J, Kranzler HR. Placebo-controlled trial of zonisamide for the treatment of alcohol dependence. J Clin Psychopharmacol. 2010;30(3):318–22.
183. Addolorato G, Caputo F, Capristo E, Janiri L, Bernardi M, Agabio R, et al. Rapid suppression of alcohol withdrawal syndrome by baclofen. Am J Med. 2002;112(3):226–9.
184. Addolorato G, Leggio L, Abenavoli L, Caputo F, Gasbarrini G. Baclofen for outpatient treatment of alcohol withdrawal syndrome. J Fam Pract. 2005;54(1):24.
185. Addolorato G, Leggio L, Abenavoli L, Agabio R, Caputo F, Capristo E, et al. Baclofen in the treatment of alcohol withdrawal syndrome: a comparative study vs diazepam. Am J Med. 2006;119(3):276 e13–8.
186. Addolorato G, Leggio L, Ferrulli A, Cardone S, Vonghia L, Mirijello A, et al. Effectiveness and safety of baclofen for

maintenance of alcohol abstinence in alcohol-dependent patients with liver cirrhosis: randomised, double-blind controlled study. Lancet. 2007;370(9603):1915–22.
187. Leggio L, Ferrulli A, Zambon A, Caputo F, Kenna GA, Swift RM, et al. Baclofen promotes alcohol abstinence in alcohol dependent cirrhotic patients with hepatitis C virus (HCV) infection. Addict Behav. 2012;37(4):561–4.
188. Lyon JE, Khan RA, Gessert CE, Larson PM, Renier CM. Treating alcohol withdrawal with oral baclofen: a randomized, double-blind, placebo-controlled trial. J Hosp Med. 2011;6(8):469–74.
189. Addolorato G, Caputo F, Capristo E, Colombo G, Gessa GL, Gasbarrini G. Ability of baclofen in reducing alcohol craving and intake: II—preliminary clinical evidence. Alcohol Clin Exp Res. 2000;24(1):67–71.
190. Addolorato G, Caputo F, Capristo E, Domenicali M, Bernardi M, Janiri L, et al. Baclofen efficacy in reducing alcohol craving and intake: a preliminary double-blind randomized controlled study. Alcohol Alcohol. 2002;37(5):504–8.
191. Bucknam W. Suppression of symptoms of alcohol dependence and craving using high-dose baclofen. Alcohol Alcohol. 2007;42(2):158–60.
192. Flannery BA, Garbutt JC, Cody MW, Renn W, Grace K, Osborne M, et al. Baclofen for alcohol dependence: a preliminary open-label study. Alcohol Clin Exp Res. 2004;28(10): 1517–23.
193. Drake RG, Davis LL, Cates ME, Jewell ME, Ambrose SM, Lowe JS. Baclofen treatment for chronic posttraumatic stress disorder. Ann Pharmacother. 2003;37(9):1177–81.
194. Grant BF, Stinson FS, Dawson DA, Chou SP, Dufour MC, Compton W, et al. Prevalence and co-occurrence of substance use disorders and independent mood and anxiety disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. Arch Gen Psychiatry. 2004;61(8):807–16.
195. Garbutt JC, Kampov-Polevoy AB, Gallop R, Kalka-Juhl L, Flannery BA. Efficacy and safety of baclofen for alcohol dependence: a randomized, double-blind, placebo-controlled trial. Alcohol Clin Exp Res. 2010;34(11):1849–57.
196. Leggio L, Garbutt JC, Addolorato G. Effectiveness and safety of baclofen in the treatment of alcohol dependent patients. CNS Neurol Disord Drug Targets. 2010;9(1):33–44.
197. Colloca L, Miller FG. How placebo responses are formed: a learning perspective. Philos Trans R Soc Lond B Biol Sci. 2011;366(1572):1859–69.
198. Marsot A, Imbert B, Alvarez JC, Grassin-Delyle S, Jaquet I, Lancon C, et al. High variability in the exposure of baclofen in alcohol-dependent patients. Alcohol Clin Exp Res. 2014;38(2): 316–21.
199. Leggio L, Zywiak WH, McGeary JE, Edwards S, Fricchione SR, Shoaff JR, et al. A human laboratory pilot study with baclofen in alcoholic individuals. Pharmacol Biochem Behav. 2013;103(4): 784–91.
200. Johnson BA, Swift RM, Addolorato G, Ciraulo DA, Myrick H. Safety and efficacy of GABAergic medications for treating alcoholism. Alcohol Clin Exp Res. 2005;29(2):248–54.
