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Review

Glutamatergic medications for the treatment of drug and behavioral addictions

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ABSTRACT

Historically, most pharmacological approaches to the treatment of addictive disorders have utilized either substitution-based methods (i.e., nicotine replacement or opioid maintenance) or have targeted monoaminergic or endogenous opioidergic neurotransmitter systems. However, substantial evidence has accumulated indicating that ligands acting on glutamatergic transmission are also of potential utility in the treatment of drug addiction, as well as various behavioral addictions such as pathological gambling. The purpose of this review is to summarize the pharmacological mechanisms of action and general clinical efficacy of glutamatergic medications that are currently approved or are being investigated for approval for the treatment of addictive disorders. Medications with effects on glutamatergic transmission that will be discussed include acamprosate, N-acetylcysteine, D-cycloserine, gabapentin, lamotrigine, memantine, modafinil, and topiramate. We conclude that manipulation of glutamatergic neurotransmission is a relatively young but promising avenue for the development of improved therapeutic agents for the treatment of drug and behavioral addictions.

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Contents

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1. Introduction

Drug addiction, defined by the American Psychiatric Association as *substance dependence* (American Psychiatric Association, 2002), has numerous maladaptive psychological and behavioral manifestations including: loss of control over drug intake, taking drugs in greater quantities than intended, repeated unsuccessful attempts at quitting or reducing drug use, continued drug use despite negative consequences, and the emergence of drug-specific symptoms of tolerance and/or withdrawal. In addition to numerous intangible humanistic factors such as the disruption of families and interpersonal relationships, social dysfunction, and loss of life, the socioeconomic burden that drug addiction places on society is enormous (Cartwright, 2008; Gilson and Kreis, 2009; Malliarakis and Lucey, 2007; Rehm et al., 2009; Spanagel, 2009; Thavorncharoensap et al., 2009). In recent years it has become evident that the neural substrates underlying addiction to drugs of abuse overlap considerably with those of non-drug "behavioral" addictions (i.e., pathological gambling, pornography/internet addiction, etc.) (Grant et al., 2010a).

To date, medications that have been developed to aid in the treatment of addictive disorders have shown only moderate success. Known barriers that compromise the efficacy of medication-based approaches to treatment to addiction disorders include poor medication compliance, adverse side effects, safety issues, variable medication responses within treatment groups, poor integration of medication management into psychosocial or cognitive-behavioral therapies, inaccessibility to medications or adequate health care, and relapse following discontinuation of the therapeutic medication (Koob et al., 2009; Montoya and Vocci, 2008; O'Brien, 2008; Ross and Peselow, 2009; Zahm, 2010). While numerous medications of various classes that have been approved for other medical conditions are currently being investigated as potential aids in the treatment of addictive disorders, the only medications approved specifically for the treatment thus far in the United States are varenicline, buproprion, and nicotine replacement therapies for smoking cessation, long-acting opioids (i.e., methadone or buprenorphine) for opiate dependence, and disulfiram, naltrexone, and acamprosate for alcohol dependence. No medications to aid in the treatment of addiction to cocaine, methamphetamine, or marijuana are currently approved, nor are any approved for the treatment of behavioral addictions.

The purpose of the present review is to provide a summary of the pharmacological mechanisms of action and general clinical efficacy of medications acting on glutamatergic transmission in the treatment of addictive disorders. These medications include acamprosate, N-acetylcysteine, D-cycloserine, gabapentin, lamotrigine, memantine, modafinil, and topiramate. It should be noted that many of these medications have mechanisms of action that include multiple neurotransmitter systems, and perhaps with the exception of D-cycloserine, none is known to selectively target glutamatergic transmission or specific glutamate receptors. However, there is a strong body of preclinical evidence arising from over two decades of animal studies suggesting a critical role for glutamate transmission and glutamate receptors in drug reward, reinforcement, and relapse (Bird and Lawrence, 2009; Bowers et al., 2010; Gass and Olive, 2008; Kalivas et al., 2009; Moussawi and Kalivas, 2010; Olive, 2009, 2010; Reissner and Kalivas, 2010; Tzschentke and Schmidt, 2003; Uys and LaLumiere, 2008). For an overview of glutamatergic transmission and glutamate receptors, the reader is referred to the review by Sanacora in the current issue (*publisher – please insert correct page numbers here*). In addition, the small but growing body of literature on the use of these medications to treat behavioral addictions such as compulsive gambling, and studies on this topic will also be reviewed.

