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Therapeutic potential of NMDA receptor antagonists in the treatment of alcohol and substance use disorders

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Despite the fact that the use of alcohol, nicotine and other drugs is the major external factor contributing to mortality in industrialised countries, there are few medications available to treat alcohol and substance use disorders. In recent years, major advances have been made in the understanding of the neurobiological basis for these disorders and these advances should lead to the development of new pharmacotherapeutics. A substantial amount of the research suggests that N-methyl-D-aspartate (NMDA) receptor neurotransmission contributes to mediating the behavioural effects of alcohol and other drugs of abuse. This research supports the therapeutic potential of NMDA receptor antagonists in alcohol and substance use disorders. In this paper the authors present their opinion on the goals and stages of pharmacological treatment of these complex psychiatric disorders. Available preclinical research using designs that model aspects of alcohol and substance use disorders is summarised, with an emphasis on research published in the last two years. In animal models, NMDA antagonists inhibit physical dependence and the reinforcing effects of a variety of abused substances. The ability of NMDA antagonists to inhibit tolerance to drug effects and contribute possible antidepressant and anxiolytic effects are also important from the perspective of drug development. This review summarises the relevant clinical laboratory and treatment data. Finally, it presents the status of the current development of NMDA receptor antagonists and discusses candidates with the greatest potential for clinical development.

Keywords: alcohol, cocaine, glutamate, nicotine, NMDA receptor antagonists, opiates


1. Introduction

Alcohol and other drug (AOD) dependence are chronic and relapsing disorders that are an enormously destructive public health problem. In the United States, mortality that can be attributed to these disorders is greater than mortality attributable to all other factors combined [1]. There are currently a limited number of available medications to treat alcohol, opioid and nicotine dependence and no medication to treat cocaine, stimulants, or cannabis dependence. Success rate of available treatments is relatively low; only 30 - 50% of patients completely abstains for one year after completion...
of the most successful treatment programs. Despite recent advances in the understanding of the neurobiological basis for these disorders and the development of new psychotherapeutic approaches, there is a lack of viable pharmacological treatments. At the same time societal and political pressures for the development of effective and inexpensive treatments continue.

Substances that are abused by humans, including opiates, psychostimulants, marijuana, alcohol and sedatives, differ in chemical structures and acute pharmacological effects. However, the pathological, compulsive pattern of their intake share many common features. This suggests that a limited number of neural pathways may mediate the ‘addictive’ qualities of AOD. If there is a common neural substrate that is central to the development and the maintenance of AOD dependence, it might be a target for pharmacological treatments. We have previously suggested [2] that NMDA receptors constitute the common target component of this pathway. Preclinical research suggests that antagonists of this receptor modulate pathophysiological processes common to the development, maintenance and expression of AOD dependence and have a potential to be developed as pharmacotherapeutics. Preliminary results from clinical trials encourage further clinical development.

In this review we will summarise most recent evidence supporting the potential therapeutic effects of clinically promising and available NMDA receptor antagonists. A more complete review of preclinical research can be found elsewhere [2 and references therein]. Other recent review articles summarise the role of glutamate in physiological states and clinical applications of glutamate antagonists [3,4].

2. Goals for treatment and currently used medications

The primary goal of the pharmacological treatment of AOD dependence is to help patients decrease or eliminate the use of drugs and alcohol and prevent them from relapsing. This goal is usually accomplished in stages that involve normalisation of behavioural and psychological disturbances that emerge and persist in early (days) and late (weeks to months) abstinence and increase the likelihood of relapse. Where available, medications are used to facilitate transition to early abstinence and psychosocial interventions are a mainstay of treatment in the later stages. Unfortunately, rates of treatment completion and long-term abstinence remain low, hence the need for advancement in treatment methods. In particular, the development of medications that will assist in maintaining long-term abstinence can substantially improve effectiveness of treatment.

In the majority of cases, people who have chronically used AOD will develop physical dependence, a neuroadaptive change resulting from chronic drug exposure. As a result, they will experience symptoms of withdrawal (abstinence syndrome, AS) when they abruptly stop or decrease the amount of the used substance. Cessation of use of the abused substance and, associated with it, elimination of physiological dependence, is frequently a necessary initial step in the treatment of AOD dependence. This stage of treatment is commonly identified as detoxification. The longer the duration of the detoxification the more manageable the symptoms of withdrawal become. Medications are frequently necessary in the detoxification from alcohol and sedatives (barbiturates, benzodiazepines) since it can be complicated by life-threatening consequences such as seizures and autonomic instability. Successful alleviation of the AS associated with opioid, nicotine and cannabis dependence greatly increases the likelihood of the transition to abstinence.

