Neuropsychopharmacology REVIEWS (2012) 37, 163–177

Novel Therapeutic Strategies for Alcohol and Drug Addiction: Focus on GABA, Ion Channels and Transcranial Magnetic Stimulation

Giovanni Addolorato[1], Lorenzo Leggio[1,2], F Woodward Hopf[3], Marco Diana[4] and Antonello Bonci*[,5,6,7]

[1]Institute of Internal Medicine, Catholic University of Rome, Rome, Italy; [2]Brown University Medical School, Department of Behavioral and Social Science, Center for Alcohol and Addiction Studies, Providence, RI, USA; [3]Department of Neurology, Ernest Gallo Clinic and Research Center, University of California, San Francisco, CA, USA; [4]Department of Drug Sciences, G Minardi' Cognitive Neuroscience Laboratory, University of Sassari, Sassari, Italy; [5]NIDA Intramural Research Program, Baltimore, MD, USA; [6]Department of Neurology, UCSF, San Francisco, CA, USA; [7]Solomon H Snyder Department of Neuroscience, Johns Hopkins School of Medicine, Baltimore, MD, USA

Drug addiction represents a major social problem where addicts and alcoholics continue to seek and take drugs despite adverse social, personal, emotional, and legal consequences. A number of pharmacological compounds have been tested in human addicts with the goal of reducing the level or frequency of intake, but these pharmacotherapies have often been of only moderate efficacy or act in a sub-population of humans. Thus, there is a tremendous need for new therapeutic interventions to treat addiction. Here, we review recent interesting studies focusing on gamma-aminobutyric acid receptors, voltage-gated ion channels, and transcranial magnetic stimulation. Some of these treatments show considerable promise to reduce addictive behaviors, or the early clinical studies or pre-clinical rationale suggest that a promising avenue could be developed. Thus, it is likely that within a decade or so, we could have important new and effective treatments to achieve the goal of reducing the burden of human addiction and alcoholism.

Neuropsychopharmacology Reviews (2012) **37,** 163–177; doi:10.1038/npp.2011.216; published online 26 October 2011

Keywords: alcoholism; addiction; pharmacotherapy; GABA; ion channels; transcranial magnetic stimulation

INTRODUCTION

Drug addiction is a chronic, relapsing condition with a multifactorial etiology that includes genetic, neurobiological, psychological, and environmental components (Koob, 2006). Protracted behavior modification, cognitive behavioral therapy, psychological counseling, and mutual support groups (eg, Alcoholic Anonymous) have been considered the most effective long-term treatments. However, increasing knowledge of the neurobiological mechanisms underlying the development and persistence of addiction has led to wider recognition of drug addiction as a clinical disorder (Jupp and Lawrence, 2010). In particular, specific brain neurotransmitter systems associated with the various phases of addiction (acute initial effects, repeated intoxication, withdrawal, and relapse) have been identified. Accordingly, treatment has progressed from social and behavioral approaches alone to 'adjunct' pharmacotherapy interventions.

Since the 1980s, the number of medications found to be potentially effective in treating addictive disorders, as well as the rate of approval of new medications for specific addictive disorders, has increased. For example, in the United States, Food and Drug Administration (FDA)-approved medications exist for nicotine, alcohol, and opioid addiction, with progress being made to develop agents for psychostimulant (amphetamines and cocaine) use disorders (Lingford-Hughes *et al*, 2010). Specifically, bupropion and varenicline have FDA approval for use with nicotine, and future options might exist with endocannabinoid antagonists and GABAergic agents. Aversive agents,

*Correspondence: Dr A Bonci. NIDA Intramural Research Program, Baltimore, MD, USA; Department of Neurology, UCSF, San Francisco, CA, USA; & Solomon H Snyder Department of Neuroscience, Johns Hopkins School of Medicine, Baltimore, MD, USA. Tel: +1 44 3740 2463, Fax: +1 44 3740 2855, E-mail: antonello.bonci@nih.gov; antonello.bonci@ucsf.edu
Received 8 March 2011; revised 8 July 2011; accepted 27 July 2011

opiate antagonists, and glutamate-based interventions are currently approved to treat alcoholism, with future promise with GABAergic, serotonergic, and endocannabinoid system agents. Opiate addiction is treated by approved agonist and antagonist *mu*-opioid medications, with future potential for agents that can modulate stress systems (eg, CRF). Although no pharmacotherapies are approved currently for cocaine use disorders, promising lines of research include agents that affect dopaminergic (Yao *et al*, 2010), GABAergic, serotonergic, and glutamatergic systems. Corticotropin-releasing factor receptor (CRFR) antagonists have also shown to be effective against ethanol intake in preclinical studies (Zorrilla and Koob, 2010), together with novel ALDH-inhibitors (Arolfo *et al*, 2009). In addition, pharmacogenetics and pharmacogenomics may also offer valuable strategies (Siu and Tyndale, 2007) in the near future.

Although there are promising new pharmacological treatments for alcohol and drug addiction, only a few medications are approved for use in humans and often only a sub-population of humans shows therapeutic benefit from these treatments (Spanagel, 2009). Thus, there is a substantial need for innovative ways to provide effective therapies for alcohol and drug abuse disorders. As there are many reviews addressing new pharmacological interventions for addiction (eg, Koob *et al*, 2009; Spanagel, 2009), in this review we focus on gamma-aminobutyric acid (GABA), which we believe has considerable evidence for pharmacotherapeutic potential, and ion channels, whereas repetitive transcranial magnetic stimulation (rTMS) modulation of dopamine (DA) signalling may hold promise in the near future.

This review does not cover the whole recent and current efforts in identifying novel neuropharmacological targets for alcohol and drugs of abuse. Rather, we wanted to provide examples of three different stages of development in the field of addictions neuropharmacology, that is, (1) an example of a neuropharmacological target (ie, GABA) already translated from bench to bedside; and (2) an example of a target, which can be translated into research clinical studies in the very near future, ie, ion channels, as well as (3) describing rTMS, which we believe holds promise as a non-pharmacological intervention for treatment of addiction.

NOVEL THERAPEUTIC STRATEGIES AGAINST ALCOHOL AND SUBSTANCE ABUSE DISORDERS

GABA as a Therapeutic Target for Addiction

A considerable literature has brought many advances in understanding the role of the GABA system in alcohol and addiction mechanisms. GABA is the major inhibitory neurotransmitter in the central nervous system (CNS) and binds $GABA_A$ receptors that are a family of chloride ion channels that predominately mediate rapid inhibitory neurotransmission throughout the CNS (Kumar *et al*, 2009); activation of $GABA_A$ receptors by GABA results in an influx of chloride ions, which hyperpolarizes the membrane leading to neuronal inhibition. Moreover, $GABA_A$ receptors are heteromeric protein complexes consisting of several homologous membrane-spanning glycoprotein subunits that generate various subunit compositions and may account for variable sensitivity to modulatory drugs such as benzodiazepines, barbiturates, neuroactive steroids, ethanol, and general anesthetics (Olsen and Sieghart, 2009).

In addition to its actions on ionotropic $GABA_A$ receptors, GABA activates a class of metabotropic $GABA_B$ receptors that have an important inhibitory role in the CNS. $GABA_B$ receptors are heterodimers made up of two homologous subunits (GB1 and GB2) and belong to the family C (class III) group of G protein-coupled receptors (Weiner and Valenzuela, 2006). The $GABA_B$ receptors have a role in the reinforcement process, which represents a mechanism whereby a behavior is strengthened by the event that follows the behavior (Cousins *et al*, 2002; Fadda *et al*, 2003) and has been hypothesized to modulate a variety of alcohol- and drug-related reward and reinforcement behaviors, through both pre- and postsynaptic action (Colombo *et al*, 2004; Walker and Koob, 2007).

It is generally recognized that the mesolimbic DA pathway originating in the ventral tegmental area (VTA) and interacting stress circuitry have an important role in the development of addiction (Koob, 1992; Melis *et al*, 2005). GABAergic neurons in the VTA are a primary inhibitory regulator of DA neurons, and, for example, opioid receptor activation on these GABA neurons reduces GABAergic inhibition of DA neurons (Luscher and Malenka, 2011). In addition, a subset of VTA GABA receptors may be implicated in the development of addictive behavior. In particular, it has been reported that activation of central GABAergic neurotransmission (particularly through $GABA_B$ receptors of the VTA) is closely connected with mesolimbic dopaminergic neurotransmission during rewarding processes (Diana *et al*, 2003; Fadda *et al*, 2003; Steffensen *et al*, 2009).

Thus, both clinical and preclinical studies have focused on the GABA system as a potential pharmacotherapeutic target for the treatment of alcohol and drug abuse disorders. Alcohol-related behaviors represent an interesting example of preclinical studies. Acute exposure to ethanol potentiates $GABA_A$ receptor function by complex effects on pre- and postsynaptic elements of GABAergic synapses (Fleming *et al*, 2009) and accordingly, induces a CNS depression secondary to enhanced inhibitory transmission. On the other hand, chronic ethanol exposure seems to induce compensatory adaptations to the acute facilitatory effects of ethanol on GABAergic synapses (Steffensen *et al*, 2009; Diana *et al*, 2003), such as marked changes in the expression of specific $GABA_A$ receptor subunits and alterations in the subunit composition of these receptors, which are primarily responsible for alterations in GABAergic signalling associated with chronic ethanol exposure (Weiner and Valenzuela, 2006). These adaptive changes are thought to lead to a pronounced hypofunction of

GABAergic neurotransmission and possibly the development of tolerance to the effects of ethanol on these synapses (Weiner and Valenzuela, 2006).

Regarding alcohol intake behaviors, negative allosteric modulators of the $GABA_A$ receptor reduce alcohol intake in several alcohol-preferring lines of rats (Wegelius *et al*, 1993). Moreover, antagonism of $GABA_A$ receptors within VTA or increasing the activity of those receptors in the nucleus accumbens suppressed alcohol consumption in alcohol-preferring P rats, suggesting the particular importance of these nuclei in alcohol dependence (Vengeliene *et al*, 2008). In addition, $GABA_B$ direct agonists such as baclofen or positive allosteric modulators, dose-dependently reduces oral alcohol self-administration as well as alcohol's reinforcing and motivational properties (Colombo *et al*, 2004; Maccioni and Colombo, 2009; Tyacke *et al*, 2010), suggesting that pharmacological activation of the $GABA_B$ receptor may represent a potentially effective pharmacotherapy for drug addiction in humans (Maccioni and Colombo, 2009; Tyacke *et al*, 2010).

Here, we will present some examples of medications that work on the GABA system and represent promising therapies for the treatment of alcohol and drugs use disorders, ie, baclofen, gabapentin, and topiramate. It should also be noted that these medications are not direct dopaminergic drugs and may act outside the DA system. In general, we first focus on studies related to alcohol, since there are more studies relative to other abused drugs and thus it is simpler to evaluate the overall clinical efficacy for alcohol use disorders.

Baclofen

Baclofen is a selective $GABA_B$ receptor agonist; in particular, it can act presynaptically to hyperpolarize synaptic terminals, inhibiting the influx of calcium and preventing the release of the excitatory neurotransmitters glutamate and aspartate. It is used as an antispasticity agent in multiple sclerosis, cerebral palsy, various spinal cord lesions, and other neurological conditions (Davidoff, 1985). Baclofen is well-absorbed after oral administration and undergoes little liver metabolism ($\sim$15%), being primarily eliminated by renal excretion; about 85% of a single oral dose is excreted unchanged in the urine (Davidoff, 1985).

Preclinical pharmacological and behavioral data indicate that baclofen effectively suppresses acquisition and maintenance of alcohol drinking behavior, relapse-like drinking, and alcohol's reinforcing, rewarding, stimulating, and motivational properties in rats and mice (Cousins *et al*, 2002; Maccioni and Colombo, 2009). Furthermore, administration of baclofen has been reported to inhibit the severity of the alcohol withdrawal syndrome (AWS), including anxiety-related behaviors, tremors, and seizures in rats made physically dependent on alcohol (Colombo *et al*, 2000; Knapp *et al*, 2007). Different lines of experimental evidence suggest that mesolimbic DA neurons are involved in the mediation of alcohol intake and reinforcement (Weiss and Porrino, 2002; Melis *et al*, 2005). The activation of $GABA_B$ receptors, located on the cell body of DA neurons by $GABA_B$ receptor agonists may exert an inhibitory action on the DA neurons (Yoshida *et al*, 1994; Westerink *et al*, 1996). In particular, a preliminary microdialysis experiment demonstrated that baclofen suppressed alcohol-stimulated DA release in the shell of the nucleus accumbens of rats (Colombo *et al*, 2004). Thus, preclinical studies support the use of baclofen as an anti-addictive agent, and provide a possible cellular mechanism.