201. Gallimberti L, Ferri M, Ferrara SD, Fadda F, Gessa GL. Gamma-hydroxybutyric acid in the treatment of alcohol dependence: a double-blind study. Alcohol Clin Exp Res. 1992;16(4):673–6.
202. Addolorato G, Castelli E, Stefanini GF, Casella G, Caputo F, Marsigli L, et al. An open multicentric study evaluating 4-hydroxybutyric acid sodium salt in the medium-term treatment of 179 alcohol dependent subjects. GHB Study Group. Alcohol Alcohol. 1996;31(4):341–5.
203. Ferrara SD, Zotti S, Tedeschi L, Frison G, Castagna F, Gallimberti L, et al. Pharmacokinetics of gamma-hydroxybutyric acid in alcohol dependent patients after single and repeated oral doses. Br J Clin Pharmacol. 1992;34(3):231–5.
204. Addolorato G, Cibin M, Caputo F, Capristo E, Gessa GL, Stefanini GF, et al. Gamma-hydroxybutyric acid in the treatment of alcoholism: dosage fractioning utility in non-responder alcoholic patients. Drug Alcohol Depend. 1998;53(1):7–10.
205. Addolorato G, Leggio L, Ferrulli A, Caputo F, Gasbarrini A. The therapeutic potential of gamma-hydroxybutyric acid for alcohol dependence: balancing the risks and benefits. A focus on clinical data. Expert Opin Investig Drugs. 2009;18(5):675–86.
206. Weight FF. Cellular and molecular physiology of alcohol actions in the nervous system. Int Rev Neurobiol. 1992;33:289–348.
207. Lovinger DM, White G, Weight FF. Ethanol inhibits NMDA-activated ion current in hippocampal neurons. Science. 1989;243(4899):1721–4.
208. Peoples RW, Weight FF. Ethanol inhibition of *N*-methyl-D-aspartate-activated ion current in rat hippocampal neurons is not competitive with glycine. Brain Res. 1992;571(2):342–4.
209. Lovinger DM. Developmental decrease in ethanol inhibition of *N*-methyl-D-aspartate receptors in rat neocortical neurons: relation to the actions of ifenprodil. J Pharmacol Exp Ther. 1995;274(1):164–72.
210. Grant KA, Colombo G. Discriminative stimulus effects of ethanol: effect of training dose on the substitution of *N*-methyl-D-aspartate antagonists. J Pharmacol Exp Ther. 1993;264(3): 1241–7.
211. Hundt W, Danysz W, Holter SM, Spanagel R. Ethanol and *N*-methyl-D-aspartate receptor complex interactions: a detailed drug discrimination study in the rat. Psychopharmacology (Berl). 1998;135(1):44–51.
212. Krystal JH, Petrakis IL, Webb E, Cooney NL, Karper LP, Namanworth S, et al. Dose-related ethanol-like effects of the NMDA antagonist, ketamine, in recently detoxified alcoholics. Arch Gen Psychiatry. 1998;55(4):354–60.
213. Krupitsky EM, Neznanova O, Masalov D, Burakov AM, Didenko T, Romanova T, et al. Effect of memantine on cue-induced alcohol craving in recovering alcohol-dependent patients. Am J Psychiatry. 2007;164(3):519–23.
214. Bienkowski P, Koros E, Kostowski W, Danysz W. Effects of *N*-methyl-D-aspartate receptor antagonists on reinforced and non-reinforced responding for ethanol in rats. Alcohol. 1999;18(2–3):131–7.
215. Bisaga A, Evans SM. Acute effects of memantine in combination with alcohol in moderate drinkers. Psychopharmacology (Berl). 2004;172(1):16–24.
216. Nagy J. Renaissance of NMDA receptor antagonists: do they have a role in the pharmacotherapy for alcoholism? IDrugs. 2004;7(4):339–50.
217. Evans SM, Levin FR, Brooks DJ, Garawi F. A pilot double-blind treatment trial of memantine for alcohol dependence. Alcohol Clin Exp Res. 2007;31(5):775–82.
218. De Witte P, Littleton J, Parot P, Koob G. Neuroprotective and abstinence-promoting effects of acamprosate: elucidating the mechanism of action. CNS Drugs. 2005;19(6):517–37.
219. Blednov YA, Harris RA. Metabotropic glutamate receptor 5 (mGluR5) regulation of ethanol sedation, dependence and consumption: relationship to acamprosate actions. Int J Neuropsychopharmacol. 2008;11(6):775–93.