Two major classes of medications are currently used during the detoxification phase of treatment. Pharmacologically equivalent agonists are given to replace the abused substance and to decrease the likelihood of substantial AS. Detoxification takes place slowly as the agonist dose is decreased and the intensity of the AS is reduced. This method is used in the detoxification from opioids (using methadone), alcohol and other sedative-hypnotics (using long-acting benzodiazepines or barbiturates) and tobacco (using nicotine replacement therapies). Alternatively, medications are used to suppress the intensity of a spontaneous or precipitated withdrawal by targeting individual components of the AS. Clonidine, an $\alpha_2$-adrenergic agonist, is used to suppress autonomic arousal during opioid, alcohol and tobacco withdrawal. Benzodiazepines are used to reduce withdrawal dysphoria (opioid and nicotine withdrawal). Analgesics, antidiarrheals and anti-emetics are also used as ancillary medications.
Treatment that is limited to detoxification is rarely sufficient in the treatment of AOD dependence. The first month of abstinence is associated with a very high relapse rate. Some of the reasons for relapse may include symptoms of persisting dysphoria and anhedonia. Others include high reactivity to environmental cues associated with AOD use and stress. Medications can be used to alleviate these psychological disturbances. Antidepressants, anxiolytics, or antipsychotics can be used to treat pre-existing or emerging psychiatric disturbances. Medication can also be used to inhibit the reinforcing effects of AOD, in case of a return to their use. This will prevent the escalation of use and full relapse. Such medications work by a several known mechanisms. First, pharmacological antagonists block the pharmacological effect of a given substance, thereby preventing its behavioural effects. This is the basis for the use of naltrexone in the treatment of opioid dependence. Second, pharmacological agonists produce high levels of cross-tolerance, thereby preventing symptoms of withdrawal and reducing subjective effects if a given substance is taken. The most effective available medications for AOD, methadone in the treatment of opioid dependence or nicotine replacement therapies in the treatment of nicotine dependence, work by this mechanism. Third, aversive agents have the potential to induce an unpleasant response if combined with a given substance, thereby counteracting any positive effects from it. This is how disulfiram is used in the treatment of alcohol dependence. In all those circumstances, the reinforcing effects of AOD are decreased and drug-taking behaviour is gradually extinguished.

There are several effective medications that exert their effect by yet unknown mechanisms. Bupropion, a noradrenaline/dopamine re-uptake inhibitor and a nicotinic receptor antagonist, has been found to facilitate smoking cessation. It has been suggested that bupropion may work by reducing the dysphoria which frequently emerges in early abstinence. Acamprosate, a synthetic analogue of amino acid neurotransmitters, modulates NMDA receptor activity and has been found to be effective in extending abstinence in detoxified, alcohol-dependent patients. Acamprosate reduces drinking frequency and may exert its anti-alcohol effect by reducing the reinforcing effects of alcohol. Naltrexone, an opioid antagonist, has been found to reduce drinking frequency and extend abstinence in detoxified alcoholic patients. Naltrexone appears to modulate the subjective effects of alcohol, thereby decreasing its reinforcing effects.

### 3. Ideal ‘anti-addictive’ medication

An ‘ideal medication’ should alleviate the AS associated with chronic alcohol, opiate, nicotine and cannabis use and facilitate transition to abstinence. In detoxified patients it will decrease craving, dysphoria, anxiety and anhedonia associated with early abstinence. It will attenuate sensitised reactivity to environmental cues and stress and diminish craving associated with them. In abstinent patients who start using again, an ‘ideal medication’ will decrease the reinforcing effects of AOD’s and therefore will prevent progression to the full relapse following episodic lapses. If such an ‘ideal medication’ is used in patients who are actively using, it will decrease the reinforcing effects of AOD’s and therefore will decrease the amount of drugs used and the adverse health consequences associated with them. An ‘ideal medication’ should be safe in combination with AOD’s, have a low abuse potential and possibly have mild subjective effects that will foster compliance with it. It is unknown if a single class of agents can be identified to ‘fulfil’ the role of a single medication or whether several therapeutics will be used to treat various components of AOD dependence. Substances that are antagonists at the NMDA receptor site have several of the properties that would make them candidates for development as ‘anti-addictive’ medications. These include effects on physical dependence and modulation of the reinforcing effects of AOD’s. Below, we summarise available data (citing most recent publications) from preclinical models of drug dependence as well as early human data that attempt to verify animal data in clinical settings.