2. Glutamatergic medications for the treatment of substance use disorders

2.1. Acamprosate

2.1.1. Mechanism of action

Acamprosate (calcium acetylhomotaurine) is derived from homotaurine, a nonspecific γ-aminobutyric acid (GABA) agonist. The molecule is N-acetylated to facilitate penetration across the blood–brain barrier, and is formulated as a calcium salt to increase absorption of the compound from the gastrointestinal tract. Despite these chemical modifications, its overall bioavailability remains poor (i.e., <20%) and requires doses in the range of 2–3 g per day to demonstrate efficacy. Many pharmacological mechanisms of action of acamprosate have been proposed, but the first studies suggesting that acamprosate exerts its actions through glutamatergic mechanisms were reported by =Zeise et al. (1990, 1993). These investigators showed that acamprosate reduced the excitation of neuronal firing evoked by iontophoretic application of L-glutamate onto cortical neurons in vivo, and inhibited excitatory postsynaptic potentials (EPSPs) evoked by glutamate and N-methyl-D-aspartate (NMDA). Additional evidence for a NMDA antagonist-like mechanism of action of acamprosate came from studies demonstrating that this compound antagonizes NMDA-evoked excitatory postsynaptic currents (EPSCs) in hippocampal neurons (Rammes et al., 2001) and up-regulates NMDA receptor subunit expression in a similar fashion to that observed following treatment with the non-competitive NMDA antagonist MK-801 (Putzke et al., 1996; Rammes et al., 2001). However, some investigators have found no effect of acamprosate on NMDA-mediated synaptic transmission in the CA1 region of the hippocampus (Popp and Lovinger, 2000), while others have found that acamprosate actually potentiates NMDA receptor function in the CA1 region of the hippocampus (Madamba et al., 1996) and in the nucleus accumbens (Berton et al., 1998). Despite these inconsistent electrophysiological findings, binding studies have confirmed an interaction of acamprosate with the spermidine-, glutamate- and/or MK-801-sensitive binding site of the NMDA receptor (al Qatari et al., 1998; Harris et al., 2002; Naassila et al., 1998), and as such acamprosate is often referred to nonspecifically as an "NMDA modulator" (Fig. 1). Although the precise molecular target(s) of acamprosate are still not firmly established (Kiefer and Mann, 2010; Reilly et al., 2008), most current theories posit that acamprosate restores the imbalances between excitatory and inhibitory amino acid neurotransmission that result from chronic alcohol consumption (De Witte et al., 2005; Kiefer and Mann, 2010; Spanagel et al., 2005; Umhau et al., 2010).

2.1.2. Clinical efficacy

The first demonstration of the clinical efficacy of acamprosate in reducing the incidence of relapse in alcoholics was published in the mid-1980s (Lhuintre et al., 1985). Over the years, acamprosate has