The first human open-label pilot study showed the ability of baclofen (10 mg three times a day (t.i.d.) over 4 weeks) in reducing alcohol craving and intake in 10 alcohol-dependent individuals (Addolorato *et al*, 2000). These encouraging results led the same researchers to test baclofen in a randomized, double-blind, placebo-controlled design (Addolorato *et al*, 2002) in which baclofen (10 mg t.i.d.) or placebo was administered for 4 weeks to 39 alcohol-dependent subjects. Results of this study showed baclofen's efficacy, with respect to placebo, in reducing alcohol intake, craving scores, and state anxiety, and in increasing cumulative abstinence duration. Subsequent open-label 12-week pilot studies have further confirmed the role of baclofen in reducing alcohol intake and craving and anxiety scores, and promoting alcohol abstinence (Flannery *et al*, 2004; Leggio *et al*, 2008a, b). In both studies, baclofen was reasonably tolerated and no serious adverse events were reported. The most common side effects were sleepiness, tiredness, and vertigo, which tended to resolve within 1–2 weeks of drug treatment.

Recently, these findings were extended in a larger double-blind placebo-controlled trial involving 84 alcohol-dependent patients affected by liver cirrhosis (Addolorato *et al*, 2007). Considering the safe profile of baclofen evidenced in previous studies (Addolorato *et al*, 2000, 2002; Flannery *et al*, 2004) and its prevalent renal excretion (Davidoff, 1985), baclofen was tested in a population of more severe alcoholic patients who are usually excluded from alcohol-related pharmacological trials because of the risk of exacerbating liver disease. Consistent with previous observations, this study showed a significant effect of baclofen (10 mg t.i.d.), compared with placebo, in reducing alcohol craving and intake and in promoting total alcohol abstinence. Baclofen was well tolerated: as in previous studies, the most common reported side effects were headache, tiredness, vertigo, and sleepiness, and no patients reported serious side effects or significant changes in number connection test performance. The safety of baclofen in patients with alcoholic liver disease has been confirmed by a small study where baclofen was administered for at least 5 months in patients with alcoholic hepatitis (Avanesyan and Runyon, 2010). Together, these data suggest baclofen may represent a promising pharmacotherapy for alcohol-dependent patients affected by alcoholic liver disease. However, in contrast to previous studies (Addolorato *et al*, 2000, 2002, 2007; Flannery *et al*, 2004), another 12-week clinical trial (Garbutt *et al*, 2010)

did not find significant differences between baclofen (10 mg t.i.d.) and placebo in reducing heavy drinking and craving, nor in increasing the percentage of abstinence. In this study, adverse events were relatively mild, with only two individuals stopping baclofen because of fatigue and severe tendonitis. A possible explanation of the difference in outcomes across trials could be the different severity of alcohol dependence of the enrolled patients (Flannery and Garbutt, 2008; Garbutt, 2009; Garbutt *et al*, 2010; Leggio *et al*, 2010a, b). In particular, a recent analysis of previous positive and negative baclofen studies has shown a difference in baseline alcohol drinking, withdrawal severity, and anxiety (Leggio *et al*, 2010a, b).

All studies reported above tested baclofen at a dose of 10 mg t.i.d. However, the safety and the manageability of baclofen led researchers to test baclofen at higher doses. Two case reports showed a significant reduction of alcohol consumption achieved with high doses of baclofen, specifically up to 140 mg/day (Bucknam, 2007) and up to 270 mg/day (Ameisen, 2005). Moreover, the safety of baclofen at higher doses has been confirmed by a recent pilot laboratory study testing 80 mg baclofen in combination with intoxicating doses of alcohol in 18 non-treatment-seeking social drinkers who did not meet the criteria for alcohol dependence (Evans and Bisaga, 2009). Finally, the role of different doses of baclofen (10 mg or 20 mg t.i.d.) in alcohol dependence has been explored in a randomized double-blind placebo-controlled 12-week trial, initially planned as a multisite trial called the *International Baclofen Interventional Study* (IBIS) and involving sites in Europe and Australia. However, in several sites, there was a large loss at follow-up of subjects and the unavailability of all outcome measures at all time-points. Nonetheless, a secondary analysis of the Italian sample (42 patients enrolled; 14 were randomly allocated to placebo, 14 to the group treated with baclofen 10 mg t.i.d., and 14 to the group treated with baclofen 20 mg t.i.d.) showed a significant dose-response effect. Specifically, compared with the patients given placebo, patients allocated into the baclofen 10 mg group had a 53% of reduction in the number of drinks per day and patients in the baclofen 20 mg group had a 68% of reduction in the number of drinks per day. The effect of baclofen 20 mg t.i.d. was significantly higher than that of baclofen 10 mg t.i.d., showing a dose–effect relationship (Addolorato *et al*, 2011). Both doses of baclofen were well tolerated.

The role of baclofen has also been reported in the management of AWS. Preclinical data showed that baclofen reduces the severity of AWS in rats made physically dependent on alcohol (Colombo *et al*, 2000; Knapp *et al*, 2007). On the basis of preliminary promising results in humans (Addolorato *et al*, 2002), a randomized study compared baclofen (10 mg t.id. for 10 consecutive days) with the 'gold standard' diazepam (0.5–0.75 mg/kg/day for 6 consecutive days, tapering the diazepam dose by 25% daily from day 7 to day 10) in the treatment of moderate to severe AWS, showing a comparable efficacy of the two drugs in reducing AWS symptoms, at least in the uncomplicated form of AWS (Addolorato *et al*, 2006). Additional preliminary evidence further confirms these observations: a chart review showed that baclofen prevented the development of AWS symptoms (Stallings and Schrader, 2007), and a placebo-controlled randomized study, where subjects with AWS received baclofen 10 mg t.i.d. or placebo, showed that the need for benzodiazepines to control symptoms of AWS was significantly lower in the baclofen group (Gessert *et al*, 2010).

In conclusion, considering its efficacy in the management of AWS, in reducing alcohol craving, and in promoting alcohol abstinence, baclofen might be considered a promising new drug for the treatment of alcohol dependence, particularly in alcoholic patients with alcoholic liver disease. However, larger studies are needed to confirm the present findings and to expand the information on the safety of higher doses of baclofen in the treatment of alcohol dependence. In clinical settings, a reasonable concern is that baclofen can be very sedating. The clinical trials summarized above did not report sedation as a major safety concern when administering baclofen to alcohol-dependent individuals (including people who continued drinking during these studies), an observation probably due to cross-tolerance between baclofen and alcohol (Addolorato *et al* 2005). Nonetheless, future studies will need to address carefully the role of sedation in the use of baclofen in the treatment of alcohol dependence.

Baclofen also shows promise for treating substance abuse disorders other than for alcohol. Preclinical studies with rodents have suggested that administration of $GABA_B$ agonists including baclofen and $GABA_B$-positive receptor modulators have anti-motivational effects and decreases self-administration of nicotine (Fattore *et al*, 2002; Paterson *et al*, 2004, 2008), cocaine (Roberts *et al*, 1996; Brebner *et al*, 2002), methamphetamine, (Ranaldi and Poeggel, 2002), and heroin (Spano *et al*, 2007).

Concerning the effect of baclofen on nicotine, a human laboratory study conducted by Cousins *et al*, (2001) investigated the effects of a single dose of baclofen on subjective effects of smoking in non-treatment-seeking smokers, showing that although baclofen did not reduce cigarette craving or smoking, it produced changes in sensory aspects of smoking that may facilitate smoking cessation. Moreover, a 9-week double-blind placebo-controlled trial tested the effect of baclofen 20 mg four times a day (q.i.d.) in 30 smokers (Franklin *et al*, 2009) and found that baclofen was significantly superior to placebo in reducing the primary outcome, the number of cigarettes smoked per day. These preliminary results indicate the importance to investigate further the role of baclofen as a smoking cessation agent (Franklin *et al*, 2009, 2011).

Baclofen has also been tested as a treatment for cocaine use disorder. A human brain imaging study indicated that baclofen may blunt the limbic activation that occurs with cocaine cues (Brebner *et al*, 2002). In the first human open-label study, 10 cocaine-dependent subjects were treated with

baclofen (20 mg t.i.d.), showing a trend toward reduced cocaine craving and self-reported cocaine consumption (Ling *et al*, 1998). Subsequently, Shoptaw *et al* (2003), in a randomized clinical trial involving cocaine-dependent subjects who were treated for 16 weeks with baclofen (20 mg t.i.d. or placebo), did not identify statistically significant differences for craving or cocaine use between the baclofen and placebo groups. On the other hand, in a *post hoc* analysis, a trend was identified toward reduced cocaine use in the subset of subjects with heavier cocaine use. However, a recent multisite, double-blind study comparing the safety and efficacy of baclofen (60 mg/day) *vs* placebo in an 8-week treatment of subjects with severe cocaine dependence (Kahn *et al*, 2009) did not show significant differences between the baclofen and placebo groups in regard to cocaine use and craving. A possible explanation of this result could be the addiction severity of the enrolled cocaine-dependent patients or the need for a higher baclofen dose; further studies are needed to clarify these aspects. However, at present, there is no evidence to support the use of baclofen to treat cocaine use disorders.

On the basis of some preclinical evidence (Ranaldi and Poeggel, 2002), a randomized placebo-controlled clinical trial compared the efficacy of two GABAergic medications, baclofen, (20 mg t.i.d.) and gabapentin (800 mg t.i.d.) in the treatment of methamphetamine dependence, showing that while gabapentin was not effective in treating methamphetamine dependence, baclofen had a small treatment effect compared with placebo. Future clinical studies testing the effect of baclofen on methamphetamine dependence may be warranted. Finally, preclinical data suggest a role of baclofen in decreasing the spontaneous self-administration of heroin in rats (Xi and Stein, 2000; Brebner *et al*, 2002). While clinical treatment studies are missing, preliminary clinical evidence suggests the ability of baclofen in reducing symptoms of opiate withdrawal (Akhondzadeh *et al*, 2000).

Gabapentin

Gabapentin is a non-benzodiazepine anticonvulsant GABA analog, presently approved by the FDA as an adjunctive treatment for partial seizures. Its mechanism of action is not completely understood; gabapentin seems to exert its effect by selectively inhibiting voltage-gated Ca2 + -channels and increasing GABA neurotransmission, as well as modulating the excitatory amino acids at *N*-methyl-D-aspartic acid (NMDA) receptor sites (McLean, 1999; Field *et al*, 1997; Brown *et al*, 1996). Gabapentin has been suggested as a potential medication for the treatment of alcohol and drug addiction, given that gabapentin has a mild adverse events profile, does not produce cognitive impairment, and has no abuse potential (Johnson *et al*, 2005c). A recent study highlighted the safety of this drug when administered with alcohol in non-treatment-seeking alcoholics, especially with regard to side effects such as stimulation, sedation, and intoxication (Voronin *et al*, 2004). In addition, the extrahepatic metabolism and urinary excretion of gabapentin represents an important advantage in alcoholic and other drug-addicted patients often affected by liver disease (McLean, 1994).

The pharmacodynamics and pharmacokinetics of gabapentin suggest this drug could be well suited to treat AWS (Bonnet *et al*, 1999). On the basis of promising data from animal experiments (Watson *et al*, 1997; Bailey *et al*, 1998; Dooley *et al*, 2000), preliminary clinical studies were designed to establish the possible efficacy of gabapentin in the treatment of alcohol-dependent patients affected by AWS. Open-label studies suggest a generally positive effect of gabapentin in AWS (Myrick and Anton, 1998; Bonnet *et al*, 1999, 2003, 2010; Chatterjee and Ringold, 1999; Bozikas *et al*, 2002). A retrospective study analyzed both out- and inpatients treated with gabapentin (starting dose 1200 mg daily) in the treatment of AWS. The researchers found positive outcomes as evidenced by reduction of CIWA-Ar scores, completion of gabapentin administration and the positive relationship between prior ethanol use and inpatient 'as needed' benzodiazepine use, suggesting that gabapentin works well for mild-to-moderate alcohol withdrawal (Voris *et al*, 2003). Moreover, consistent with a previous study on alcoholic patients with sleep disturbances (Karam-Hage and Brower, 2000, 2003), a recent double-blind study comparing gabapentin to lorazepam showed that gabapentin was superior to lorazepam in reducing sleep disturbances and sleeplessness in patients with multiple previous AWS episodes (Malcolm *et al*, 2007).

Some additional comparative studies between gabapentin and other AWS treatments have been performed. A randomized open-label controlled trial of gabapentin and phenobarbital in the treatment of AWS demonstrated no difference between the two drugs in withdrawal symptoms, psychological distress, or serious adverse events (Mariani *et al*, 2006). Another double-blind randomized clinical trial comparing gabapentin (900 mg or 1200 mg daily) and lorazepam in the treatment of AWS showed that gabapentin was well tolerated and effectively diminished AWS symptoms (especially at the higher dose) and reduced the probability of drinking during alcohol withdrawal and in the immediate post-withdrawal week as compared with lorazepam (Myrick *et al*, 2009). In contrast with these positive results, a double-blind placebo-controlled study did not find gabapentin superior to placebo as an adjunct to clomethiazole in treatment of acute AWS. The primary effectiveness measure was the amount of as-needed clomethiazole ('rescue medication') required in the first 24 h of AWS. This study reported that gabapentin was no more effective than placebo in the management of AWS and did not ameliorate severe AWS. The researchers suggested that these negative results could be explained by the too low entry dose (400 mg increased to 1600 mg in the first 24 h) (Bonnet *et al*, 2003). On the basis of these results, the same researchers conducted an open trial to test a higher gabapentin entry dose (800 mg gabapentin loaded up to

3200 mg in the first 24 h) in patients affected by severe AWS and found that gabapentin was helpful only in reducing less severe and less complicated acute AWS (Bonnet *et al*, 2010).