#### 3.1 NMDA receptor antagonists inhibit physical dependence

##### 3.1.1 Studies of drug dependence in animal models

Chronic exposure to several abused drugs (nicotine, alcohol, opioids, sedatives and cannabis) results in development of physical dependence that becomes evident upon cessation of drug administration with the emergence of a withdrawal syndrome. Various neurotransmitter systems have been explored in search for a mechanism of dependence and withdrawal syndrome. Glutamate receptors are
distributed throughout the body and play an important role in neural plasticity. Thus, they are in the unique position to be involved in the development and expression of most, if not all, neuroanatomically scattered signs of physical dependence on various abused drugs. For instance, adaptations in the NMDA receptor complex have been observed in different brain areas during chronic exposure to and upon withdrawal from opioids [5], ethanol [6], diazepam [7] and barbiturates [8].

Experimental studies on the effects of NMDA receptor antagonists on drug dependence typically employ one of the three main designs. The first type of procedure assesses the development of dependence when NMDA receptor antagonists are co-administered with the drug used to establish dependence (e.g., morphine). A second study design focuses on the maintenance of dependence and is somewhat similar to the development studies: NMDA receptor antagonists are co-administered with the abused drug in animals with pre-established dependence. A third research protocol is perhaps the most relevant to the clinical situation, as it assesses the effects of NMDA receptor antagonists on expression of drug dependence, i.e., intensity of the withdrawal signs in animals pretreated with NMDA receptor antagonists just before the expected emergence of withdrawal.

3.2 NMDA receptor antagonists retard development of dependence

Overall, a limited range of compounds with NMDA receptor antagonistic activity have been tested using this study protocol. In the majority of reported studies, the prototypic NMDA receptor antagonist, MK801 (dizocilpine), which acts as a high-affinity antagonist of NMDA-gated ion channel, significantly retarded development of opioid dependence in animals that were treated with a combination of this NMDA receptor antagonist and morphine. The degree of dependence that developed was estimated by administration of the opioid receptor antagonist naloxone. This precipitates various withdrawal signs in morphine-dependent animals (somatic and behavioural signs, hyperalgesia and noradrenaline release in hippocampus) [9]. It should also be noted that the inhibitory effects of NMDA receptor antagonists are expressed upon both systemic and central (intracerebroventricular) administration [10]. Development of other types of dependence such as benzodiazepine dependence is also retarded by co-administration of NMDA receptor antagonists [11].

3.3 NMDA receptor antagonists reverse established dependence

Two studies document the ability of NMDA receptor antagonists to reverse pre-existing opioid dependence. Both of these studies showed significant reduction of morphine dependence by the uncompetitive antagonists, memantine and MRZ 2/579, the competitive antagonist NPC 17742, as well as the glycine site antagonists, MRZ 2/570 and L-701,324 [12,13].

3.4 NMDA receptor antagonists attenuate expression of dependence

3.4.1 Opioid dependence

Opioid dependence is the most extensively studied aspect of drug dependence with NMDA receptor antagonists. Expression of both opioid antagonist precipitated and spontaneous (natural) withdrawal is inhibited by NMDA receptor antagonists. Significant reductions in the intensity of morphine withdrawal have been reported after acute pretreatment with high- and low-affinity uncompetitive antagonists, competitive antagonists, glycine and polyamine site antagonists, as well as NMDAR1 subunit antisense oligonucleotide [14–17]. The list of tested compounds includes a number of clinically available drugs such as memantine, dextromethorphan and ketamine [16,18,19]. These studies have assessed various classical somatic and autonomic signs of withdrawal, as well as biochemical markers including increase of acetylcholine and noradrenaline release in the hippocampus and locus coeruleus, decrease in dopamine release in the ventral striatum, facilitation of c-fos expression in the amygdala, mesolimbic system and frontal cortex, ileum contractions, cardiovascular pressor responses and electrophysiological correlates of opioid withdrawal (increase in the firing rate of neurones in the locus coeruleus, medulla and spinal cord) [15,20]. There is also evidence that progressive intensification of the withdrawal signs (e.g., hyperalgesia) associated with repeated opioid abstinence is mediated via NMDA receptor activation [21]. Ability of NMDA receptor antagonists to block the expression of opioid withdrawal is consistent with the frequently reported increase in glutamate release in opioid-withdrawn animals [22] and facilitation of the withdrawal signs by glutamate receptor agonist...
administration [23]. In summary, effects of NMDA receptor antagonists may be interpreted as the result of interference with the trigger mechanisms of the withdrawal responses. In support of this contention, suppressive effects of a single administration of NMDA receptor antagonists may extend beyond the limits set by their half-life profiles [14].