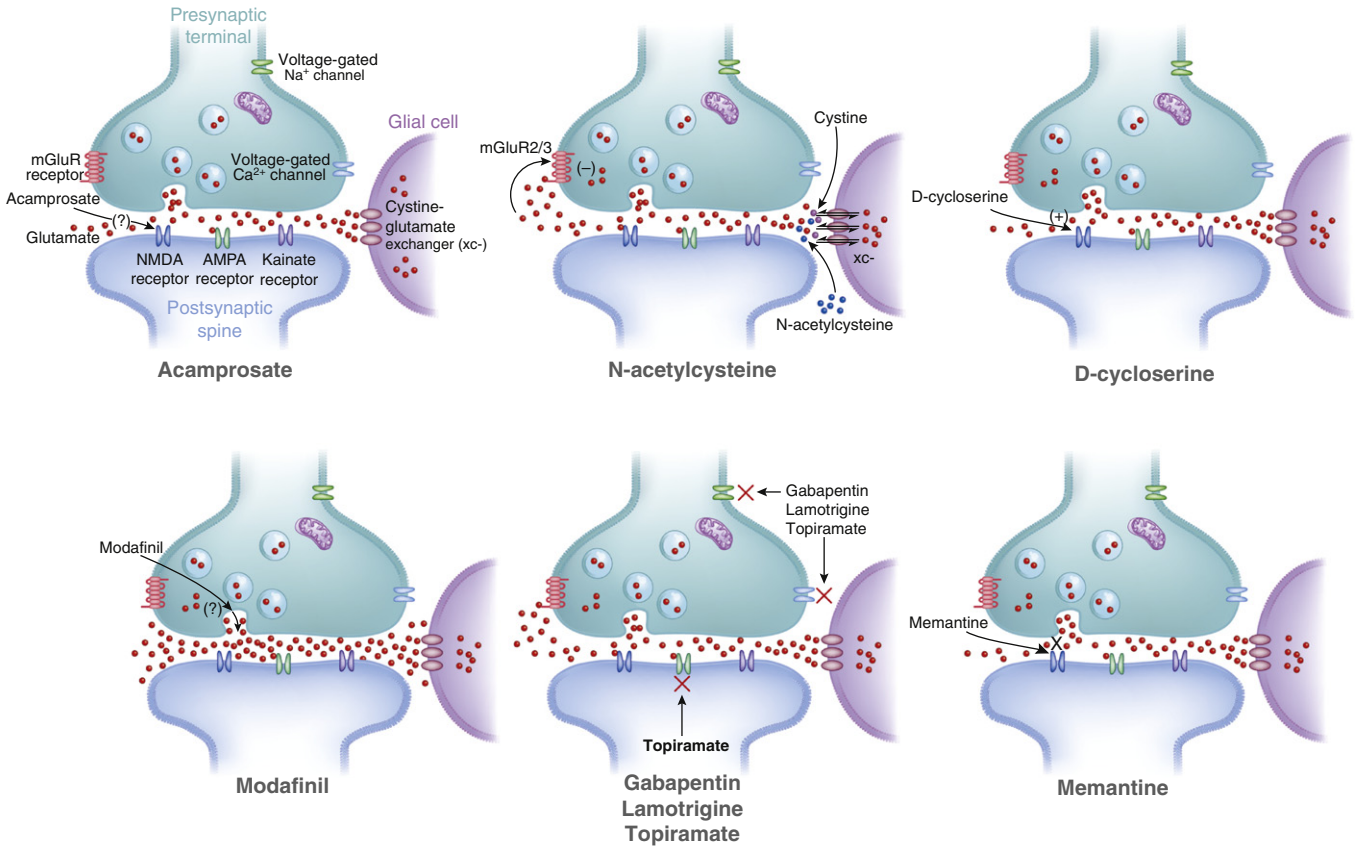

Fig. 1. Putative glutamatergic mechanisms of action of 8 anti-addiction medications. *Acamprosate* — The molecular target(s) of acamprosate is still uncertain, but several studies have indicated it modulates the activity of NMDA receptors and restores balance between excitatory and inhibitory neurotransmission that is altered by chronic alcohol consumption. *N-acetylcysteine (NAC)* is a cystine prodrug that stimulates the cystine-glutamate exchanger (xc-) on glia to normalize extracellular levels of glutamate, which are reduced in the nucleus accumbens during cocaine withdrawal. This normalization of extracellular glutamate levels restores glutamatergic tone on release-inhibiting presynaptic mGluR2/3 receptors, which in turn inhibits the ability of exposure to cocaine (and perhaps cocaine-associated cues) to elevate extracellular glutamate and evoke cocaine craving or relapse. *D-cycloserine (DCS)* is a partial agonist at the glyine co-agonist binding site on NR1 subunits that are intrinsic to all NMDA receptors, and thus DCS potentiates cation influx through the NMDA receptor complex. *Modafinil* has numerous actions on neurons and its precise molecular targets have yet to be identified. However, several microdialysis studies have shown that modafinil increases extracellular levels of glutamate in various brain regions. *Gabapentin, lamotrigine,* and *topiramate* are anticonvulsants that have numerous mechanisms of action, one of which is the reduction of the release of glutamate by blocking cation influx through presynaptic Na^+ and Ca^{2+} channels. Topiramate has the unique ability to also antagonize GluR5-containing AMPA receptors. *Memantine* is a non-competitive NMDA receptor antagonist.

demonstrated effect sizes ranging from small to moderate in reducing overall alcohol consumption, subjective measures of alcohol craving, and promoting abstinence, as reviewed in recent meta-analyses (Kennedy et al., 2010; Kiefer and Mann, 2010; Kranzler and Gage, 2008; Mann et al., 2008; Mason and Heyser, 2010a,b; Rosner et al., 2010; Snyder and Bowers, 2008). Due to its poor oral bioavailability, large doses of acamprosate (typically in the 2–3 g per day range) are needed in order to observe efficacy. However, a recent large multi-center study of over 1200 alcohol-dependent patients (known as the Combined Medications and Behavioral Interventions, or "COMBINE" study) found that acamprosate was no more effective than placebo in reducing the incidence of relapse in a medically managed setting (Anton et al., 2006). Other recent studies have also demonstrated a lack of efficacy of acamprosate in reducing alcohol consumption or craving, or promoting abstinence (Donovan et al., 2008; Laaksonen et al., 2008; Morley et al., 2006; Richardson et al., 2008). The reasons for these negative findings, especially in light of numerous previous positive findings (summarized in the meta-analyses cited above), are still being debated. Some investigators have suggested that a significant "placebo effect" in the COMBINE study might have masked any beneficial effects of acamprosate (Weiss et al., 2008), and that improvements in nondrinking related outcomes measures such as quality of life were in fact superior in acamprosate- versus placebo-treated patients in the COMBINE study (LoCastro et al., 2009). Others have suggested that initiation of acamprosate treatment following detoxification produces reductions in alcohol craving as opposed to when given during active alcohol consumption (Kampman et al., 2009), as was done in the COMBINE study. The requirement for three doses per day may be a compliance barrier for some patients. Decreased motivation to initiate treatment among depressed as compared to non-depressed alcoholics significantly affects treatment compliance in acamprosate-treated patients (Lejoyeux and Lehert, 2011). Finally, other motivational factors such as having a treatment goal of complete abstinence as opposed to moderate drinking appear to have beneficial effects in patients treated with acamprosate as compared with placebo (Mason et al., 2006; Mason and Lehert, 2010). It is likely that, as with any psychotropic medication, specific subsets of patients may respond better to acamprosate than others. Additional research is clearly needed to determine precisely what these beneficial motivational, methodological, outcome measure, or perhaps genetic factors are in order to identify alcoholics that are most likely to exhibit a positive response to acamprosate.