220. Mann K, Lehert P, Morgan MY. The efficacy of acamprosate in the maintenance of abstinence in alcohol-dependent individuals: results of a meta-analysis. Alcohol Clin Exp Res. 2004;28(1):51–63.
221. Lhuintre JP, Daoust M, Moore ND, Chretien P, Saligaut C, Tran G, et al. Ability of calcium bis acetyl homotaurine, a GABA agonist, to prevent relapse in weaned alcoholics. Lancet. 1985;1(8436):1014–6.

222. Paille FM, Guelfi JD, Perkins AC, Royer RJ, Steru L, Parot P. Double-blind randomized multicentre trial of acamprosate in maintaining abstinence from alcohol. Alcohol Alcohol. 1995;30(2):239–47.
223. Pelc I, Verbanck P, Le Bon O, Gavrilovic M, Lion K, Lehert P. Efficacy and safety of acamprosate in the treatment of detoxified alcohol-dependent patients: a 90-day placebo-controlled dose-finding study. Br J Psychiatry. 1997;171:73–7.
224. Hammarberg A, Nylander I, Zhou Q, Jayaram-Lindstrom N, Reid MS, Franck J. The effect of acamprosate on alcohol craving and correlation with hypothalamic pituitary adrenal (HPA) axis hormones and beta-endorphin. Brain Res. 2009;1305(Suppl):S2–6.
225. Kiefer F, Witt SH, Frank J, Richter A, Treutlein J, Lemenager T, et al. Involvement of the atrial natriuretic peptide transcription factor GATA4 in alcohol dependence, relapse risk and treatment response to acamprosate. Pharmacogenomics J. 2011;11(5): 368–74.
226. Savas MC, Gullu IH. Disulfiram-ethanol test reaction: significance of supervision. Ann Pharmacother. 1997;31(3):374–5.
227. Suh JJ, Pettinati HM, Kampman KM, O'Brien CP. The status of disulfiram: a half of a century later. J Clin Psychopharmacol. 2006;26(3):290–302.
228. de Sousa A. An open randomized study comparing disulfiram and acamprosate in the treatment of alcohol dependence. Alcohol Alcohol. 2005;40(6):545–8.
229. Petrakis IL, Poling J, Levinson C, Nich C, Carroll K, Rounsaville B. Naltrexone and disulfiram in patients with alcohol dependence and comorbid psychiatric disorders. Biol Psychiatry. 2005;57(10):1128–37.
230. Rogers WK, Benowitz NL, Wilson KM, Abbott JA. Effect of disulfiram on adrenergic function. Clin Pharmacol Ther. 1979;25(4):469–77.
231. Petrakis IL, Poling J, Levinson C, Nich C, Carroll K, Ralevski E, et al. Naltrexone and disulfiram in patients with alcohol dependence and comorbid post-traumatic stress disorder. Biol Psychiatry. 2006;60(7):777–83.
232. Karamanakos PN, Pappas P, Stephanou P, Marselos M. Differentiation of disulfiram effects on central catecholamines and hepatic ethanol metabolism. Pharmacol Toxicol. 2001;88(2):106–10.
233. Krampe H, Ehrenreich H. Supervised disulfiram as adjunct to psychotherapy in alcoholism treatment. Curr Pharm Des. 2010;16(19):2076–90.
234. Franck J, Jayaram-Lindstrom N. Pharmacotherapy for alcohol dependence: status of current treatments. Curr Opin Neurobiol. 2013;23(4):692–9.
235. Tizabi Y, Bai L, Copeland RL Jr, Taylor RE. Combined effects of systemic alcohol and nicotine on dopamine release in the nucleus accumbens shell. Alcohol Alcohol. 2007;42(5):413–6.
236. Chatterjee S, Bartlett SE. Neuronal nicotinic acetylcholine receptors as pharmacotherapeutic targets for the treatment of alcohol use disorders. CNS Neurol Disord Drug Targets. 2010;9(1):60–76.
237. Ericson M, Lof E, Stomberg R, Soderpalm B. The smoking cessation medication varenicline attenuates alcohol and nicotine interactions in the rat mesolimbic dopamine system. J Pharmacol Exp Ther. 2009;329(1):225–30.
238. Bito-Onon JJ, Simms JA, Chatterjee S, Holgate J, Bartlett SE. Varenicline, a partial agonist at neuronal nicotinic acetylcholine receptors, reduces nicotine-induced increases in 20% ethanol operant self-administration in Sprague–Dawley rats. Addict Biol. 2011;16(3):440–9.