Gabapentin has also been investigated in controlling protracted abstinence in alcohol-dependent patients. In randomized, double-blind, placebo-controlled trials, gabapentin was effective in reducing alcohol craving and intake (Furieri and Nakamura-Palacios, 2007) and in delaying the onset to heavy drinking (Brower *et al*, 2008). Moreover, a proof-of-concept study on the effectiveness of gabapentin (1200 mg) *vs* placebo in a sample of non-treatment-seeking cue-reactive alcohol-dependent individuals found a significant attenuating effect of gabapentin on several measures of subjective and affectively evoked alcohol craving and a significant improvement of several measures of sleep quality and minimal side effects. These results suggest that gabapentin may be effective for treating the protracted abstinence phase in alcohol dependence (Mason *et al*, 2009). Another trial evaluated a medication combination of intravenous flumazenil (2 mg of incremental bolus for 2 consecutive days) and oral gabapentin (up to 1200 mg for 39 days) *vs* placebo in treating alcohol-dependent patients, showing more efficacy in the subgroup of alcoholic patients who experienced more severe alcohol withdrawal (Anton *et al*, 2009). However, the specificity of this effect is preliminary and needs further exploration as to validity and mechanism of action. Finally, a recent trial reported that the combination of gabapentin (up to 1200 mg/day) to naltrexone resulted in significantly improved drinking outcomes over naltrexone alone, and history of alcohol withdrawal was associated with better response in the naltrexone-gabapentin group (Anton *et al*, 2011).

Gabapentin has also been tested in the treatment of other drugs of abuse. Based on preclinical data showing the ability of gabapentin to exert dose-dependent protection against cocaine-induced seizures (Gasior *et al*, 1999), preliminary open-label studies showed that gabapentin was able to reduce cocaine craving (Raby, 2000) and that gabapentin is safe and well tolerated in cocaine-dependent patients (Myrick *et al*, 2001). However, a more recent study evaluating the safety and efficacy of reserpine, gabapentin, or lamotrigine *vs* an unmatched placebo control as a treatment for cocaine dependence found no improvement in the subjective measures of cocaine dependence in the gabapentin and lamotrigine groups, although all groups showed a good safety profile (Berger *et al*, 2005). Gabapentin has also been tested in the treatment of opioid-dependent patients, but the results of these studies are inconclusive. Martínez-Raga *et al* (2005) showed that co-adjuvant administration of gabapentin in seven heroin-dependent individuals was associated with some therapeutic use in the treatment of opiate dependence, while a subsequent double-blind, randomized, placebo-controlled trial of adjunctive gabapentin (900 mg daily) in methadone-assisted detoxification reported no significant advantage of gabapentin over placebo in controlling opiate withdrawal symptoms (Kheirabadi *et al*, 2008).

In conclusion, gabapentin represents a promising new pharmacotherapy intervention for addiction, although future studies are needed understand further the role of gabapentin in this field.

Topiramate

Topiramate, a sulfamate-substituted fructose-1,6-diphosphate analog (Johnson, 2004) with strong anticonvulsant properties (Shank *et al*, 2000) increases $GABA_A$-facilitated neuronal activity and also antagonizes AMPA and kainate glutamate receptors (Topamax, Ortho-McNeil Pharmaceutical: Raritan, NJ, 2003; Shank *et al*, 2000) with a consequent reduction of DA release in the nucleus accumbens (Johnson, 2004; Ait-Daoud *et al*, 2006). Moreover, topiramate modulates ionotropic channels (Ait-Daoud *et al*, 2006), inhibiting L-type calcium channels, limiting the activity of voltage-dependent sodium channels and facilitating potassium conductance, all of which can contribute to the hyperactivity and resulting anxiety of withdrawal (Johnson, 2004). Another mechanism of action for topiramate is weak inhibition of the carbonic anhydrase isoenzymes, CA-II and CA-IV, in the brain and in the kidney (Dodgson *et al*, 2000; Johnson, 2004), which could be responsible for a taste perversion of carbonated drinks (Dessirier *et al*, 2000). Topiramate has an almost complete oral absorption with high bioavailability (80%). The drug is not widely metabolized and is predominantly eliminated (70%) unchanged in the urine (Shank *et al*, 2000).

Several studies suggest a role for topiramate in treating alcohol use disorders, although further studies are needed to confirm the present findings. The first clinical trial with 150 alcohol-dependent patients (Johnson *et al*, 2003) showed topiramate's efficacy in reducing alcohol dependence and promoting abstinence. In this trial, topiramate was significantly more effective than placebo in reducing drinking variables (drinks per day, drinks per drinking day, percentage of heavy drinking days, plasma γ-glutamyl transferase ratio), and in increasing the percentage of abstinent days (Johnson *et al*, 2003). Topiramate was effective in reducing obsessive thoughts about alcohol, automaticity of drinking, and interference because of drinking (Johnson *et al*, 2003), as evidenced by the 14-item Obsessive Compulsive Drinking Scale (Anton *et al*, 1995). No serious adverse events were reported during the trial (Johnson *et al*, 2003).

These results were confirmed in a larger 14-week clinical trial with 371 alcohol-dependent patients and performed across 17 US sites (Johnson *et al*, 2007). In addition to confirming the efficacy of topiramate on alcohol drinking (Johnson *et al*, 2007), this trial also showed effects of topiramate on physical health, alcohol craving, and psychosocial well-being. Outcome measures of physical health included liver function tests, hematological, and biochemical measures (plasma cholesterol and bicarbonate and urine pH level), vital signs (blood pressure, pulse, and temperature), and BMI. Topiramate was superior to placebo

in improving physical health outcomes and measures of psychosocial functioning (Johnson *et al*, 2008). Altogether, these results suggest that topiramate has greater efficacy than placebo to improve the quality of life, decrease the severity of alcohol dependence, and reduce the detrimental consequences associated with heavy drinking. The therapeutic effect size of topiramate is remarkable, and benefits appear to increase over time (Kenna *et al*, 2009a, b).

Although topiramate's adverse event profile seems favorable, some aspects need to be considered. For example, the US FDA recently changed topiramate's pregnancy classification to category D, based on new data reviewed by the North American Drug Pregnancy Registry showing an increased risk of oral clefts in infants exposed to topiramate as a single therapy for epilepsy in the first trimester of pregnancy (Medwatch, 2011). Furthermore, clinically significant adverse cognitive effects have been described in association with the use of topiramate, including memory deficit, language problems and impaired attention, vigilance, and psychomotor speed (Park and Kwon, 2008). These effects are dosage-dependent and become prominent for doses higher than 75 mg/day (Park and Kwon, 2008). However, when titrated slowly, doses of 300 mg/day were tolerated by most patients. Since the drug seems to be effective during the first 5 weeks of treatment (before the target dosage of 300 mg/day), it might be reasonable that lower doses may be clinically effective. Most titration-related adverse events tend to resolve during treatment. It is conceivable that a lower dosage can maintain the drug's efficacy on alcohol dependence, with a safer profile in term of adverse events. Indeed, a preliminary human laboratory study suggests that topiramate (200 mg/day) is able to reduce the stimulating effects of alcohol ingestion compared with placebo (Miranda *et al*, 2008). Future research may include the combination of topiramate with other medications (see, eg, Kenna *et al*, 2009a, b), as well as the identification of endophenotypes with different responses to topiramate-induced side-effects (see, eg, Ray *et al*, 2009).

In addition, preclinical studies and knowledge of the drug's unique mechanisms of action support the notion that topiramate can also reduce withdrawal symptoms, prevent relapse, and promote long-term abstinence, suggesting that topiramate may be useful as a 'harm-reduction strategy' in alcohol-dependent patients who cannot attain abstinence (Johnson *et al*, 2004a).

Owing to its modulation of dopaminergic activity in the corticomesolimbic system, topiramate has also been investigated as a potential drug in the treatment of several dependencies, including nicotine. A subgroup analysis of a clinical trial comparing topiramate *vs* placebo as treatment for alcohol dependence showed higher levels of spontaneous abstinence from smoking in participants receiving topiramate as treatment for alcohol dependence (Johnson *et al*, 2005a, b, c). Trials investigating topiramate as a specific treatment for smoking cessation led to controversial results. In particular, Khazaal *et al* (2006) found a significant rate of smoking cessation in a small sample of patients treated with topiramate, while Anthenelli *et al* (2006) did not find statistical differences between topiramate and placebo, although a trend of reduction in smoked cigarettes was found in male smokers treated with topiramate. A secondary analysis of an 8-week placebo-controlled, randomized clinical trial examining the safety and efficacy of topiramate for patients with schizoaffective disorder, bipolar type, showed a lack of effect on smoking in this subtype of patients (Weinberger *et al*, 2008). Finally, Baltieri *et al* (2009) found a reduction in cigarette smoking among alcoholic patients treated with topiramate. In conclusion, data on the use of topiramate for smoking cessation are potentially promising, but more research is needed to test this role of topiramate.

As for cocaine use disorders, a pilot trial tested topiramate in cocaine dependence and showed that topiramate-treated subjects were more likely to be abstinent from cocaine compared with placebo-treated subjects (Kampman *et al*, 2004). The usefulness of topiramate in cocaine dependence could be related to its ability to reduce craving for cocaine, as measured by the Minnesota Cocaine Craving Scale, and demonstrated by a recent small open-label clinical trial conducted on 28 cocaine-dependent outpatients (Reis *et al*, 2008). Finally, based on the data on cocaine dependence, randomized controlled trials investigating topiramate's efficacy in the treatment of methamphetamine have been designed and are in progress.

VOLTAGE- AND CALCIUM-DEPENDENT ION CHANNELS AS THERAPEUTIC TARGETS FOR ADDICTION

Voltage- and calcium-gated ion channels are critical modulators of neuronal excitability, and thus represent potent targets for modulation of neuronal function. In general, they are expressed in many types of neurons throughout the brain as well in non-neuronal tissues. As a result of their widespread distribution and potent regulation of cellular activity, modulators of ion channel function would be expected to have a broad number of physiological effects, many of which could be negative or even fatal. Thus, unlike agents that target receptors for neurotransmitters and neuromodulators, relatively few drugs that target ion channels have been examined in humans despite the presence of highly selective reagents for many types of ion channels. Thus, we will focus this section somewhat more on preclinical rodent studies in order to establish the rationale for targeting a particular ion channel in the context of substance abuse. In addition, some studies have identified functional neuroadaptations in ion channel activity after drug exposure, which may contribute to increased motivation for abused substances. However, it is important to note that an ion channel could still contribute critically to drug-related behavior, for example, by regulating neural activity in a brain region critical for

expression of that behavior, without functional neuroadaptations in that channel.

L-Type Calcium Channels: Rodent Studies

There is considerable literature examining the impact of L-type voltage-dependent calcium channel (LVDCC) blockers (LCCBs) of different classes, including the 1,4-dihydropyridine (DHP) derivatives israpidine, nimodipine, and nifedipine, and the phenylalkylamine verapamil on drug-related behaviors. DHP LCCBs are used in humans to treat cardiovascular diseases such as hypertension, arrhythmias, and angina because of their potent action as dilators of peripheral and coronary arteries. However, rodent studies have been particularly encouraging for the possibility that such antagonists could also reduce drug-related behaviors.

Of particular interest is the possibility that LCCBs could reduce acute rewarding effects of addictive substances, where LCCBs would counteract the drive for drugs and abuse liability. Thus, LCCBs block development of conditioned place preference (CPP) (Suzuki *et al*, 1992; Biala and Langwinski, 1996; Shibasaki *et al*, 2010; but see Martin-Iverson *et al*, 1997), where CPP is thought to develop because the acute rewarding properties of abused drugs becomes paired with a particular environment. In addition, drug self-administration is likely maintained, at least in part, by the acute reinforcing effects of abused drugs (Everitt and Robbins, 2005; Sanchis-Segura and Spanagel, 2006), and LCCBs reduce self-administration of alcohol (Engel *et al*, 1988; Rezvani and Janowsky, 1990; Pucilowski *et al*, 1992; De Beun *et al*, 1996; Gardell *et al*, 1997; Cramer *et al*, 1998), cocaine (Kuzmin *et al*, 1992; Martellotta *et al*, 1994), and morphine (Kuzmin *et al*, 1992). LCCBs also reduce intake of sucrose (Calcagnetti and Schechter, 1992), saccharin (Pucilowski *et al*, 1992), and food (De Beun *et al*, 1996), suggesting that LCCBs might reduce reward more generally or perhaps have nonspecific effects on motor activity. However, LCCBs do not decrease water intake in water-deprived rats (Calcagnetti and Schechter, 1992), indicating that not all forms of motivated behavior are sensitive to LCCBs, and that LCCB effects on other drug and natural rewards may not simply reflect nonspecific motor effects. Finally, of interest for human therapies, lower doses of the LCCB isradipine and the opiate receptor blocker naltrexone in combination decrease cocaine and ethanol rewarding effects in rats (Cramer *et al*, 1998). This combination therapy with lower doses could act against addictive behaviors with decreased potential for side effects.