Regarding the utility of acamprosate in treating addiction to other drugs of abuse or behavioral addictions such as pathological gambling, large-scale studies are non-existent, and the few studies that have been published have reported mixed results. For example, a recent case report supported the potential utility of acamprosate in treating pathological gambling (Raj, 2010). On the other hand, Kampman and colleagues recently reported that in a double-blind placebo-controlled trial of 60 cocaine-dependent patients, acamprosate showed no

beneficial effects on cocaine use, craving, or withdrawal symptoms as compared to patients receiving placebo (Kampman et al., 2011). These latter findings are particularly disappointing since several rodent studies have shown that acamprosate attenuates the conditioned rewarding effects of cocaine as well as drug- and cue-primed reinstatement of cocaine-seeking behavior (Bowers et al., 2007; Mcgeehan and Olive, 2003, 2006). However, given the small sample size and high dropout rate of the study by Kampman and colleagues, the possibility remains that acamprosate may be beneficial in the treatment of cocaine addiction in a as of yet undefined subset of cocaine-dependent individuals.

2.2. N-acetylcysteine (NAC)

2.2.1. Mechanism of action

NAC is an N-acetylated derivative of the naturally occurring amino acid cysteine. Once inside major internal organs including the brain, NAC is deacetylated to form free cysteine, and homodimerization of two cysteine molecules via a disulfide bond results in the formation of cystine. Thus, NAC is considered a cystine pro-drug that binds to the cystine-glutamate exchanger (often referred to as system xc-) and promotes the synthesis of glutathione (Baker et al., 2002; McBean, 2002). Through this mechanism NAC has proven clinical efficacy as a mucolytic agent and in the treatment of acetaminophen overdose. However, in addition to promoting glutathione synthesis, system xc- is an antiporter protein that transports extracellular cystine into glial cells and intracellular glutamate from inside glia into the extracellular environment. The resulting effect of NAC is an elevation of extracellular glutamate levels, which are reduced during protracted cocaine withdrawal (Baker et al., 2002, 2003; Kau et al., 2008; Madayag et al., 2007; Melendez et al., 2005; Moran et al., 2005). This "normalization" of extracellular glutamate levels restores glutamatergic tone on presynaptic release-regulating group II metabotropic glutamate receptors (mGluR2/3, Moran et al., 2005; see Fig. 1) and prevents the ability of a subsequent cocaine challenge to increase extracellular glutamate levels in the nucleus accumbens. The end result is an inhibition of the ability of acute cocaine exposure to reinstate cocaine-seeking behavior (Amen et al., 2011; Baker et al., 2003; Kau et al., 2008; Madayag et al., 2007; Moran et al., 2005; Moussawi et al., 2009).

2.2.2. Clinical efficacy

Based on these findings from animal studies, several studies on the efficacy of NAC to reduce cocaine use, craving, withdrawal symptoms, and relapse in human cocaine addicts have recently been published. In a small safety and tolerability study (n = 13 subjects), it was demonstrated that NAC (1200 mg/day for two days) was well-tolerated by cocaine addicts and produced slight trends in reductions in self-reports of cocaine use, craving and withdrawal symptoms (LaRowe et al., 2006). Small follow-up studies (n = 15–23 subjects) have confirmed that similar doses of NAC are well-tolerated by cocaine addicts and actually produce significant reductions in cocaine use and craving in treatment-seeking outpatient cocaine-dependent individuals (Amen et al., 2011; LaRowe et al., 2007; Mardikian et al., 2007). Importantly, however, a recent pilot study showed that NAC does not reduce subjective feelings of a cocaine "high" or "rush" following exposure to video of cocaine-associated cues, but does attenuate craving evoked by acute IV cocaine exposure (Amen et al., 2011). While these latter results may appear to be in disagreement with those of LaRowe, Mardikian, and colleagues, who found reductive effects of NAC on cue-evoked cocaine craving, the extremely small sample size of the study by Amen and colleagues (n = 4 subjects) may limit its interpretability. Regardless, these preliminary results provide encouraging data that NAC may be of potential use in the treatment of cocaine addiction, and additional multi-center clinical trials are needed to confirm these results on a larger scale.

With regards to other drugs of abuse, a recent small clinical trial (n = 29 subjects) investigated the potential efficacy of NAC in aiding in smoking cessation (Knackstedt et al., 2009). The results of this study showed that NAC treatment (2400 mg/day) reduces the number of cigarettes smoked relative to the number of cigarettes smoked by subjects receiving placebo, but NAC treatment did not reduce plasma carbon monoxide levels, nicotine withdrawal symptoms, or nicotine craving. Another small pilot study (n = 24 subjects) demonstrated that NAC reduced marijuana use and craving in marijuana-dependent young adults aged 18–21 compared to placebo (Gray et al., 2010). As for non-drug addictions, a small clinical trial (n = 23 subjects) showed that NAC (mean effective dose 1477 mg/day) lowered scores on the Yale Brown Obsessive Compulsive Scale Modified for Pathological Gambling [PG-YBOCS] (Grant et al., 2007), and it has been shown to be effective in reducing compulsive nail-biting associated with bipolar disorder in three patients (Berk et al., 2009). Finally, NAC was also shown to suppress hair-pulling in a double-blind study of 50 patients with trichotillomania (Grant et al., 2009).