3.4.2 Ethanol dependence

Similar to what is usually found in opioid-dependent animals, withdrawal from chronic ethanol results in significant facilitation of glutamate release that is likely to be associated with hypersensitivity or increased number of NMDA receptors [25]. All site-selective NMDA receptor antagonists tested to date (high- and low-affinity uncompetitive antagonists, competitive, glycine site and polyamine site antagonists) have shown a significant capacity for blocking the expression of various signs of the ethanol withdrawal syndrome, ranging from seizures, motor hyperactivity and learning deficits to decreases in spontaneous neurone firing and extracellular mesolimbic dopamine concentration [25, 26]. Epileptiform activity and seizures triggered by cessation of ethanol administration are reduced by acute application of NMDA receptor antagonists both in vitro [27] and in vivo upon systemic and local intracerebral administration [28]. These effects may at least in part be due to the ability of ethanol to inhibit the NMDA receptor complex in a non-competitive manner. Thus, NMDA receptor antagonists may be 'substituting' for ethanol and, thereby, reducing the withdrawal intensity.

3.4.3 Sedative-hypnotics dependence

Similar to ethanol withdrawal, expression of barbiturate [29] and benzodiazepine dependence [30] is significantly prevented by acute injections of NMDA receptor antagonists (uncompetitive antagonists, competitive, glycine and polyamine site antagonists). Repetitive withdrawal from benzodiazepines is subject to progressive sensitisation that is prevented by NMDA receptor antagonists [31].

3.5 NMDA receptor antagonists attenuate interoceptive and other components of drug withdrawal

The most adequate laboratory animal procedures that assess the interoceptive effects of the states produced by drugs or drug withdrawal are based on drug discrimination methodology. In morphine-dependent rats trained to discriminate between injections of naloxone (i.e., state of withdrawal) and its vehicle, NMDA receptor antagonists (uncompetitive antagonists and competitive antagonists) significantly antagonise the naloxone cue as well as the discriminative stimuli produced by the spontaneous withdrawal state (tested 24 h after the last morphine injection) [16]. These findings are corroborated by results of other studies that focused more specifically on aversive motivational aspects of the withdrawal. Uncompetitive antagonists such as memantine have been shown to prevent establishment of place aversions conditioned to the morphine withdrawal state [19].

Opioid withdrawal dramatically affects a number of behavioural responses in laboratory animals. These behavioural alterations persist even when the somatic and autonomic signs fade. For example, facilitation of aggressive behaviour is observed following the cessation of repeated morphine injections and is maximally expressed at 48 h post-morphine. Acute administration of NMDA receptor antagonists (memantine and MRZ 2/579) significantly attenuated this withdrawal-facilitated aggression at dose levels that do not impair spontaneous motor activity or aggressive behaviour in non-dependent subjects [32]. Finally, there is some preliminary evidence that morphine-dependent animals self-administer NMDA receptor antagonists, a result that may be interpreted as a 'self-medication' of the withdrawal state. In these experiments, morphine withdrawal was found to facilitate the acquisition of iv. self-administration of dizocilpine by rats that had no history of any drug self-administration [33].

There is very little information available regarding withdrawal from drugs other than opioids. One of the available examples suggests that competitive NMDA receptor antagonists may have a capacity to decrease anxiety-like behaviours triggered by ethanol withdrawal [34].

4. Drug dependence: human data

4.1 The effects of NMDA antagonists on naloxone-precipitated opioid withdrawal

Several clinically available medications have been studied using naloxone-precipitated opioid withdrawal in volunteers who are maintained on a steady dose of opioid. Rosen et al., [35], studied the effects of dextromethorphan using a counterbalanced
design. They found a considerable inter-individual and session-to-session variability in response to dextromethorphan but no overall medication effect was found. This study however might have had limited statistical power to detect the medication effect. Another uncompetitive antagonist, memantine, has been studied using a multiple baseline design [36]. In this model, a single dose of memantine attenuated the expression of naloxone-precipitated withdrawal for up to three days. Another medication that modulates glutamatergic neurotransmission at the NMDA receptor site, D-cycloserine, a partial agonist at the glycine-binding site did not affect the severity of withdrawal symptomatology [37].