It would also be valuable therapeutically if LCCBs could reduce drug-related behaviors during abstinence. In this regard, LCCBs prevent expression of reinstatement for cocaine after extinction of responding for cocaine (Anderson *et al*, 2008) and expression of CPP (Martin-Iversen and Reimer, 1994; Biala and Weglinska, 2004, 2008), although intra-nucleus accumbens LCCBs actually enhance CPP (Chartoff *et al*, 2006). Thus, LCCBs can reduce behaviors that developed in association with drug intake, but whose expression occurs independent from acute drug intake, supporting the possibility that LCCBs could promote abstinence in human addicts.

Other studies have examined the impact of LCCBs on physical signs apparent during early withdrawal from drug exposure. The adverse motivational state associated with withdrawal can promote renewed drug intake (Koob, 2009; Koob and Volkow, 2010), and agents that reduce these effects could be useful therapeutically in human addicts. Thus, LCBBs reduce withdrawal signs related to morphine (Bongianni *et al*, 1986; Baeyens *et al*, 1987; Ramkumar and el-Fakahany, 1988; Antkiewicz-Michaluk *et al*, 1990; Esmaeili-Mahani *et al*, 2008), nicotine (Jackson and Damaj, 2009), and ethanol (Bone *et al*, 1989; Watson and Little, 2002). LCCBs had no general anticonvulsant action against bicuculline- or pentylenetetrazol-induced seizures (Watson and Little, 2002), suggesting a more specific impact on drug-related physical signs rather than a more general effect on seizures and convulsions. In addition, LCCBs reduce the development of tolerance to nicotine (Biala and Budzynska 2008), ethanol (Wu *et al*, 1987; Pucilowski *et al*, 1989), and morphine (Biala and Weglinska, 2006; Contreras *et al*, 1988; but see Khalilzadeh *et al*, 2008), as well as the development of drug-related anxiety (Biala and Kruk, 2008), suggesting that LCCBs not only can reduce withdrawal acutely, but also can decrease the tolerance and dependence, which contribute to withdrawal. Thus, LCCBs might alleviate negative somatic signs during early withdrawal and help promote abstinence.

Rodent studies have also been useful in suggesting potential mechanisms through which LCCBs could reduce drug effects. For example, LCCBs reduce drug-related increases in DA levels in the striatum or nucleus accumbens (Nacc) (Engel *et al*, 1988; Pani *et al*, 1990; Mills *et al*, 1998; Biala and Weglinska, 2006), in agreement with a role for DA in drug reward (Di Chiara, 2002) and a contribution of LVDCCs to enhancing midbrain DA neuron firing (Marinelli *et al*, 2006). In addition to midbrain LVDCCs, LVDCCs within the Nacc are implicated in regulation of cocaine reinstatement (Anderson *et al*, 2008) and CPP (Chartoff *et al*, 2006). Finally, altered LCCB levels have been observed after exposure to several different drugs (Ramkumar and el-Fakahany, 1988; Antkiewicz-Michaluk *et al*, 1990; Bernstein and Welch, 1995; Hu, 2007; Haller *et al*, 2008; Shibasaki *et al*, 2010).

L-Type Calcium Channels: Human Studies

LCCBs have shown promise in humans in the ability to reduce withdrawal symptoms after long-term intake of several addictive substances (Shulman *et al*, 1998; Jiménez-Lerma *et al*, 2002), a feature of crucial importance given that negative symptoms related to withdrawal can promote further drug seeking (Koob, 2009). LCCBs also reduce the development of tolerance to morphine (Vaupel *et al*, 1993; Santillan *et al*, 1998). Interestingly, LCCBs modify vascular tone in alcohol withdrawal but not abstinence (Kähkönen

et al, 2008), in agreement with the observation in rodent studies of LVDCC neuroadaptations during early withdrawal. Thus, LCCBs may reflect an effective treatment of withdrawal symptoms in human addicts.

Other studies of LCCBs in primates and humans have generally not been as encouraging as those from rodent studies of addiction-related behaviors. For example, several studies have indicated that LCCBs reduce the acute, subjective, and perhaps rewarding effects of psychostimulants (Muntaner *et al*, 1991; Johnson *et al*, 1999) and morphine (Vaupel *et al*, 1993, Santillan *et al*, 1998), while others have not (Hasegawa and Zacny 1997; Johnson *et al*, 2004b), and LCCBs have no effect on ethanol intoxication (Perez-Reyes *et al*, 1992). Some results have been considered particularly encouraging; for example, an LCCB-mediated increased the ability to refuse further doses of methamphetamine (Johnson *et al*, 1999). However, LCCBs have also been reported to enhance some subjective effects of abused drugs (Vaupel *et al*, 1993; Roache *et al*, 2005). The explanation for these mixed results is unclear, since divergent results have been seen even in studies examining drug-dependent individuals with a double-blind design. One possibility is that the primary effects of different LCCBs on vascular tone could interact with the subjective experience of drugs of abuse, although the time course of LCCB vascular effects and drug-related effects are very different, making this possibility unlikely (Muntaner *et al*, 1991; Johnson *et al*, 1999). Further, monkey studies have found reductions in self-administration of ethanol (Rezvani *et al*, 1991) but not cocaine (Schindler *et al*, 1995). Thus, the exact impact of LCCBs on acute effects of different drugs or alcohol in humans remains unclear, although LCCBs could be effective *vs* alcohol addiction. In addition, it would be particularly interesting if LCCBs reduced craving or intake with more long-term treatment. However, several studies have found no effect of LCCBs on craving, cognitive function or intake in longer-term trials in abstinent cocaine-dependent patients (Rosse *et al*, 1994; Johnson *et al*, 2005a, b, c; Malcolm *et al*, 2005). Taken together, these studies present a more cautious and uncertain assessment of the use of LCCBs for treatment of human addiction relative to the potent effects on drug-related behaviors in rodents, although LCCBs may represent a valuable therapy to reduce withdrawal symptoms and associated relapse.

Other Calcium Channel Antagonists

In addition to LDVCCs, other types of calcium channels may represent pharmacological targets for addiction, in particular N- and T-type calcium channels (NVDCC and TVDCC). NVDCCs regulate presynaptic release of transmitters at many synapses (Snutch, 2005). The NVDCC blocker ziconotide is a powerful analgesic drug approved for the treatment of severe chronic pain in humans (McGivern 2007), and other NVDCC blockers are being developed for use in humans to treat stroke and pain (Giordanetto *et al*, 2011). Such blockers might also help treat addiction, since rodent studies have shown that NVDCCs promote alcohol intake (Newton *et al*, 2004) and that NDVCC blockers are antinociceptive, potentiate morphine analgesia, and attenuate morphine tolerance and physical dependence and withdrawal (Meng *et al*, 2008). Also, NP078585, a blocker of NVDCCs and TVDCCs in human trials for chronic pain, reduces the intoxicating and reinforcing effects of ethanol and abolishes stress-induced reinstatement for alcohol in rats (Newton *et al*, 2008). These effects on alcohol behaviors were not observed in NVDCC knockout mice, suggesting action through NVDCCs.

TVDCCs have been considered for treating human conditions including hypertension, epilepsy, and neuropathic pain as well as drug addiction, and Merck has the TVDCC blocker TTT-A8 in phase I testing, with the ultimate goal of using it to treat sleep disorders (Giordanetto *et al*, 2011). Rodent studies show that TVDCCs decrease nicotine self-administration and reinstatement (Uslaner *et al*, 2010). Although the mechanism of action is uncertain, one possibility is through TVDCC regulation of midbrain DA neuron firing (Marinelli *et al*, 2006). Thus, preclinical rodent studies suggest that NVDCC and TVDCC blockers, some of which are already being tested in humans, might represent novel therapeutic interventions for addiction.

Sk-Type Calcium-Activated Potassium Channels

Recent work has identified SK-type (small conductance) calcium-activated potassium channels (SK) as a novel therapeutic intervention for alcoholism (Hopf *et al*, 2007, 2010a, 2011; Mulholland *et al*, 2010). Long-term alcohol intake, either operant or under intermittent-access two-bottle choice, is associated with reduced SK function in the Nacc core but not Nacc shell or dorsal striatum (Hopf *et al*, 2010a, 2011). Decreased SK function enhances Nacc core excitability, which could enhance motivation for alcohol, given the importance of the Nacc in the expression of many goal-directed and motivated behaviors (Everitt and Robbins, 2005; Sanchis-Segura and Spanagel, 2006). Interestingly, local infusion of an SK activator only reduced alcohol intake in regions where SK function was reduced; SK activators also had no effect on sucrose intake in animals trained to self-administer sucrose (Hopf *et al*, 2010a). Together, these results suggest that SK activators only reduce alcohol intake under conditions where the SK neuroadaptation is present. We also showed that chlorzoxazone, an FDA-approved SK activator used for decades as a centrally acting myorelaxant, significantly reduces excessive alcohol intake in rats with intermittent access to ethanol, but does not reduce the more moderate alcohol intake in rats with continuous access to alcohol (Hopf *et al*, 2011). Alcohol intake in intermittent-access rats shows a number of other features, which have been considered to perhaps model some aspects of human alcoholism, including escalation of intake, sensitivity to compounds that reduce alcohol intake in human alcoholics (Steensland *et al*, 2007;

Simms *et al*, 2008; McKee *et al*, 2009) and aversion-resistant and perhaps compulsive alcohol intake (Hopf *et al*, 2010b). Thus, the SK activator chlorzoxazone may represent a potent and immediately accessible treatment for human alcoholism.

Chronic ethanol exposure in mice also reduces SK currents in the hippocampus, which facilitates NMDA receptor currents, and SK activators reduce alcohol-related withdrawal hyperexcitability and seizures (Mulholland *et al*, 2010). Repeated alcohol exposure also reduces SK function in midbrain DA neurons, and is associated with sensitized responses to cocaine (Hopf *et al*, 2007). Thus, alcohol-related SK neuro-adaptations may occur in a number of brain regions and contribute to different aspects of alcohol-related behaviors.

Lamotrigine

Lamotrigine, which inhibits sodium channel activity, is used clinically to treat epilepsy. In rodents, lamotrigine reduces alcohol relapse and reinstatement (Vengeliene *et al*, 2007). Also, bipolar disorder is associated with high rates of substance abuse, and preliminary studies show that lamotrigine reduces alcohol craving and intake in human alcoholics with bipolar disorder (Rubio *et al*, 2006) and cocaine craving and intake in addicts with bipolar disorder (Brown *et al*, 2006). Lamotrigine may also reduce alcohol craving in schizophrenics (Kalyoncu *et al*, 2005). Thus, lamotrigine represents an accessible and perhaps effective treatment for human addiction.

Future Research Directions: Transcranial Magnetic Stimulation

Experimental evidence suggests that the mesolimbic DA system is hypofunctional in the addicted brain (Melis *et al*, 2005). Alcohol-dependent rats and mice show a profound reduction of spontaneous firing rate and burst firing of Nacc-projecting VTA DA-containing neurons (Diana *et al*, 1993; Bailey *et al*, 2001), resulting in a concomitant reduction of microdialysate DA in the Nacc (Diana *et al*, 1993). Further, this reduced dopaminergic activity outlasts somatic signs of withdrawal (Diana *et al*, 1996), thereby suggesting a role for DA in the lasting consequences of alcohol dependence while perhaps excluding the possibility of a DA role in somatic aspects of withdrawal. Further, pre-dependence DA levels in the Nacc are restored when ethanol is made available again and self-administered (Weiss *et al*, 1996) or passively administered (Diana *et al*, 1996). These observations are paralleled by intracranial self-stimulation studies that reported ethanol-withdrawn subjects are capable of maintaining ICSS behavior provided that the current intensity is increased (Schulteis *et al*, 1995). This important observation strongly indicates that the neural substrate of the ICSS behavior is hyperpolarized, or more refractory, in alcohol-dependent subjects as compared with non-alcoholic controls. As the neural substrate of ICSS (Yeomans, 1989; Yeomans *et al*, 1993) involves DA axons near the electrode, these results are complementary to those reported above and well fit with a hypofunction of DA neurons. These observations may suggest that 'boosting' DA neurons to produce more available DA in the synaptic cleft could alleviate some of the symptoms of addiction and alcoholism, thereby acquiring a therapeutic character. In theory, this could be achieved by two different strategies: (1) DA-potentiating drugs (eg, Swift, 2010) and (2) rTMS (eg, Keck *et al*, 2002; Feil and Zangen, 2010). Although DA-containing neurons are located deeply in the brainstem, making them inaccessible to direct rTMS stimuli, DA neurons may be reached indirectly through neurons located elsewhere in the brain. For example, the dorsolateral prefrontal cortex (DLPfcx), the brain region targeted in many rTMS studies (eg, Amiaz *et al*, 2009), projects monosynaptically to the VTA, which contains the cell bodies of DA-producing cells (Carr and Sesack, 2010). Indeed, these cortical neurons could be 'used' as the primary target of the rTMS stimulus to produce, ultimately, an increase in DA availability in the synaptic cleft in the Nacc. Schematically the hypothesized circuit would be the following: rTMS—>DLPfcx—>VTA—> DA increase in forebrain projection site (ie, Nacc). In fact, although the cellular mechanism through which TMS acts remains unclear, we believe it is reasonable to propose that TMS can modulate the DA system (albeit indirectly, perhaps through modulation of the GABA system within the Pfcx) and, in this way, alleviate addiction symptoms; in a similar vein, TMS has been proposed to improve Parkinson's symptoms through modulation of DA (Shimamoto *et al*, 2001). Although many technical details for optimal stimulation parameters need further investigation and optimization, rTMS appears to deserve careful experimental scrutiny as a potential therapeutic tool in alcoholics and other addicts. Indeed, with its nearly absent systemic effects, minimal side effects, and a low degree of invasiveness, rTMS may offer the first opportunity for an efficacious, non-pharmacological, therapeutic tool in alcoholism and other chemical dependencies.