Although all of the aforementioned clinical studies are preliminary and utilized relatively small sample sizes, the seemingly consistent anti-addictive properties of NAC provide compelling evidence that this medication, as well as other compounds that restore glutamate homeostasis (Knackstedt et al., 2010; Sari et al., 2009), may potentially prove to be effective pharmacotherapeutic aids in the treatment of drug and behavioral addictions.

2.3. D-cycloserine (DCS)

2.3.1. Mechanism of action

DCS (D-4-amino-3-isoxazolidone) is a derivative of the naturally occurring amino acid serine. It acts as co-agonist at the glycine-binding site on the NR1 subunit of the NMDA receptor, which is present in all NMDA receptors in the central nervous system. DCS is insufficient to activate NMDA receptors on its own, and requires the presence of glutamate binding to the receptor in order to exert its effects. Activation of the glycine binding site by DCS enhances NMDA functioning by increasing calcium influx through these receptors without causing neurotoxicity (Sheinin et al., 2001; see Fig. 1).

2.3.2. Clinical efficacy

As a result of its ability to enhance NMDA receptor function, DCS is believed to facilitate synaptic plasticity and certain forms of learning, including Pavlovian associative learning and extinction learning, and as such it has been reported to successfully facilitate the extinction of fear responses in anxiety disorder patients during cue exposure therapy in numerous clinical studies (reviewed in Davis et al., 2006; Myers et al., 2011; Myers and Davis, 2007). With regards to addiction, animal studies have shown DCS facilitates the extinction of a cocaine-induced conditioned place preference (CPP) (Botreau et al., 2006; Thanos et al., 2009), reduces reacquisition of cocaine self-administration by enhancing extinction learning (Nic Dhonnchadha et al., 2010), and also attenuates the reinstatement of cocaine-seeking in a context-independent manner (Torregrossa et al., 2010). However, only a few clinical studies on the effects of DCS on addictive behaviors have been conducted thus far.

Santa Ana et al. (2009) recently reported that in 12 nicotine-dependent cigarette smokers undergoing cue exposure therapy, administration of DCS (50 mg) significantly attenuated physiological (i.e., skin conductance) responses as well as subjective urge-to-smoke ratings in response to presentation of smoking-associated cues as compared to placebo treated subjects (n = 13). DCS treated subjects also demonstrated reduced expired carbon monoxide levels at a follow-up assessment one week later, although no effects on general smoking behavior was found. These preliminary findings suggest that DCS may be beneficial in augmenting the effects of cue exposure

therapy during attempts at cessation of cigarette smoking. On the contrary, however, another recent study showed that the same dose of DCS actually produced a trend toward increases in subjective reports of cocaine craving in 5 cocaine-dependent individuals (Price et al., 2009). The timing of DCS administration in treatment-seeking patients may be of relevance for these apparent discordant findings. Along these lines, it is worthy to note that a recent animal study showed that infusions of DCS into the basolateral amygdala actually potentiated the reconsolidation of cocaine-associated memories in cocaine self-administering rats (Lee et al., 2009). Clearly more studies are needed to evaluate the possibility that DCS may actually enhance, rather than facilitate the extinction of, the incentive salience of cocaine-associated cues. In addition, studies need to be conducted to determine if DCS enhances the efficacy of cue exposure therapy in humans addicted to drugs of abuse other than cocaine or nicotine, as are studies on the effects of DCS on non-drug addictions.

2.4. Gabapentin

2.4.1. Mechanism of action

Gabapentin is an anticonvulsant medication that has a general inhibitory effect on neuronal transmission by inhibiting presynaptic voltage-gated Na^+ and Ca^{2+} channels (Dickenson and Ghandehari, 2007; Landmark, 2007; Rogawski and Loscher, 2004). As a result, gabapentin inhibits the release of various neurotransmitters, including glutamate, as illustrated in Fig. 1 (Coderre et al., 2007; Cunningham et al., 2004; Dooley et al., 2000; Fink et al., 2000; Maneuf et al., 2004; Maneuf and McKnight, 2001; Shimoyama et al., 2000). Gabapentin also acts on calcium channels containing a2d-1 subunits to block the ability of thrombospondin released from glial cells to promote excitatory synapse formation (Eroglu et al. 2009).