4.2 Preliminary treatment trials

Koyuncuoglu and co-workers conducted three separate clinical trials using dextromethorphan (DXM) for detoxification from opioids. The first of these studies was an in-patient double-blind, randomised trial comparing DXM (360 mg/day) with an active control chlorpromazine (96 mg/day) [38]. In addition, all patients received diazepam (40 mg/day). Reports of craving for heroin as well as observer-rated abstinence scores were significantly lower in the group that received DXM. There was also a favourable medication effect on completion of treatment. Out of 48 patients enrolled in the study, 15 from the chlorpromazine group and one from DXM group left the study in the first 24 h. While no one from the CPZ group completed the study, 17 patients from the DXM group completed the 8-day trial. Two other studies were open label trials that evaluated the usefulness of DXM in combination with chlorpromazine [39] or DXM in combination with tizanidine, a glutamate release inhibitor, CPZ and diazepam [40] for out-patient detoxification from heroin. In these studies 68 and 96% of patients, respectively completed an 8-day detoxification. The remaining patients relapsed to heroin use in the first three days of detoxification, when abstinence symptoms were most severe. The interpretation of results from these studies are confounded by the use of multiple adjunct medications, several of which are known to alleviate the severity of the abstinence syndrome and the use of CPZ, medication known to have many undesirable side effects, as an active control. Nevertheless, the results of the controlled study are however encouraging. The effectiveness of DXM was further supported by another open-label study [41]. Six heroin-dependent patients were recruited and treated with DXM 375 mg/day for 6 days. No other medications were used except ibuprofen, acetaminophen and hydroxyzine as needed. Two patients requested a change to methadone during the first day of treatment and neither of them completed detoxification. The remaining patients completed the study after having rapid and complete attenuation of withdrawal by the fourth day of treatment. Patients tolerated DXM well and side effects were minimal. In another in-patient open label pilot study [42] memantine, 30 - 60 mg p.o. daily for two to three days, was given to five patients who were opioid-dependent, as confirmed by a naloxone challenge. No other standing medications were offered, except rescue doses of OTC preparations, clonidine, clonazepam, zolpidem and prochlorperazine. Multiple measures of abstinence were used to evaluate the severity of withdrawal signs and symptoms. All patients completed detoxification, confirmed by a negative naloxone challenge. The length of detoxification was four to five days. Most patients experienced mild/moderate symptoms of opioid withdrawal for a duration of one to two days and requested treatment with additional medications. Patients tolerated memantine well, with minimal side effects.

5. NMDA receptor antagonists inhibit rewarding effects of drugs of abuse

5.1 Reinforcing effects of abused drugs: Animal data

There is a growing body of evidence that NMDA receptor antagonists may interfere with the unconditioned and conditioned behaviours induced by abused drugs. These studies focus mainly on those properties of abused drugs that contribute to the development, maintenance, extinction and reinstatement of drug-taking behaviours. One of the major reasons for evaluating NMDA receptor antagonists as potential anti-addictive medications is that glutamate receptors (including NMDA-subtypes) are vastly represented in brain reward areas where they may act to mediate the reinforcement-related signals and/or modify the effects of other neurotransmitter systems presumably involved in drug-taking behaviours (e.g., dopamine). A number of learned behaviours and responses need to be established to initiate and maintain drug-taking behaviours. Knowing the role of NMDA receptors in neural plasticity of learning and memory processes, it is logical to expect that NMDA receptors...
receptor antagonists may affect drug-related learned behaviours.

5.2 Primary reinforcing properties

Most drugs abused by humans are readily self-administered by laboratory animals. In laboratory conditions, drug self-administration behaviour can be useful in assessing the ‘anti-addictive’ properties of experimental medications. Similar to the physical dependence studies, NMDA receptor antagonists have been tested during both acquisition and maintenance of self-administration behaviour. Acquisition experiments revealed the ability of NMDA receptor antagonists (uncompetitive antagonists, competitive and glycine site antagonists) to impair the establishment of iv. morphine self-administration in both mice and rats [43,44]. These effects are evidenced as a substantial downward shift of the morphine dose-response curve. Acquisition of iv. cocaine self-administration was also found to be inhibited by pretreatment with NMDA receptor antagonists, mainly dizocilpine [45]. However, these results are difficult to interpret since similar disrupting effects would have been observed if cocaine itself was administered non-contingently prior to the self-administration sessions. Similarly, controversial results were obtained in maintenance studies where dizocilpine was used. Dizocilpine is known to exert effects that are often synergistic with those of cocaine [46]. In line with this evidence, dizocilpine was found to increase the break points for self-administration maintained under a progressive ratio schedule of cocaine delivery [47,48], thus increasing the reinforcing effects of cocaine. These data strongly argue for the use of other NMDA receptor antagonists that would be devoid of these effects. Accordingly, low-affinity uncompetitive antagonists, dextromethorphan [49] and memantine [47] are capable of inhibiting iv. cocaine self-administration.