CONCLUSIONS

In spite of the tremendous advances made recently in elucidating the neurobiological underpinnings of addiction, expectancies of consequent therapeutic improvements have fallen short. Here, we reviewed some of the most promising candidates for future therapeutics for alcoholism and addiction. GABAergic drugs such as topiramate, baclofen, and gabapentin, together with various channel blockers, may yield promise for satisfactory treatment of alcohol and drug abuse. In particular, most of the GABA treatments work on alcohol and smoking, although clinical studies do not provide evidence that they work on psychostimulants. While considerable work has already been done with GABA treatments in terms of translation from bench to bedside

(indeed, topiramate, baclofen, and gabapentin are sometimes used off-label for alcohol dependence both in the United States and in Europe), on the other hand, more efforts are needed to understand optimal doses and the best responders to such treatments. Channel blockers represent a novel target, which can be translated into research clinical studies in the very near future, especially by using medications already approved for other indications (see, eg, Hopf *et al*, 2011). Finally, consideration should be also given to rTMS, as it may represent the first 'electrophysiological' approach to substance abuse disorders and may provide significant advantages such as an absence of systemic side effects, limited CNS side-effects, safety, and efficacy.

DISCLOSURE

The authors declare no conflict of interest.

REFERENCES

Addolorato G, Caputo F, Capristo E, Colombo G, Gessa GL, Gasbarrini G (2000). Ability of baclofen in reducing alcohol craving and intake: II-preliminary clinical evidence. *Alcohol Clin Exp Res* **24**: 67–71.

Addolorato G, Caputo F, Capristo E, Janiri L, Bernardi M, Agabio R *et al* (2002). Rapid suppression of alcohol withdrawal syndrome by baclofen. *Am J Med* **112**: 226–229.

Addolorato G, Leggio L, Abenavoli L, Agabio R, Caputo F, Capristo E *et al* (2006). Baclofen in the treatment of alcohol withdrawal syndrome: a comparative study *vs* diazepam. *Am J Med* **119**: 276 e213–278.

Addolorato G, Leggio L, Abenavoli L, Caputo F, Gasbarrini G (2005). Tolerance to baclofen's sedative effect in alcohol-addicted patients: no dissipation after a period of abstinence. *Psychopharmacology (Berl)* **178**: 351–352.

Addolorato G, Leggio L, Ferrulli A, Cardone S, Bedogni G, Gasbarrini G, *et al*, and the Baclofen Study Group (2011). Dose-response effect of baclofen in reducing daily alcohol intake in alcohol-dependent subjects: secondary analysis of a randomized double-blind placebo controlled trial. *Alcohol Alcohol* **46**: 312–317.

Addolorato G, Leggio L, Ferrulli A, Cardone S, Vonghia L, Mirijello A *et al* (2007). Effectiveness and safety of baclofen for maintenance of alcohol abstinence in alcohol-dependent patients with liver cirrhosis: randomised, double-blind controlled study. *Lancet* **370**: 1915–1922. **First randomized clinical trial in the field of alcohol pharmacotherapy that targeted alcohol-dependent individuals with severe liver disease. Results support the safety and effectiveness of baclofen in promoting alcohol abstinence in such a population**.

Ait-Daoud N, Malcolm RJ, Johnson BA (2006). An overview of medications for the treatment of alcohol withdrawal and alcohol dependence with an emphasis on the use of older and newer anticonvulsants. *Addict Behav* **31**: 1628–1649.

Akhondzadeh S, Ahmadi-Abhari SA, Assadi SM, Shabestari OL, Kashani AR, Farzanehgan ZM (2000). Double-blind randomized controlled trial of baclofen *vs* clonidine in the treatment of opiates withdrawal. *J Clin Pharm Ther* **25**: 347–353.

Ameisen O (2005). Complete and prolonged suppression of symptoms and consequences of alcohol-dependence using high-dose baclofen: a self-case report of a physician. *Alcohol Alcohol* **40**: 147–150.

Amiaz R, Levy D, Vainiger D, Grunhaus L, Zangen A (2009). Repeated high-frequency transcranial magnetic stimulation over the dorsolateral prefrontal cortex reduces cigarette craving and consumption. *Addiction* **104**: 653–660.

Anderson SM, Famous KR, Sadri-Vakili G, Kumaresan V, Schmidt HD, Bass CE *et al* (2008). CaMKII: a biochemical bridge linking accumbens dopamine and glutamate systems in cocaine seeking. *Nat Neurosci* **11**: 344–353. **Nacc D1-like dopamine receptors reinstate cocaine seeking by activating L-VDCCs, ultimately leading to increased surface glutamate receptor levels**.

Anthenelli RM, Blom TJ, McElroy SL, Keck PE Jr (2008). Preliminary evidence for gender-specific effects of topiramate as a potential aid to smoking cessation. *Addiction* **103**: 687–689.

Antkiewicz-Michaluk L, Michaluk J, Romanska I, Vetulani J (1990). Cortical dihydropyridine binding sites and a behavioral syndrome in morphine-abstinent rats. *Eur J Pharmacol* **180**: 129–135.

Anton RF, Moak DH, Latham P (1995). The Obsessive Compulsive Drinking Scale: a self-rated instrument for the quantification of thoughts about alcohol and drinking behavior. *Alcohol Clin Exp Res* **19**: 92–99.

Anton RF, Myrick H, Baros AM, Latham PK, Randall PK, Wright TM *et al* (2009). Efficacy of a combination of flumazenil and gabapentin in the treatment of alcohol dependence: relationship to alcohol withdrawal symptoms. *J Clin Psychopharmacol* **29**: 334–342. **Elegant randomized clinical trial that showed an effect of gabapentin, as combined with flumazenil, in treating alcohol-dependent individuals with high pre-treatment alcohol withdrawal symptoms**.

Anton RF, Myrick H, Wright TM, Latham PK, Baros AM, Waid LR *et al* (2011). Gabapentin combined with naltrexone for the treatment of alcohol dependence. *Am J Psychiatry* **168**: 709–717.

Arolfo MP, Overstreet DH, Yao L, Fan P, Lawrence AJ, Tao G *et al* (2009). Suppression of heavy drinking and alcohol seeking by a selective ALDH-2 inhibitor. *Alcohol Clin Exp Res* **33**: 1935–1944. **Preclinical evidence of a potential therapeutic role of a selective reversible ALDH-2 for alcohol dependence**.

Avanesyan A, Runyon BA (2010). Utilization of baclofen in maintenance of alcohol abstinence in patients with alcoholic hepatitis in a real-life clinical setting. *Hepatology* **52**: 1104A.

Bailey CP, Molleman A, Little HJ (1998). Comparison of the effects of drugs on hyperexcitability induced in hippocampal slices by withdrawal from chronic ethanol consumption. *Br J Pharmacol* **123**: 215–222.

Bailey CP, O'Callaghan MJ, Croft AP, Manley SJ, Little HJ (2001). Alterations in mesolimbic dopamine function during the abstinence period following chronic ethanol consumption. *Neuropharmacology* **41**: 989–999.

Baltieri DA, Daró FR, Ribeiro PL, Andrade AG (2009). Effects of topiramate or naltrexone on tobacco use among male alcohol-dependent outpatients. *Drug Alcohol Depend* **105**: 33–41.

Baeyens JM, Esposito E, Ossowska G, Samanin R (1987). Effects of peripheral and central administration of calcium channel blockers in the naloxone-precipitated abstinence syndrome in morphine-dependent rats. *Eur J Pharmacol* **137**: 9–13.

Berger SP, Winhusen TM, Somoza EC, Harrer JM, Mezinskis JP, Leiderman DB *et al* (2005). A medication screening trial evaluation of reserpine, gabapentin and lamotrigine pharmacotherapy of cocaine dependence. *Addiction* **100**: 58–67.

Bernstein MA, Welch SP (1995). Alterations in L-type calcium channels in the brain and spinal cord of acutely treated and morphine-tolerant mice. *Brain Res* **696**: 83–88.

Biala G, Budzynska B (2008). Calcium-dependent mechanisms of the reinstatement of nicotine-conditioned place preference by drug priming in rats. *Pharmacol Biochem Behav* **89**: 116–125.

Biala G, Kruk M (2008). Calcium channel antagonists suppress cross-tolerance to the anxiogenic effects of D-amphetamine and nicotine in the mouse elevated plus maze test. *Prog Neuropsychopharmacol Biol Psychiatry* **32**: 54–61. **Calcium-channel-dependent mechanisms are involved in enhancement of anxiety with chronic amphetamine and nicotine**.

Biala G, Langwinski R (1996). Effects of calcium channel antagonists on the reinforcing properties of morphine, ethanol and cocaine as measured by place conditioning. *J Physiol Pharmacol* **47**: 497–502.

Biala G, Weglinska B (2004). Calcium channel antagonists attenuate cross-sensitization to the rewarding and/or locomotor effects of nicotine, morphine and MK-801. *J Pharm Pharmacol* **56**: 1021–1028.

Biala G, Weglinska B (2006). On the mechanism of cross-tolerance between morphine- and nicotine-induced antinociception: involvement of calcium channels. *Prog Neuropsychopharmacol Biol Psychiatry* **30**: 15–21.

Bone GH, Majchrowicz E, Martin PR, Linnoila M, Nutt DJ (1989). A comparison of calcium antagonists and diazepam in reducing ethanol withdrawal tremors. *Psychopharmacology* **99**: 386–388.

Bongianni F, Carla V, Moroni F, Pellegrini-Giampietro DE (1986). Calcium channel inhibitors suppress the morphine-withdrawal syndrome in rats. *Br J Pharmacol* **88**: 561–567.

Bonnet U, Banger M, Leweke FM, Maschke M, Kowalski T, Gastpar M (1999). Treatment of alcohol withdrawal syndrome with gabapentin. *Pharmacopsychiatry* **32**: 107–109.

Bonnet U, Banger M, Leweke FM Specka M, Müller BW, Hashemi T, Nyhuis PW *et al* (2003). Treatment of acute alcohol-withdrawal with gabapentin: results from a controlled two-center trial. *J Clin Psychopharmacol* **23**: 514–518.

Bonnet U, Hamzavi-Abedi R, Specka M, Wiltfang J, Lieb B, Scherbaum N (2010). An open trial of gabapentin in acute alcohol withdrawal using an oral loading protocol. *Alcohol Alcohol* **45**: 143–145.

Bozikas V, Petrikis P, Gamvrula K, Savvidou I, Karavatos A (2002). Treatment of alcohol withdrawal with gabapentin. *Prog Neuropsychopharmacol Biol Psychiatry* **26**: 197–199.

Brebner K, Childress AR, Roberts DC (2002). A potential role for GABA(B) agonists in the treatment of psychostimulant addiction. *Alcohol Alcohol* **37**: 478–484.

Brower KJ, Myra Kim H, Strobbe S, Karam-Hage MA, Consens F, Zucker RA (2008). A randomized double-blind pilot trial of gabapentin *vs* placebo to treat alcohol dependence and comorbid insomnia. *Alcohol Clin Exp Res* **32**: 1429–1438.

Brown JP, Boden P, Singh L, Gee NS (1996). Mechanism of action of gabapentin. *Rev Contemp Pharmacother* **7**: 203–214.

Brown ES, Perantie DC, Dhanani N, Beard L, Orsulak P, Rush AJ (2006). Lamotrigine for bipolar disorder and comorbid cocaine dependence: a replication and extension study. *J Affect Disord* **93**: 219–222.

Bucknam W (2007). Suppression of symptoms of alcohol dependence and craving using high-dose baclofen. *Alcohol Alcohol* **42**: 158–160.

Calcagnetti DJ, Schechter MD (1992). Attenuation of drinking sweetened water following calcium channel blockade. *Brain Res Bull* **28**: 967–973.

Carr DB, Sesack SR (2010). Dopamine terminals synapse on callosal projection neurons in the rat prefrontal cortex. *J Comp Neurol* **425**: 275–283.

Cramer CM, Gardell LR, Boedeker KL, Harris JR, Hubbell CL, Reid LD (1998). Isradipine combined with naltrexone persistently reduces the reward-relevant effects of cocaine and alcohol. *Pharmacol Biochem Behav* **60**: 345–356.