2.4.2. Clinical efficacy

Numerous studies have shown that gabapentin is efficacious in alleviating the somatic symptoms of alcohol withdrawal (Bonnet et al., 1999; Bozikas et al., 2002; Mariani et al., 2006; Martinez-Raga et al., 2004; Myrick et al., 1998; Rustembegovic et al., 2004; Voris et al., 2003), which often presents with moderate to severe CNS hyperexcitability and convulsions. Gabapentin has also been shown to be superior to the benzodiazepine lorazepam in reducing sleep disturbances associated with alcohol withdrawal (Malcolm et al., 2007). Yet to date, clinical studies on the therapeutic efficacy of gabapentin in reducing drug use, craving, or relapse have yielded mixed results. Several studies have demonstrated that gabapentin (with dose ranges of 600–1200 mg/day) does not reduce the use of cocaine in addicted individuals (Bisaga et al., 2006; Gonzalez et al., 2007), while other studies have shown that gabapentin indeed decreases active cocaine use and craving (Berger et al., 2005; Myrick et al., 2001; Raby, 2000; Raby and Coomaraswamy, 2004), perhaps by attenuating the discriminative stimulus effects of cocaine (Haney et al., 2005). Recent studies have shown that gabapentin (600–1500 mg/day) reduces craving for and use of alcohol (Furieri and Nakamura-Palacios, 2007; Mason et al., 2009; Myrick et al., 2009), and prolongs abstinence from alcohol use in alcohol-dependent subjects (Brower et al., 2008). However, other investigators have shown no effects of similar doses of gabapentin on alcohol craving (Bisaga and Evans, 2006; Myrick et al., 2007). In addition, it has been reported that gabapentin does not reduce methamphetamine use (Heinzerling et al., 2006), has limited effects on promoting abstinence from smoking (White et al., 2005), and does not ameliorate subjective withdrawal symptoms in opiate-dependent subjects (Kheirabadi et al., 2008). Taken together, these data suggest that gabapentin is effective for the treatment of alcohol withdrawal symptoms and may have some efficacy for reducing craving for alcohol or cocaine (though not all studies support this notion), but this medication is not likely to have any efficacy in reducing addiction to cigarettes, methamphetamine, or alleviating opiate withdrawal symptoms. To our knowledge, gabapentin has not been tested for efficacy in the treatment of behavioral addictions.

2.5. Lamotrigine

2.5.1. Mechanism of action

Similar to gabapentin, lamotrigine is an anticonvulsant that inhibits presynaptic voltage-gated Na^+ and Ca^{2+} channels (Dickenson and Ghandehari, 2007; Landmark, 2007; Rogawski and Loscher, 2004), thereby inhibiting the release of various neurotransmitters, including glutamate (see Fig. 1; Ahmad et al., 2004; Cunningham and Jones, 2000; Leach et al., 1986; Lees and Leach, 1993; Lingamaneni and Hemmings, 1999; Sitges et al., 2007; Teoh et al., 1995; Waldmeier et al., 1995, 1996; Wang et al., 2001). Lamotrigine carries an uncommon but serious risk of causing a severe skin rash, known as Stevens–Johnson Syndrome. The risk of occurrence of this side effect can be significantly lowered by gradual dose titration, usually starting at a dose of 25 mg/day and tapering up weekly to doses in the range of 200–300 mg/day.

2.5.2. Clinical efficacy

Like gabapentin, lamotrigine inhibits the somatic signs of alcohol withdrawal (Krupitsky et al., 2007b). Recent clinical studies show that lamotrigine also appears to exhibit efficacy in reducing craving for and use of cocaine (Berger et al., 2005; Brown et al., 2003, 2006; Margolin et al., 1998; Pavlovic, 2011), although it appears to leave the subjective effects of cocaine unaltered (Winther et al., 2000). Similar reductive effects of lamotrigine on craving for alcohol (Rubio et al., 2006) and abused inhalants (Shen, 2006) have been reported. These findings suggest that lamotrigine may be of clinical benefit in the treatment of addiction to cocaine, alcohol or abused inhalants. Studies on the potential efficacy of lamotrigine in the treatment of behavioral addictions or addictions to opiates, nicotine, or psychostimulants such as methamphetamine are lacking.

2.6. Memantine

2.6.1. Mechanism of action

Memantine is a noncompetitive antagonist at the NMDA receptor (Fig. 1) and is used primarily for the treatment of cognitive decline in Alzheimer's disease. In addition to its antagonist actions at NMDA receptors, memantine also blocks the serotonin type 3 receptor ($5\text{-}HT_3$) as well as nicotinic acetylcholine receptors. Although some abuse substances such as phencyclidine, ketamine, dextromethorphan or alcohol have antagonist properties at the NMDA receptor, memantine is one of the few NMDA receptor antagonists that is generally well-tolerated by humans and does not appear to carry an abuse potential (Vosburg et al., 2005).

2.6.2. Clinical efficacy

In addition to being efficacious at reducing withdrawal symptoms in detoxifying alcoholics (Krupitsky et al., 2007b) and opiate addicts (Bisaga et al., 2001), memantine (typical doses in the 30–60 mg/day range) has been reported to be superior to placebo in attenuating on-going drinking and/or craving for alcohol in alcoholic subjects (Arias et al., 2007; Bisaga and Evans, 2004; Krupitsky et al., 2007a). This amelioration of craving for alcohol may be a result of the alcohol-like subjective effects of memantine (Bisaga and Evans, 2004; Krupitsky et al., 2007a). However, a larger placebo-controlled study indicated that memantine does not reduce on-going drinking behavior in alcohol-dependent patients (Evans et al., 2007). Memantine has been reported to decrease the subjective effects of cigarette smoking (Jackson et al., 2009) and intravenous heroin (Comer and Sullivan, 2007); however, particularly at higher doses, memantine can increase the subjective and cardiovascular effects of cocaine (Collins et al., 1998, 2007). Collectively, these data suggest that memantine may be

of potential use in the detoxification of alcohol- or opiate-dependent patients, and perhaps as a pharmacological adjunct for the treatment of alcoholism. However, its potential efficacy for treating addiction to other drugs of abuse remains unknown, and it appears that it may be contraindicated for treating cocaine addiction. Nonetheless, a recent open label pilot study showed that memantine decreased PG-YBOCS scores and time spent gambling in 29 pathological gamblers (Grant et al., 2010b), suggesting that memantine may be of potential use in the treatment of behavioral addictions such as pathological gambling.

