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

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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,

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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 (~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.i.d. 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 to 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, Khazaa *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 (LVDC) blockers (LCCBs) of different classes, including the 1,4-dihydropyridine (DHP) derivatives isradipine, 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-Iversen *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, LCCBs 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 Budzinska, 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 LVDCs to enhancing midbrain DA neuron firing (Marinelli *et al*, 2006). In addition to midbrain LVDCs, LVDCs 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.

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