Oral self-administration of ethanol was reduced in animals pretreated with various NMDA receptor antagonists such as low-affinity uncompetitive antagonists [50,51 however see 52]. Suppression of ethanol intake by NMDA receptor antagonists (low-affinity uncompetitive antagonists) was also demonstrated using the ‘alcohol deprivation effect’ paradigm, [51] another model for self-administration behaviour.

Response-reinforcement learning is thought to be critically dependent on NMDA receptor activation in the mesolimbic system [53]. Accordingly, oral self-administration of ethanol was found to be inhibited following the local administration of an NMDA receptor antagonist into the ventral striatum [54]. Similar data were obtained for iv. self-administration of cocaine but not heroin [55].

5.3 Discriminative stimulus effects

The most straightforward explanation for the ‘anti-addictive’ properties of NMDA receptor antagonists would be that these compounds interfere with the interoceptive stimulus effects of abused drugs. However, apart from the ability to produce intermediate levels of responding, NMDA receptor antagonists do not fully substitute or significantly reduce morphine- or cocaine-appropriate responding in drug discrimination studies [19,56,57]. For ethanol discrimination, appreciable levels of substitution for the ethanol cue were repeatedly demonstrated with NMDA receptor antagonists [51,58] suggesting that this mechanism is at least in part responsible for the reduction in ethanol-related behaviours observed in animals treated with NMDA receptor antagonists.

5.4 Secondary reinforcing effects

Place conditioning is the procedure most commonly used to assess the ability of NMDA receptor antagonists to modulate drug-conditioned behaviours. Both development and expression of place preferences conditioned with morphine [19,59,60], cocaine [61], amphetamine [62,63] and ethanol [64] were reported to be prevented by NMDA receptor antagonists (uncompetitive antagonists, competitive, glycine and polyamine site antagonists). These findings are supported by the still limited evidence generated using other types of drug conditioning paradigms such as conditioned facilitation of intracranial self-stimulation [65] and conditioned reinstatement of iv. cocaine self-administration [66]. Interestingly, NMDA receptor blockade may effectively counteract the ability of abused drugs (amphetamine) to potentiate the response for conditioned reward [67].

Similar to what was described above, conditioning studies have also indicated essential differences among various NMDA receptor antagonists. For instance, NMDA receptor antagonists were shown to inhibit development and/or expression of drug-conditioned motor activity [68]. However, at least for high-affinity uncompetitive antagonists, their own psychostimulant properties may obscure the effects on drug-conditioned responses.
6. Reinforcing potential of abused drugs: human data

The only published study that evaluated effects of NMDA receptor antagonists on drug self-administration by humans assessed the effects of memantine on smoked cocaine self-administration [69]. Eight cocaine smokers were treated with memantine (20 mg/day) or placebo in a double-blind, crossover design for 8 - 10 days before testing. Memantine did not change the number of times participants chose various doses of cocaine over the monetary alternative reinforcers. However, memantine significantly increased reports of subjective effects following cocaine including ratings of 'high,' 'potency,' and 'quality.' There was a trend towards increased ratings of 'I want cocaine' during memantine maintenance. This finding is in contrast to an animal study showing attenuating effects of memantine on cocaine self-administration [47], but is consistent with findings demonstrating that NMDA antagonists may potentiate the acute effects of cocaine [48]. There are several problems with interpretation of the findings from human laboratory models and the lack of consistency with the preclinical results. First, that the dose of NMDA antagonists used in humans is lower than respective dose used in preclinical research. Second, cocaine-taking behaviour in non-treatment seeking humans under laboratory conditions is very difficult to disrupt pharmacologically, although cocaine use in clinical settings is also difficult to stop. Third, the relevance of laboratory animal or human data to the treatment setting is difficult to ascertain because we do not yet have any effective medications for cocaine dependence.

Another agent that has been found to be effective in the treatment of alcohol dependence is acamprosate. It is sometimes claimed that therapeutic effects of acamprosate are related to action at NMDA receptors, but clear-cut proof is still missing and several other mechanisms are plausible [70].