2.7. Modafinil

2.7.1. Mechanism of action

Modafinil is a CNS stimulant originally designed to enhance wakefulness and vigilance in the treatment of narcolepsy and excessive daytime sleepiness caused by sleep apnea or shiftwork. Modafinil is sometimes prescribed as an off-label treatment for attention-deficit/hyperactivity disorder. Although its neuropharmacological mechanisms of action are not yet fully understood, modafinil does not appear to act as a monoamine releaser as is the case for amphetamine-like stimulants. Rather, modafinil may act by stimulating α-adrenoceptors, suppressing GABA release, weakly inhibiting the dopamine transporter, or stimulating hypothalamic orexin-containing neurons (Ballon and Feifel, 2006; Martinez-Raga et al., 2008). Other mechanisms of action that have been reported include reductions in circulating free radicals and cytotoxicity induced by sleep deprivation (Gerrard and Malcolm, 2007). While most studies suggest a dopaminergic basis for its stimulant effects (Andersen et al., 2010; Volkow et al., 2009; Wisor and Eriksson, 2005), modafinil has been shown to elevate extracellular levels of glutamate in numerous brain regions including the dorsal striatum, hippocampus and diencephalon (see Fig. 1) (Ferraro et al., 1997, 1998, 1999) without affecting glutamate synthesis (Perez de la Mora et al., 1999). Modafinil is considered to have low abuse potential (Martinez-Raga et al., 2008), although reports of abuse potential at high doses (Andersen et al., 2010) and non-medical use are increasing (Ballon and Feifel, 2006). As a result modafinil is currently classified as a Schedule IV controlled substance by the Drug Enforcement Administration. Clinically effective doses of modafinil are typically in the range of 200–400 mg/day.

2.7.2. Clinical efficacy

Numerous clinical reports have shown that modafinil demonstrates potential efficacy in the treatment of cocaine addiction (Martinez-Raga et al., 2008). In a small placebo-controlled drug-interaction study by Dackis and colleagues, it was reported that modafinil (200 mg/day) blunted the euphorigenic effects of intravenous cocaine in cocaine addicts (Dackis et al., 2003), and these findings were later independently replicated (Malcolm et al., 2006). A double-blind placebo-controlled study of treatment-seeking cocaine-dependent outpatients showed that modafinil (400 mg/day) significantly reduced daily cocaine use and prolonged abstinence (Dackis et al., 2005). A recent multi-center clinical trial found that modafinil decreased cocaine use and craving in cocaine-dependent subjects without co-morbid alcohol dependence (Anderson et al., 2009). Although these data demonstrate that modafinil might be of use in the treatment of cocaine addiction, it is possible that some of the beneficial effects might be due to decreases in peak plasma concentrations of cocaine in the presence of modafinil (Donovan et al., 2005). Modafinil has also produced nonsignificant trends toward decreases in active methamphetamine use among abusers of this drug (Shearer et al., 2009), and reductions in gambling behaviors in impulsive problematic gamblers (Zack and Poulos, 2009). Despite these positive results indicating a potential for modafinil in treating psychostimulant addicts and pathological gamblers, a recent study indicated that modafinil is ineffective in reducing cigarette smoking and actually produces more signs of withdrawal and negative affect than in placebo treated smokers (Schnoll et al., 2008). Thus, modafinil does not appear to be well suited for use in the treatment of smoking cessation.

From a neurochemical viewpoint, it is somewhat confusing as to why a drug like modafinil, which increases extracellular glutamate levels, results in reductions in cocaine intake, in light of numerous animal studies having shown that blockade of glutamatergic neurotransmission (i.e., by administration of ionotropic glutamate receptor antagonists, postsynaptic mGluR antagonists, or presynaptic mGluR2/3 agonists that suppress glutamate release) reduces cocaine reinforcement and/or reinstatement of cocaine-seeking behavior (Gass and Olive, 2008; Kalivas et al., 2009; Knackstedt and Kalivas, 2009; Olive, 2009; Tzschentke and Schmidt, 2003). One possible hypothesis for the mechanism of action of modafinil in reducing cocaine craving is by normalizing the reductions in extracellular glutamate that are observed in the nucleus accumbens during cocaine withdrawal, and attenuate the ability of cocaine or cocaine-related cues to evoke craving (similar to the hypothesized mechanism of action for NAC — Fig. 1). Further studies are needed to test this hypothesis.