Chartoff EH, Pliakas AM, Carlezon Jr WA (2006). Microinjection of the L-type calcium channel antagonist diltiazem into the ventral nucleus accumbens shell facilitates cocaine-induced conditioned place preferences. *Biol Psychiatry* **59**: 1236–1239. **In contrast to other studies showing that systemic L-type VDCC blockers reduce many symptoms associated with abuse drugs, this interesting study found that inhibiting L-channels within a subregion of the nucleus accumbens actually enhances cocaine conditioned place preference**.

Chatterjee CR, Ringold AL (1999). A case report of reduction in alcohol craving and protection against alcohol withdrawal by gabapentin. *Clin Psychiatry* **60**: 617.

Colombo G, Addolorato G, Agabio R, Carai MA, Pibiri F, Serra S *et al* (2004). Role of GABAB receptor in alcohol dependence: reducing effect of baclofen on alcohol intake and alcohol motivational properties in rats and amelioration of alcohol withdrawal syndrome and alcohol craving in human alcoholics. *Neurotox Res* **6**: 403–414. **This publication included the description of an elegant experiment that demonstrated baclofen suppressed alcohol-stimulated dopamine release in the nucleus accumbens (microdialysis experiment)**.

Colombo G, Agabio R, Carai MAM, Lobina C, Pani M, Reali R *et al* (2000). Ability of baclofen in reducing alcohol intake and withdrawal severity: I—preclinical evidence. *Alcohol Clin Exp Res* **24**: 58–66.

Contreras E, Tamayo L, Amigo M (1988). Calcium channel antagonists increase morphine-induced analgesia and antagonize morphine tolerance. *Eur J Pharmacol* **148**: 463–466.

Cousins MS, Roberts DC, de Wit H (2002). GABA(B) receptor agonists for the treatment of drug addiction: a review of recent findings. *Drug Alcohol Depend* **65**: 209–220.

Cousins MS, Stamat HM, de Wit H (2001). Effects of a single dose of baclofen on self-reported subjective effects and tobacco smoking. *Nicotine Tob Res* **23**: 123–129.

Davidoff RA (1985). Antispasticity drugs: mechanisms of action. *Ann Neurol* **17**: 107–116.

De Beun R, Schneider R, Klein A, Lohmann A, De Vry J (1996). Effects of nimodipine and other calcium channel antagonists in alcohol-preferring AA rats. *Alcohol* **13**: 263–271.

Dessirier JM, Simons CT, Carstens MI, O'Mahony M, Carstens E (2000). Psychophysical and neurobiological evidence that the oral sensation elicited by carbonated water is of chemogenic origin. *Chem Senses* **25**: 277–284.

Diana M, Brodie M, Muntoni A, Puddu MC, Pillolla G, Steffensen S *et al* (2003). Enduring effects of chronic ethanol in the CNS: basis for alcoholism. *Alcohol Clin Exp Res* **27**: 354–361.

Diana M, Pistis M, Carboni S, Gessa GL, Rossetti ZL (1993). Profound decrement of mesolimbic dopaminergic neuronal activity during ethanol withdrawal syndrome in rats: electrophysiological and biochemical evidence. *Proc Natl Acad Sci USA* **1**: 7966–7969. **First demonstration of a tonically impaired DA system in alcohol-dependent rats**.

Diana M, Pistis M, Muntoni A, Gessa G (1996). Mesolimbic dopaminergic reduction outlasts ethanol withdrawal syndrome: evidence of protracted abstinence. *Neuroscience* **71**: 411–415. **Alcohol-withdrawal induced DA impoverishment is long lasting**.

Di Chiara G (2002). Nucleus accumbens shell and core dopamine: differential role in behavior and addiction. *Behav Brain Res* **137**: 75–114.

Dodgson SJ, Shank RP, Maryanoff BE (2000). Topiramate as an inhibitor of carbonic anhydrase isoenzymes. *Epilepsia* **41**: S35–S39.

Dooley DJ, Donovan CM, Pugsley TA (2000). Stimulus-dependent modulation of [(3)H]norepinephrine release from rat neocortical slices by gabapentin and pregabalin. *J Pharmacol Exp Ther* **295**: 1086–1093.

Engel JA, Fahlke C, Hulthe P, Hård E, Johannessen K, Snape B *et al* (1988). Biochemical and behavioral evidence for an interaction between ethanol and calcium channel antagonists. *J Neural Transm* **74**: 181–193.

Esmaeili-Mahani S, Fathi Y, Motamedi F, Hosseinpanah F, Ahmadiani A (2008). L-type calcium channel blockade attenuates morphine withdrawal: *in vivo* interaction between L-type calcium channels and corticosterone. *Horm Behav* **53**: 351–357.

Evans SM, Bisaga A (2009). Acute interaction of baclofen in combination with alcohol in heavy social drinkers. *Alcohol Clin Exp Res* **33**: 19–30.

Everitt BJ, Robbins TW (2005). Neural systems of reinforcement for drug addiction: from actions to habits to compulsion. *Nat Neurosci* **8**: 1481–1489.

Fadda P, Scherma M, Fresu A, Collu M, Fratta W (2003). Baclofen antagonizes nicotine-, cocaine-, and morphine-induced dopamine release in the nucleus accumbens of rat. *Synapse* **50**: 1–6.

Fattore L, Cossu G, Martellotta MC, Fratta W (2002). Baclofen antagonizes intravenous self-administration of nicotine in mice and rats. *Alcohol Alcohol* **37**: 495–498.

Feil J, Zangen A (2010). Brain stimulation in the study and treatment of addiction. *Neuroscience Biobehav Rev* **34**: 559–574. **Overview of rTMS application in addiction as research tool and therapeutic potential**.

Field MJ, Oles RJ, Lewis AS, McVlerary S, Hughes J, Singh L (1997). Gabapentin (neurontin) and S (+)-3-isobutylgaba represent a novel class of selective antihyperalgesic agents. *Br J Pharmacol* **121**: 1513–1522.

Flannery B, Garbutt JC (2008). Comparison of U.S. and Italian human baclofen trials: why the difference? *Alcohol Clin Exp Res* **32**: 276A.

Flannery BA, Garbutt JC, Cody M, Renn W, Osborne M, Crosby K *et al* (2004). Baclofen for alcohol dependence: a preliminary open-label study. *Alcohol Clin Exp Res* **28**: 1517–1523.

Fleming RL, Manis PB, Morrow AL (2009). The effects of acute and chronic ethanol exposure on presynaptic and postsynaptic gamma-aminobutyric acid (GABA) neurotransmission in cultured cortical and hippocampal neurons. *Alcohol* **43**: 603–618.

Franklin TR, Harper D, Kampman K, Kildea-McCrea S, Jens W, Lynch KG *et al* (2009). The GABA B agonist baclofen reduces cigarette consumption in a preliminary double-blind placebo-controlled smoking reduction study. *Drug Alcohol Depend* **103**: 30–36.

Franklin TR, Wang Z, Sciortino N, Harper D, Li Y, Hakun J *et al* (2011). Modulation of resting brain cerebral blood flow by the GABA B agonist, baclofen: a longitudinal perfusion fMRI study. *Drug Alcohol Depend* **117**: 176–183. **Clinical evidence of a modulatory action of baclofen in brain regions involved in motivated behavior**.

Furieri FA, Nakamura-Palacios EM (2007). Gabapentin reduces alcohol consumption and craving: a randomized, double-blind, placebo-controlled trial. *J Clin Psychiatry* **68**: 1691–1700.

Garbutt JC (2009). The state of pharmacotherapy for the treatment of alcohol dependence. *J Subst Abuse Treat* **36**: S15–S23.

Garbutt JC, Kampov-Polevoy AB, Gallop R, Kalka-Juhl L, Flannery BA (2010). Efficacy and safety of baclofen for alcohol dependence: a randomized, double-blind, placebo-controlled trial. *Alcohol Clin Exp Res* **34**: 1849–1857.

Gardell LR, Reid LD, Boedeker KL, Liakos TM, Hubbell CL (1997). Isradipine and naltrexone in combination with isradipine interact with a period of abstinence to reduce rats' intakes of an alcoholic beverage. *Alcohol Clin Exp Res* **21**: 1592–1598.

Gasior M, Ungard JT, Witkin JM (1999). Preclinical evaluation of newly approved and potential antiepileptic drugs against cocaine-induced seizures. *J Pharmacol Exp Ther* **290**: 1148–1156.

Gessert CE, Lyon JE, Khan R, Renier CM (2010). Oral baclofen in the management of alcohol withdrawal: a randomized, double-blind, placebo-controlled trial. 138th Annual Meeting of the American Public Health Association, Denver, CO, USA, abstract #217050.

Giordanetto F, Knerr L, Wållberg A (2011). T-type calcium channels inhibitors: a patent review. *Expert Opin Ther Pat* **2011**: 21: 85–101.

Haller VL, Bernstein MA, Welch SP (2008). Chronic morphine treatment decreases the Cav1.3 subunit of the L-type calcium channel. *Eur J Pharmacol* **578**: 101–107.

Hasegawa AE, Zacny JP (1997). The influence of three L-type calcium channel blockers on morphine effects in healthy volunteers. *Anesth Analg* **85**: 633–638.

Hopf FW, Bowers MS, Chang SJ, Chen BT, Martin M, Seif T *et al* (2010a). Reduced nucleus accumbens SK channel activity enhances alcohol seeking during abstinence. *Neuron* **65**: 682–694. **An SK potassium channel neuro-adaptation in the NAcb core after ethanol intake seems to be necessary for driving aberrant motivation for ethanol**.

Hopf FW, Chang SJ, Sparta DR, Bowers MS, Bonci A (2010b). Motivation for alcohol becomes resistant to quinine adulteration after 3-4 months of intermittent alcohol self-administration. *Alcoh Clin Exper Res* **34**: 1565–1573.

Hopf FW, Martin M, Chen BT, Bowers MS, Mohamedi MM, Bonci A (2007). Withdrawal from intermittent ethanol exposure increases probability of burst firing in VTA neurons *in vitro*. *J Neurophysiol* **98**: 2297–2310.

Hopf FW, Simms JA, Chang SJ, Seif T, Bartlett SE, Bonci A (2011). Chlorzoxazone, an SK-type potassium channel activator used in humans, reduces excessive alcohol intake in rats. *Biol Psychiatry* **69**: 618–624. **Reduce NAcb SK channel function with chronic ethanol intake enhances NAcb excitability and ethanol intake, and the FDA-approved SK activator chlorzoxazone reduces excessive ethanol intake**.

Hu XT (2007). Cocaine withdrawal and neuro-adaptations in ion channel function. *Mol Neurobiol* **35**: 95–112.

Jackson KJ, Damaj MI (2009). L-type calcium channels and calcium/calmodulin-dependent kinase II differentially mediate behaviors associated with nicotine withdrawal in mice. *J Pharmacol Exp Ther* **330**: 152–161.

Jiménez-Lerma JM, Landabaso M, Iraurgi L, Calle R, Sanz J, Gutiérrez-Fraile M (2002). Nimodipine in opiate detoxification: a controlled trial. *Addiction* **97**: 819–824. **An encouraging study suggesting that LVDCC inhibitors can reduce opiate withdrawal symptoms in humans**.

Johnson BA (2004). Progress in the development of topiramate for treating alcohol dependence: from a hypothesis to a proof-of-concept study. *Alcohol Clin Exp Res* **28**: 1137–1144.

Johnson BA, Ait-Daoud N, Akhtar FZ, Javors MA (2005a). Use of oral topiramate to promote smoking abstinence among alcohol-dependent smokers: a randomized controlled trial. *Arch Intern Med* **165**: 1600–1605. **First preliminary evidence of a role of topiramate in promoting smoking abstinence in smokers with alcohol dependence**.

Johnson BA, Ait-Daoud N, Akhtar FZ, Ma JZ (2004a). Oral topiramate reduces the consequences of drinking and improves the quality of life of alcohol-dependent individuals: a randomized controlled trial. *Arch Gen Psychiatry* **61**: 905–912.

Johnson BA, Ait-Daoud N, Bowden CL, DiClemente CC, Roache JD, Lawson K *et al* (2003). Oral topiramate for treatment of alcohol dependence: a randomised controlled trial. *Lancet* **361**: 1677–1685.

Johnson BA, Roache JD, Ait-Daoud N, Wallace CL, Wells LT, Wang Y *et al* (2005b). Effects of isradipine on cocaine-induced changes in cognitive performance in recently abstinent cocaine-dependent individuals. *Int J Neuropsychopharmacol* **8**: 549–556.

Johnson BA, Roache JD, Ait-Daoud N, Wells LT, Mauldin JB (2004b). Effects of isradipine on cocaine-induced subjective mood. *J Clin Psychopharmacol* **24**: 180–191.

Johnson BA, Roache JD, Bordnick PS, Ait-Daoud N (1999). Isradipine, a dihydropyridine-class calcium channel antagonist, attenuates some of d-methamphetamine's positive subjective effects: a preliminary study. *Psychopharmacology* **144**: 295–300.

Johnson BA, Rosenthal N, Capece JA, Wiegand F, Mao L, Beyers K *et al*, Topiramate for Alcoholism Advisory Board; Topiramate for Alcoholism Study Group (2007). Topiramate for treating alcohol dependence: a randomized controlled trial. *JAMA* **298**: 1641–1651. **Large multi-site randomized clinical trial that demonstrated a role of topiramate for alcohol dependence**.