239. Steensland P, Simms JA, Holgate J, Richards JK, Bartlett SE. Varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, selectively decreases ethanol consumption and seeking. Proc Natl Acad Sci USA. 2007;104(30):12518–23.
240. Mitchell JM, Teague CH, Kayser AS, Bartlett SE, Fields HL. Varenicline decreases alcohol consumption in heavy-drinking smokers. Psychopharmacology (Berl). 2012;223(3):299–306.
241. Fucito LM, Toll BA, Wu R, Romano DM, Tek E, O'Malley SS. A preliminary investigation of varenicline for heavy drinking smokers. Psychopharmacology (Berl). 2011;215(4):655–63.
242. Wouda JA, Riga D, De Vries W, Stegeman M, van Mourik Y, Schetters D, et al. Varenicline attenuates cue-induced relapse to alcohol, but not nicotine seeking, while reducing inhibitory response control. Psychopharmacology (Berl). 2011;216(2): 267–77.
243. McKee SA, Harrison EL, O'Malley SS, Krishnan-Sarin S, Shi J, Tetrault JM, et al. Varenicline reduces alcohol self-administration in heavy-drinking smokers. Biol Psychiatry. 2009;66(2): 185–90.
244. Plebani JG, Lynch KG, Rennert L, Pettinati HM, O'Brien CP, Kampman KM. Results from a pilot clinical trial of varenicline for the treatment of alcohol dependence. Drug Alcohol Depend. 2013;133(2):754–8.
245. Litten RZ, Ryan ML, Fertig JB, Falk DE, Johnson B, Dunn KE, et al. A double-blind, placebo-controlled trial assessing the efficacy of varenicline tartrate for alcohol dependence. J Addict Med. 2013;7(4):277–286.
246. Le AD, Funk D, Juzytsch W, Coen K, Navarre BM, Cifani C, et al. Effect of prazosin and guanfacine on stress-induced reinstatement of alcohol and food seeking in rats. Psychopharmacology (Berl). 2011;218(1):89–99.
247. Walker BM, Rasmussen DD, Raskind MA, Koob GF. Alpha1-noradrenergic receptor antagonism blocks dependence-induced increases in responding for ethanol. Alcohol. 2008;42(2):91–7.
248. Rasmussen DD, Alexander LL, Raskind MA, Froehlich JC. The alpha1-adrenergic receptor antagonist, prazosin, reduces alcohol drinking in alcohol-preferring (P) rats. Alcohol Clin Exp Res. 2009;33(2):264–72.
249. Fox HC, Anderson GM, Tuit K, Hansen J, Kimmerling A, Siedlarz KM, et al. Prazosin effects on stress- and cue-induced craving and stress response in alcohol-dependent individuals: preliminary findings. Alcohol Clin Exp Res. 2012;36(2):351–60.
250. Simpson TL, Saxon AJ, Meredith CW, Malte CA, McBride B, Ferguson LC, et al. A pilot trial of the alpha-1 adrenergic antagonist, prazosin, for alcohol dependence. Alcohol Clin Exp Res. 2009;33(2):255–63.
251. Heilig M, Thorsell A, Sommer WH, Hansson AC, Ramchandani VA, George DT, et al. Translating the neuroscience of alcoholism into clinical treatments: from blocking the buzz to curing the blues. Neurosci Biobehav Rev. 2010;35(2):334–44.
252. Gehlert DR, Cramer J, Morin SM. Effects of corticotropin-releasing factor 1 receptor antagonism on the hypothalamic–pituitary–adrenal axis of rodents. J Pharmacol Exp Ther. 2012;341(3):672–80.
253. Gehlert DR, Cippitelli A, Thorsell A, Le AD, Hipskind PA, Hamdouchi C, et al. 3-(4-Chloro-2-morpholin-4-yl-thiazol-5-yl)-8-(1-ethylpropyl)-2,6-dimethyl-imidazo [1,2-b]pyridazine: a novel brain-penetrant, orally available corticotropin-releasing factor receptor 1 antagonist with efficacy in animal models of alcoholism. J Neurosci. 2007;27(10):2718–26.
254. Zorrilla EP, Heilig M, de Wit H, Shaham Y. Behavioral, biological, and chemical perspectives on targeting CRF(1) receptor antagonists to treat alcoholism. Drug Alcohol Depend. 2013;128(3):175–86.