2.8. Topiramate

2.8.1. Mechanism of action

Topiramate, like other anticonvulsants including gabapentin and lamotrigine, has multiple mechanisms of action, including inhibition of presynaptic voltage-gated Na^+ and Ca^{2+} channels (thereby inhibiting the release of neurotransmitters including glutamate) and activation of type A GABA ($GABA_A$) receptors (Dickenson and Ghandehari, 2007; Landmark, 2007; Rogawski and Loscher, 2004). In addition, it has recently been shown that topiramate is also an antagonist at α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors containing the GluR5 subunit (Fig. 1) (Gryder and Rogawski, 2003; Kaminski et al., 2004). These actions on AMPA receptor function are of particular interest since this glutamate receptor subtype has been highly indicated in the neuroadaptive changes produced by drugs of abuse as well as mediating drug self-administration and relapse-like behaviors (Bowers et al., 2010; Gass and Olive, 2008; Niehaus et al., 2009; Xi and Gardner, 2008). Typical effective doses of topiramate range from 75–350 mg/day.

2.8.2. Clinical efficacy

In addition to the attenuation of alcohol withdrawal symptoms similar to that observed with gabapentin and lamotrigine (Krupitsky et al., 2007b), topiramate may also aid in the amelioration of benzodiazepine withdrawal symptoms (Michopoulos et al., 2006). Numerous studies have been published in the last decade demonstrating efficacy of topiramate in attenuating alcohol's subjective effects, alcohol craving, and heavy consumption in alcoholic patients (Anderson and Oliver, 2003; Johnson et al., 2004; Kenna et al., 2009; Komanduri, 2003; Ma et al., 2006; Miranda et al., 2008; Rubio et al., 2004). The ability of topiramate to reduce compulsive drinking may be due to its ability to modulate impulsivity and improve behavioral inhibition (Rubio et al., 2009). One study even found indications that topiramate was superior to the "gold standard" anti-alcoholism medication naltrexone in prolonging abstinence and reducing ongoing drinking and relapse (Baltieri et al., 2008). Thus, topiramate appears to be a promising medication for use in the treatment of alcoholism.

With regards to other drugs of abuse, topiramate has been shown to reduce cocaine use and craving in cocaine-dependent individuals (Kampman et al., 2004; Reis et al., 2008), yet the small sample sizes of these two clinical studies are limiting (Minozzi et al., 2008). A case report indicated that topiramate reduces the use of methylenedioxymethamphetamine (MDMA, "Ecstasy") (Akhondzadeh and Hampa, 2005). In cigarette smokers, some small studies have shown beneficial effects of topiramate in promoting abstinence from smoking or

reducing overall smoking behavior (Arbaizar et al., 2008; Johnson et al., 2005; Khazaal et al., 2006). The ability of topiramate to prolong abstinence from smoking may be gender-specific, with great responses in males (Anthenelli et al., 2008). However, one study found that, similar to lamotrigine, topiramate increased the subjective effects of withdrawal from smoking as well as the rewarding effects of a smoked cigarette and did not affect cue-induced craving (Reid et al., 2007), questioning the potential use of topiramate as an aid in smoking cessation. Similarly, topiramate has been shown to enhance the subjective positive feelings produced by methamphetamine (Johnson et al., 2007). Thus, topiramate may hold promise for aiding in the treatment of addiction to alcohol and possibly cocaine and nicotine, but more studies are needed to examine its potential as a therapeutic for treating addiction to other drugs of abuse.

With regards to behavioral addictions, a handful of small studies and case reports have been published in recent years indicating that topiramate may also be of potential use in the treatment of these disorders. Thus far, positive effects of topiramate have been observed in reducing relapse to problematic gambling (Dannon et al., 2007) and reducing compulsive eating and sexual behavior (Fong et al., 2005; Khazaal and Zullino, 2006; Tata and Kockler, 2006). Clearly this avenue for treatment of non-drug addictions needs to be explored further.

3. Summary and conclusions

With regards to the eight medications reviewed here that possess a glutamatergic mechanism of action (acamprosate, NAC, DCS, gabapentin, lamotrigine, memantine, modafinil, and topiramate), we conclude that NAC, modafinil, and topiramate have the most well-documented and greatest potential for use in the treatment of drug and behavioral addictions. Certainly any of the medications reviewed here will not be a panacea for all addictions, but more likely an effective pharmacological aid to standard individual psychotherapy or cognitive-behavioral therapy approaches for treating addiction to certain drugs of abuse (particularly cocaine and alcohol) as well as non-drug addictions (particularly pathological gambling). Combined with standard retrospective or outcome measure-based attempts at identifying subtypes of individual addicts that may respond more favorably to one medication or another, with the fewest adverse side effects, the post-genomic era of today will hopefully allow researchers and clinicians to utilize pharmacogenetic approaches to identifying potential responders and non-responders to each of these medications prior to initiating treatment. The limited amount of data available for some of these compounds, such as DCS and lamotrigine, warrants larger scale multi-center studies. In addition, increased investigation with appropriate animal models into the precise glutamatergic mechanisms that mediate different aspects of the addiction cycle (i.e., compulsive drug use, withdrawal, craving, drug-seeking behavior, and relapse) will hopefully lead to more effective pharmacological approaches that can be used to intervene at specific stages of addiction.

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