Johnson BA, Rosenthal N, Capece JA, Wiegand F, Mao L, Beyers K *et al*, Topiramate for Alcoholism Advisory Board; Topiramate for Alcoholism Study Group (2008). Improvement of physical health and quality of life of alcohol-dependent individuals with topiramate treatment: US multisite randomized controlled trial. *Arch Intern Med* **168**: 1188–1199.

Johnson BA, Swift RM, Addolorato G, Ciraulo DA, Myrick H (2005c). Safety and effectiveness of GABAergic medications for treating alcoholism. *Alcohol Clin Exp Res* **29**: 248–254.

Jupp B, Lawrence AJ (2010). New horizons for therapeutics in drug and alcohol abuse. *Pharmacol Ther* **125**: 138–168.

Kahn R, Biswas K, Childress AR, Shoptaw S, Fudala PJ, Gorgon L *et al* (2009). Multi-center trial of baclofen for abstinence initiation in severe cocaine-dependent individuals. *Drug Alcohol Depend* **103**: 59–64.

Kähkönen S, Bondarenko BB, Lipsanen J, Zvartau EE (2008). Effects of verapamil, an antagonist of L-type calcium channels, on cardiovascular symptoms in alcohol withdrawal. *Neuropsychobiology* **58**: 123–127.

Kalyoncu A, Mirsal H, Pektas O, Unsalan N, Tan D, Beyazyürek M (2005). Use of lamotrigine to augment clozapine in patients with resistant schizophrenia and comorbid alcohol dependence: a potent anti-craving effect? *J Psychopharmacol* **19**: 301–305.

Kampman KM, Pettinati H, Lynch KG, Dackis C, Sparkman T, Weigley C *et al* (2004). A pilot trial of topiramate for the treatment of cocaine dependence. *Drug Alcohol Depend* **7**: 233–240. **Preliminary evidence of a role of topiramate in cocaine dependence**.

Karam-Hage M, Brower KJ (2000). Gabapentin treatment for insomnia associated with alcohol dependence. *Am J Psychiatry* **157**: 151.

Karam-Hage M, Brower KJ (2003). Open pilot study of gabapentin *vs* trazodone to treat insomnia in alcoholic outpatients. *Psychiatry Clin Neurosci* **57**: 542–544.

Keck ME, Welt T, Müller MB, Erhardt A, Ohl F, Toschi N *et al* (2002). Repetitive transcranial magnetic stimulation increases the release of dopamine in the mesolimbic and mesostriatal system. *Neuropharm* **43**: 101–109.

Kenna GA, Leggio L, Swift RM (2009a). A safety and tolerability laboratory study of the combination of aripiprazole and topiramate in volunteers who drink alcohol. *Hum Psychopharmacol* **24**: 465–472.

Kenna GA, Lomastro TL, Schiesl A, Leggio L, Swift RM (2009b). Review of topiramate: an antiepileptic for the treatment of alcohol dependence. *Curr Drug Abuse Rev* **2**: 135–142.

Khalilzadeh O, Anvari M, Khalilzadeh A, Sahebgharani M, Zarrindast MR (2008). Involvement of amlodipine, diazoxide, and glibenclamide in development ofmorphine tolerance in mice. *Int J Neurosci* **118**: 503–518.

Khazaal Y, Cornuz J, Bilancioni R, Zullino DF (2006). Topiramate for smoking cessation. *Psychiatr Clin Neurosci* **60**: 384–388.

Kheirabadi GR, Ranjkesh M, Maracy MR, Salehi M (2008). Effect of add-on gabapentin on opioid withdrawal symptoms in opium-dependent patients. *Addiction* **103**: 1495–1499.

Knapp DJ, Overstreet DH, Breese GR (2007). Baclofen blocks expression and sentization of anxiety-like behavior in an animal model of repeated stress and ethanol withdrawal. *Alcohol Clin Exp Res* **31**: 582–595.

Koob GF (1992). Drugs of abuse: anatomy, pharmacology and function of reward pathways. *Trends Pharmacol Sci* **13**: 177–184.

Koob GF (2006). The neurobiology of addiction: a neuroadaptational view relevant for diagnosis. *Addiction* **101**: 23–30.

Koob GF (2009). Dynamics of neuronal circuits in addiction: reward, antireward, and emotional memory. *Pharmacopsychiatry* **42**: S32–S41.

Koob GF, Kenneth Lloyd G, Mason BJ (2009). Development of pharmacotherapies for drug addiction: a Rosetta stone approach. *Nat Rev Drug Discov* **8**: 500–515. **Systematic evaluation of addiction as a 'cycling' disorder and rationality for phase-specific therapeutics**.

Koob GF, Volkow ND (2010). Neurocircuitry of addiction. *Neuropsychopharmacology* **35**: 217–238.

Kumar S, Porcu P, Werner DF, Matthews DB, Diaz-Granados JL, Helfand RS *et al* (2009). The role of GABA(A) receptors in the acute and chronic effects of ethanol: a decade of progress. *Psychopharmacology (Berl)* **205**: 529–564.

Kuzmin A, Zvartau E, Gessa GL, Martellotta MC, Fratta W (1992). Calcium antagonists isradipine and nimodipine suppress cocaine and morphine intravenous self-administration in drug-naive mice. *Pharmacol Biochem Behav* **41**: 497–500.

Leggio L, Cardone S, Ferrulli A, Kenna GA, Diana M, Swift RM *et al* (2010a). Turning the clock ahead: potential preclinical and clinical neuropharmacological targets for alcohol dependence. *Curr Pharm Des* **16**: 2159–2181.

Leggio L, Ferrulli A, Cardone S, Miceli A, Kenna GA, Gasbarrini G *et al* (2008a). Renin and aldosterone but not the natriuretic peptide correlate with obsessive craving in medium-term abstinent alcohol-dependent patients: a longitudinal study. *Alcohol* **42**: 375–381.

Leggio L, Ferrulli A, Malandrino N, Miceli A, Capristo E, Gasbarrini G *et al* (2008b). Insulin but not insulin growth factor-1 correlates with craving in currently drinking alcohol-dependent patients. *Alcohol Clin Exp Res* **32**: 450–458.

Leggio L, Garbutt JC, Addolorato G (2010b). Effectiveness and safety of baclofen in the treatment of alcohol dependent patients. *CNS Neurol Disord Drug Targets* **9**: 33–44.

Ling W, Shoptaw S, Majewska D (1998). Baclofen as a cocaine anti-craving medication: a preliminary clinical study. *Neuropsychopharmacology* **18**: 403–404.

Lingford-Hughes A, Watson B, Kalk N, Reid (2010). A neuropharmacology of addiction and how it informs treatment. *Br Med Bull* **96**: 93–110.

Lüscher C, Malenka RC (2011). Drug-evoked synaptic plasticity in addiction: from molecular changes to circuit remodeling. *Neuron* **69**: 650–663.

Maccioni P, Colombo G (2009). Role of the GABA(B) receptor in alcohol-seeking and drinking behavior. *Alcohol* **43**: 555–558.

Malcolm R, LaRowe S, Cochran K, Moak D, Herron J, Brady K *et al* (2005). JA controlled trial of amlodipine for cocaine dependence: a negative report. *Subst Abuse Treat* **28**: 197–204.

Malcolm R, Myrick HL, Veatch LM, Boyle E, Randall PK (2007). Self-reported sleep, sleepiness, and repeated alcohol withdrawals: a randomized, double blind, controlled comparison of lorazepam *vs* gabapentin. *J Clin Sleep Med* **3**: 24–32.

Mariani JJ, Rosenthal RN, Tross S, Singh P, Anand OP (2006). A randomized, open-label, controlled trial of gabapentin and phenobarbital in the treat-ment of alcohol withdrawal. *Am J Addict* **15**: 76–84.

Marinelli M, Rudick CN, Hu XT, White FJ (2006). Excitability of dopamine neurons: modulation and physiological consequences. *CNS Neurol Disord Drug Targets* **5**: 79–97.

Martellotta MC, Kuzmin A, Muglia P, Gessa GL, Fratta W (1994). Effects of the calcium antagonist isradipine on cocaine intravenous self-administration in rats. *Psychopharmacology* **113**: 378–380.

Martin-Iverson MT, Reimer AR (1994). Effects of nimodipine and/or haloperidol on the expression of conditioned locomotion and sensitization to cocaine in rats. *Psychopharmacology (Berl)* **114**: 315–320.

Martin-Iverson MT, Reimer AR, Sharma S (1997). Unbiased cocaine conditioned place preferences (CPP) obscures conditioned locomotion, and nimodipine blockade of cocaine CPP is due to conditioned place aversions. *Psychopharmacology* **130**: 327–333.

Martínez-Raga J, Sabater A, Perez-Galvez B, Castellano M, Cervera G (2004). Add-on gabapentin in the treatment of opiate withdrawal. *Prog Neuropsychopharmacol Biol Psychiatry* **28**: 599–601.

Mason BJ, Light JM, Williams LD, Drobes DJ (2009). Proof-of-concept human laboratory study for protracted abstinence in alcohol dependence: effects of gabapentin. *Addict Biol* **14**: 73–83. **Human laboratory evidence for a role of gabapentin in treating the protracted abstinence phase in alcohol dependence**.

McGivern JG (2007). Ziconotide: a review of its pharmacology and use in the treatment of pain. *Neuropsychiatr Dis Treat* **3**: 69–85.

McKee SA, Harrison EL, O'Malley SS, Krishnan-Sarin S, Shi J, Tetrault JM *et al* (2009). Varenicline reduces alcohol self-administration in heavy-drinking smokers. *Biol Psychiatry* **66**: 185–190.

McLean M (1994). Clinical pharmacokinetics of gabapentin. *Neurology* **44**: S17–S22.

McLean MJ (1999). Gabapentin in the management of convulsive disorders. *Epilepsia* **40**: S39–S50.

MedWatch (2011). The FDA Safety Information and Adverse Event Reporting Program. Topamax (Topiramate): label change-risk for development of cleft lip and/or cleft palate in newborns. *US Food and Drug Administration* 3/4/.

Melis M, Spiga S, Diana M (2005). The dopamine hypothesis of drug addiction: hypodopaminergic state. *Int Rev Neurobiol* **63**: 101–154. **Exhaustive evaluation of the pre-clinical and clinical literature and formal presentation of the hypodopaminergic hypothesis**.

Meng G, Wu N, Zhang C, Su RB, Lu XQ, Liu Y *et al* (2008). Analgesic activity of ZC88, a novel N-type voltage-dependent calcium channel blocker, and its modulation of morphine analgesia, tolerance and dependence. *Eur J Pharmacol* **586**: 130–138.

Mills K, Ansah TA, Ali SF, Shockley DC (1998). Calcium channel antagonist isradipine attenuates cocaine-induced motor activity in rats: correlation with brain monoamine levels. *Ann NY Acad Sci* **844**: 201–207.

Miranda Jr R, MacKillop J, Monti PM, Rohsenow DJ, Tidey J, Gwaltney C *et al* (2008). Effects of topiramate on urge to drink and the subjective effects of alcohol: a preliminary laboratory study. *Alcohol Clin Exp Res* **32**: 489–497.

Mulholland PJ, Becker HC, Woodward JJ, Chandler LJ (2011). Small conductance calcium-activated potassium type 2 channels regulate alcohol-associated plasticity of glutamatergic synapses. *Biol Psychiatry* **69**: 625–632. **Chronic alcohol intake reduced SK type potassium channel function in the hippocampus, and infusion of the SK channel activator 1-EBIO decreased withdrawal symptoms**.

Muntaner C, Kumor KM, Nagoshi C, Jaffe JH (1991). Effects of nifedipine pretreatment on subjective and cardiovascular responses to intravenous cocaine in humans. *Psychopharmacology* **105**: 37–41.

Myrick H, Anton RF (1998). Treatment of alcohol withdrawal. *Alcohol Health Res World* **22**: 38–43.

Myrick H, Henderson S, Brady KT, Malcolm R (2001). Gabapentin in the treatment of cocaine dependence: a case series. *J Clin Psychiatry* **62**: 19–23.

Myrick H, Malcolm R, Randall PK, Boyle E, Anton RF, Becker HC *et al* (2009). A double-blind trial of gabapentin *vs* lorazepam in the treatment of alcohol withdrawal. *Alcohol Clin Res Exp* **33**: 1582–1588.

Newton PM, Orr CJ, Wallace MJ, Kim C, Shin HS, Messing RO (2004). Deletion of N-type calcium channels alters ethanol reward and reduces ethanol consumption in mice. *J Neurosci* **24**: 9862–9869.

Newton PM, Zeng L, Wang V, Connolly J, Wallace MJ, Kim C *et al* (2008). A blocker of N- and T-type voltage-gated calcium channels attenuates ethanol-induced intoxication, place preference, self-administration, and reinstatement. *J Neurosci* **28**: 11712–11719.

Olsen RW, Sieghart W (2009). GABAA receptors: subtypes provide diversity of function and pharmacology. *Neuropharmacology* **56**: 141–148.

Pani L, Kuzmin A, Diana M, De Montis G, Gessa GL, Rossetti ZL (1990). Calcium receptor antagonists modify cocaine effects in the central nervous system differently. *Eur J Pharmacol* **190**: 217–221.