6.1 NMDA receptor antagonists inhibit the tolerance to drug effects

The development of drug tolerance is manifested as a shift to the right of the dose-response curve or as a decrease in the intensity of the response when a constant dose is repetitively administered. Tolerance, particularly to the analgesic effects of opiates, is no longer considered central to compulsive drug seeking and taking behaviour, but tolerance to a range of effects often accompanies dependence produced by the repeated administration of AOD. For example, tolerance to the rewarding effects of opiates has been observed in rats and humans. Corresponding neuroadaptive changes that contribute to the drug tolerance may also underlie adaptations that develop with the repeated administration of AOD like reinforcement and physical dependence. Interestingly, under some conditions we observe the development of sensitisation, that is the progressive increase of the intensity of the rewarding effects of opiates with their repeated administration.

6.2 NMDA receptor antagonists inhibit the development of morphine tolerance

As early as 1991, Trujillo and Akil [71] demonstrated the inhibitory effects of dizocilpine on the development of tolerance to the antinociceptive effects of morphine. Numerous subsequent studies revealed that co-administration of either competitive, non-competitive, or glycine site NMDA receptor antagonists, attenuate the development of tolerance to the analgesic effects of morphine in rodents [for review see 72]. Recent data demonstrate similar effects of clinically available compounds like memantine and dextromethorphan [73,74].

6.3 NMDA receptor antagonists inhibit the maintenance of morphine tolerance

In addition to studies documenting the inhibitory effects of NMDA antagonists on the development of analgesic tolerance to morphine, recent studies have demonstrated that in morphine-tolerant rats treated with an NMDA receptor antagonist, the antinociceptive response 'reverses' to a level comparable with that in animals that never received morphine. After six days of treatment with memantine, dextromethorphan or MRZ 2/579, morphine tolerant mice regained sensitivity to the initially effective dose of morphine [74]. While memantine and MRZ 2/579 co-administered with morphine appeared to reverse morphine-tolerance, dextromethorphan appeared to be ineffective in this setting [74]. If comparable reversal of established neuroadaptive changes following treatment with NMDA receptor antagonists could be established with those effects of opioids that contribute to the maintenance of drug seeking and taking behaviours (e.g., rewarding, euphoriant, dependence-inducing effects) these medications may have potential therapeutic implications.
7. Other favoured effects of NMDA receptor antagonists

7.1 Animal data

One of the most interesting developments in recent years points to the role of NMDA neurotransmission in mediating antidepressant effects. Chronic, but not acute administration of seventeen different clinically used antidepressants to mice produced adaptive changes in radioligand binding to NMDA receptors [see 75 for review]. Based on the consistency of these effects across antidepressant treatments, it has been proposed that adaptive changes in NMDA receptors may be the final common pathway for antidepressant action. These findings suggest that medications that modulate NMDA receptor neurotransmission may have antidepressant effects. Indeed, NMDA receptor antagonists mimic the effects of clinically effective antidepressants in preclinical tests predictive of antidepressant action and procedures designed to model aspects of depressive symptomatology [76]. In addition, administration of NMDA receptor antagonists to rodents may also produce anxiolytic effects [77]. This preclinical data suggests that NMDA antagonists may be effective in relieving depressive and anxiety symptoms that are frequently associated with AOD dependence and early abstinence. Considering that there might be a shared neurobiology of depression and drug dependence and that NMDA antagonists have the potential to be developed for both conditions, it is even more compelling to pursue the clinical development of these agents for AOD dependence.

7.2 Human data

The antidepressant effects of NMDA antagonists in humans were studied using ketamine, a potent NMDA uncompetitive antagonist that was given to seven patients with major depressive disorder [78]. Infusion of ketamine resulted in improvement in depressive symptoms during the three days of follow-up and returned to the pre-challenge level in 1 to 2 weeks after infusion. The acute effects of ketamine, including an increase in subjective reports of ‘high’ returned to baseline in less than 2 h after infusion, suggesting that the ‘antidepressant’ effect may be qualitatively different from the acute, psychotomimetic effect of high-affinity uncompetitive antagonists. Similar dissociation of acute subjective effects and long-lasting effects of NMDA antagonists has been noted in the laboratory study of memantine’s effects on opioid withdrawal [36].