Park SP, Kwon SH (2008). Cognitive effects of antiepileptic drugs. *J Clin Neurol* **4**: 99–106.

Paterson NE, Froestl W, Markou A (2004). The GABAB receptor agonists baclofen and CGP44532 decreased nicotine self-administration in the rat. *Psychopharmacology (Berl)* **172**: 179–186.

Paterson NE, Vlachou S, Guery S, Kaupmann K, Froestl W, Markou A (2008). Positive modulation of GABA(B) receptors decreased nicotine self-administration and counteracted nicotine-induced enhancement of brain reward function in rats. *J Pharmacol Exp Ther* **326**: 306–314.

Perez-Reyes M, White WR, Hicks RE (1992). Interaction between ethanol and calcium channel blockers in humans. *Alcohol Clin Exp Res* **16**: 769–775.

Pucilowski O, Krzascik P, Trzaskowska E, Kostowski W (1989). Different effect of diltiazem and nifedipine on some central actions of ethanol in the rat. *Alcohol* **6**: 165–168.

Pucilowski O, Rezvani AH, Janowsky DS (1992). Suppression of alcohol and saccharin preference in rats by a novel Ca2+ channel inhibitor, Goe 5438. *Psychopharmacology* **107**: 447–452.

Raby WN (2000). Gabapentin therapy for cocaine cravings. *Am J Psychiatry* **157**: 2058–2059.

Ramkumar V, el-Fakahany EE (1988). Prolonged morphine treatment increases rat brain dihydropyridine binding sites: possible involvement in development of morphine dependence. *Eur J Pharmacol* **146**: 73–83.

Ranaldi R, Poeggel K (2002). Baclofen decreases methamphetamine self-administration in rats. *Neuroreport* **13**: 1107–1110.

Ray LA, Miranda Jr R, MacKillop J, McGeary J, Tidey JW, Rohsenow DJ *et al* (2009). A preliminary pharmacogenetic investigation of adverse events from topiramate in heavy drinkers. *Exp Clin Psychopharmacol* **17**: 122–129.

Reis AD, Castro LA, Faria R, Laranjeira R (2008). Craving decrease with topiramate in outpatient treatment for cocaine dependence: an open label trial. *Rev Bras Psiquiatr* **30**: 132–135.

Rezvani AH, Grady DR, Janowsky DS (1991). Effect of calcium-channel blockers on alcohol consumption in alcohol-drinking monkeys. *Alcohol Alcohol* **26**: 161–167.

Rezvani AH, Janowsky DS (1990). Decreased alcohol consumption by verapamil in alcohol preferring rats. *Prog Neuropsychopharmacol Biol Psychiatry* **14**: 623–631.

Roache JD, Johnson BA, Ait-Daoud N, Mauldin JB, Thornton JE, Wells LT *et al* (2005). Effects of repeated-dose isradipine on the abuse liability of cocaine. *Exp Clin Psychopharmacol* **13**: 319–326.

Roberts DC, Andrews MM, Vickers GJ (1996). Baclofen attenuates the reinforcing effects of cocaine in rats. *Neuropsychopharmacology* **15**: 417–423.

Rosse RB, Alim TN, Fay-McCarthy M, Collins Jr JP, Vocci Jr FJ, Lindquist T *et al* (1994). Nimodipine pharmacotherapeutic adjuvant therapy for inpatient treatment of cocaine dependence. *Clin Neuropharmacol* **17**: 348–358.

Rubio G, López-Muñoz F, Alamo C (2006). Effects of lamotrigine in patients with bipolar disorder and alcohol dependence. *Bipolar Disord* **8**: 289–293. **The anticonvulsant drug lamotrigine reduces alcohol-related craving, as well as depression and mania, and humans with co-morbid bipolar disorder and alcohol**.

Sanchis-Segura C, Spanagel R (2006). Behavioural assessment of drug reinforcement and addictive features in rodents: an overview. *Addict Biol* **11**: 32–38.

Santillán R, Hurlé MA, Armijo JA, de los Mozos R, Flórez J (1998). Nimodipine-enhanced opiate analgesia in cancer patients requiring morphine dose escalation: a double-blind, placebo-controlled study. *Pain* **76**: 17–26.

Schindler CW, Tella SR, Prada J, Goldberg SR (1995). J Calcium channel blockers antagonize some of cocaine's cardiovascular effects, but fail to alter cocaine's behavioral effects. *Pharmacol Exp Ther* **272**: 791–798.

Shimamoto H, Takasaki K, Shigemori M, Imaizumi T, Ayabe M, Shoji H (2001). Therapeutic effect and mechanism of repetitive transcranial magnetic stimulation in Parkinson's disease. *J Neurol* **248**(Suppl.): 48–52.

Shulman A, Jagoda J, Laycock G, Kelly H (1998). Calcium channel blocking drugs in the management of drug dependence, withdrawal and craving. A clinical pilot study with nifedipine and verapamil. *Aust Fam Physician* **27**: S19–S24.

Schulteis G, Markou A, Cole M, Koob GF (1995). Decreased brain reward produced by ethanol withdrawal. *Proc Natl Acad Sci USA* **20**: 5880–5884. **Higher current thresholds in ethanol withdrawn rats suggest a decreased functioning of the brain reward circuitry**.

Shank RP, Gardocki JF, Streeter AJ, Maryanoff BE (2000). An overview of the preclinical aspects of topiramate: pharmacology, pharmacokinetics, and mechanism of action. *Epilepsia* **41**: S3–S9.

Shibasaki M, Kurokawa K, Ohkuma S (2010). Upregulation of L-type Ca(v)1 channels in the development of psychological dependence. *Synapse* **64**: 440–444.

Shoptaw S, Yang X, Rotheram-Fuller EJ, Hsieh YC, Kintaudi PC, Charuvastra VC *et al* (2003). Randomized placebo-controlled trial of baclofen for cocaine

dependence: preliminary effects for individuals with chronic patterns of cocaine use. *J Clin Psychiatry* **64**: 1440–1448.
Simms JA, Steensland P, Medina B, Abernathy KE, Chandler LJ, Wise R *et al* (2008). Intermittent access to 20% ethanol induces high ethanol consumption in Long-Evans and Wistar rats. *Alcohol Clin Exp Res* **32**: 1816–1823.
Siu EC, Tyndale RF (2007). Non-nicotinic therapies for smoking cessation. *Annu Rev Pharmacol Toxicol* **47**: 541–564.
Snutch TP (2005). Targeting chronic and neuropathic pain: the N-type calcium channel comes of age. *NeuroRx* **2**: 662–670.
Spanagel R (2009). Alcoholism: a systems approach from molecular physiology to addictive behavior. *Physiol Rev* **89**: 649–705.
Spano MS, Fattore L, Fratta W, Fadda P (2007). The GABAB receptor agonist baclofen prevents heroin-induced reinstatement of heroin-seeking behavior in rats. *Neuropharmacology* **52**: 1555–1562.
Stallings W, Schrader S (2007). Baclofen as prophylaxis and treatment for alcohol withdrawal: a retrospective chart review. *J Okla State Med Assoc* **100**: 354–360.
Steensland P, Simms JA, Holgate J, Richards JK, Bartlett SE (2007). Varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, selectively decreases ethanol consumption and seeking. *Proc Natl Acad Sci USA* **104**: 12518–12523.
Steffensen SC, Walton CH, Hansen DM, Yorgason JT, Gallegos RA, Criado JR (2009). Contingent and non-contingent effects of low-dose ethanol on GABA neuron activity in the ventral tegmental area. *Pharmacol Biochem Behav* **92**: 68–75.
Suzuki T, Shiozaki Y, Masukawa Y, Misawa M (1992). Effects of calcium antagonists on the cocaine- and methamphetamine-induced conditioned place preference. *Arukoru Kenkyuto Yakubutsu Ison* **27**: 81–90.
Swift RM (2010). Medications acting on the dopaminergic system in the treatment of alcoholic patients. *Curr Pharm Des* **16**: 2136–2140. **Up to date evaluation of dopamine-acting drugs in alcoholics**.
Tyacke RJ, Lingford-Hughes A, Reed LJ, Nutt DJ (2010). GABAB receptors in addiction and its treatment. *Adv Pharmacol* **58**: 373–396.
Uslaner JM, Vardigan JD, Drott JM, Uebele VN, Renger JJ, Lee A *et al* (2010). T-type calcium channel antagonism decreases motivation for nicotine and blocks nicotine- and cue-induced reinstatement for a response previously reinforced with nicotine. *Biol Psychiatry* **68**: 712–718.
Vaupel DB, Lange WR, London ED (1993). Effects of verapamil on morphine-induced euphoria, analgesia and respiratory depression in humans. *J Pharmacol Exp Ther* **267**: 1386–1394.
Vengeliene V, Bilbao A, Molander A, Spanagel R (2008). Neuropharmacology of alcohol addiction. *Br J Pharmacol* **154**: 299–315.
Vengeliene V, Heidbreder CA, Spanagel R (2007). The effects of lamotrigine on alcohol seeking and relapse. *Neuropharmacology* **53**: 951–957.
Voris J, Smith NL, Rao SM, Thorne DL, Flowers QJ (2003). Gabapentin for the treatment of ethanol withdrawal. *Subst Abus* **24**: 129–132.
Voronin KE, Drobes D, Myrick H, Moak D, Wang W, Anton RF (2004). Gabapentin is well tolerated but does not alter drinking in nontreatment seeking alcoholics during natural observation and in a clinical bar lab. *Alcohol Clin Exp Res* **28**: 113A.
Walker BM, Koob GF (2007). The gamma-aminobutyric acid-B receptor agonist baclofen attenuates responding for ethanol in ethanol-dependent rats. *Alcohol Clin Exp Res* **31**: 11–18. **Clear preclinical evidence of a role of baclofen in suppressing ethanol self-administration, with an increased potency of baclofen in ethanol-dependent animals**.
Watson WP, Little HJ (2002). Selectivity of the protective effects of dihydropyridine calcium channel antagonists against the ethanol withdrawal syndrome. *Brain Res* **930**: 111–122.
Watson WP, Robinson E, Little HJ (1997). The novel anticonvulsant, gabapentin, protects against both convulsant and anxiogenic aspects of the ethanol withdrawal syndrome. *Neuropharmacology* **36**: 1369–1375.
Wegelius K, Halonen T, Korpi ER (1993). Gamma-vinyl GABA decreases voluntary alcohol consumption in alcohol-preferring AA rats. *Pharmacol Toxicol* **73**: 150–152.
Weinberger AH, George TP, Perkins KA, Chengappa KN (2008). Effects of topiramate on smoking in patients with schizoaffective disorder, bipolar type. *J Clin Psychopharmacol* **28**: 247–248.
Weiner JL, Valenzuela CF (2006). Ethanol modulation of GABAergic transmission: the view from the slice. *Pharmacol Ther* **111**: 533–554.
Weiss F, Parsons LH, Schulteis G, Hyytia P, Lorang MT, Bloom FE *et al* (1996). Ethanol self-administration restores withdrawal-associated deficiencies in accumbal dopamine and 5-hydroxytryptamine release in dependent rats. *J Neurosci* **16**: 3474–3485.
Weiss F, Porrino LJ (2002). Behavioral neurobiology of alcohol addiction: recent advances and challenges. *J Neurosci* **22**: 332–337.
Westerink BHC, Kwint H-F, deVries JB (1996). The pharmacology of mesolimbic dopamine neurons: a dual-probe microdialysis study in the ventral tegmental area and nucleus accumbens of the rat brain. *J Neurosci* **16**: 2605–2611.
Wu PH, Pham T, Naranjo CA (1987). Nifedipine delays the acquisition of tolerance to ethanol. *Eur J Pharmacol* **139**: 233–236.
Xi ZX, Stein EA (2000). Increased mesolimbic GABA concentration blocks heroin self-administration in the rat. *J Pharmacol Exp Ther* **294**: 613–619.
Yao L, Fan P, Arolfo M, Jiang Z, Olive MF, Zablocki J *et al* (2010). Inhibition of aldehyde dehydrogenase-2 suppresses cocaine seeking by generating THP, a cocaine use-dependent inhibitor of dopamine synthesis. *Nat Med* **16**: 1024–1028. **Preclinical evidence of a potential therapeutic role of a selective reversible ALDH-2 for cocaine dependence via a reduction in cocaine-associated increases in dopamine release**.
Yeomans JS (1989). Two substrates for medial forebrain bundle self-stimulation: myelinated axons and dopamine axons. *Neurosci Biobehav Rev* **13**: 91–98.
Yeomans JS, Mathur A, Tampakeras M (1993). Rewarding brain stimulation: role of tegmental cholinergic neurons that activate dopamine neurons. *Behav Neurosci* **107**: 1077–1087.
Yoshida M, Yokoo H, Tanaka T, Emoto H, Tanaka M (1994). Opposite changes in the mesolimbic metabolism in the nerve terminal and cell body sites induced by locally infused in the rat. *Brain Res* **636**: 111–114.
Zorrilla EP, Koob GF (2010). Progress in corticotropin-releasing factor-1 antagonist development. *Drug Discov Today* **15**: 371–383.