8. Potential undesired side effects of NMDA receptor antagonists

There are several effects of NMDA receptor antagonists in humans that may be expected to affect clinical development of these agents. These include psychotomimetic effects, cognitive disturbances, memory impairment, neurotoxicity and abuse liability. These effects have most often been described for phencyclidine (PCP)-like uncompetitive antagonists and it is possible that novel NMDA receptor antagonists (low-affinity uncompetitive antagonists, glycine and polyamine site antagonists) may be much less prone to produce these effects [see 3 for neurotoxicity data].

PCP-like compounds are readily self-administered by laboratory animals, facilitate electrical brain stimulation and establish conditioned place preferences. In contrast, several other NMDA receptor antagonists have been shown to be ineffective in lowering thresholds of electrical brain stimulation [79,80] or in conditioned place preference experiments [19,60,64]. Some controversy however, has been generated by animal self-administration studies where clinically used, low-affinity uncompetitive antagonists (memantine, dextromethorphan) were found to substitute for PCP [81,82].

Impairment of learning and memory, reported in animals, is another potential side effect that may be associated with NMDA receptor blockade. Although these effects are not surprising in view of the suggested role of NMDA receptors in synaptic plasticity, it is not clear whether these animal data would have clinical significance. First, no learning deficits were reported for therapeutically relevant doses of NMDA receptor antagonists such as glycine site antagonists [82] or low-affinity uncompetitive antagonists [19,84]. Second, memory-impairing properties of NMDA receptor antagonists significantly depend on the behavioural history of the subjects and the experimental procedure used and may not be observed in animals already trained in the task in a different apparatus [85]. Third, under some conditions agents with NMDA antagonist properties may facilitate memory retrieval [86].
In humans, ketamine and several other NMDA antagonists produce cognitive disturbances [87]. However, there is little data on the acute cognitive effects of other NMDA antagonists, including low-affinity uncompetitive antagonists, glycine and other non-competitive antagonists. In studies that administered clinically relevant doses of memantine, no overt impairment in cognitive functioning was found [36,69]. In one study though, memantine impaired the acquisition of conditioned responses in humans [88]. The effect of long-term administration of memantine and other novel NMDA receptor antagonists on memory and cognitive functioning is not known, but it has to be noted that memantine appears to reduce memory loss in patients with degenerative cognitive disorders [89].

9. Clinical development of NMDA receptors antagonists

There are many glutamate receptor antagonists in development. However, only few have reached the late stages of development (see Table 1 for details). Several trends can be observed in the clinical development of these agents.

- Competitive NMDA receptor antagonists produce serious side effects in clinical trials for neuroprotection and are unlikely to be developed for AOD dependence

- Glycine site antagonists have none or minor side effects and may be promising for AOD dependence. These compounds however, have failed so far to show satisfactory efficacy, as tested in the treatment of stroke

- The development of uncompetitive antagonists, with different properties from PCP (e.g., lower affinity, more voltage dependency) seems to be most advanced. In fact, several of these agents are registered and/or in a late phase of development. Also, several agents which have been on the market for a long time have recently been found to block NMDA receptors [see 3]. There are preliminary clinical data that suggest the utility of this group of compounds in the treatment of AOD dependence

- Another promising trend is the development of antagonists that would be selective for NMDA receptor subtypes such as antagonists of NR1/NR2B subtypes of NMDA receptors.

Unfortunately, many of them have worrisome side effects, including prolongation of the QT interval due to blockade of potassium channels.

Unfortunately, only two of the clinically available agents, low-affinity uncompetitive antagonists, are being developed for the treatment of AOD dependence. MRZ 2/579, is being developed for alcohol dependence and dextromethorphan is being tested for opioid dependence in combination with methadone.

10. Expert opinion

Abuse of alcohol and other drugs is the major public health problem facing the world today. There is a great need to advance pharmacological treatment options in addition to continuing development of psychosocial treatments. In particular, there is a lack of medications that may prevent relapse to active use in abstinent patients. The success of agonist therapies in the treatment of opioid dependence is remarkable. On the other hand, the utility of naltrexone in the treatment of alcoholism in the USA has been limited, mainly due to the underdiagnosing of the problem and pessimism over the value of pharmacological treatments for alcoholism [90]. Therefore, in tandem with the development of novel pharmacological treatment, an effort has to be made towards the education of physicians, patients and their families regarding the availability and effectiveness of pharmacotherapy. Such effort in promoting diagnosis and treatment of depression or anxiety disorders has resulted in a tremendous increase in the use of antidepressants and the development of several novel medications.

Over the last decade there has been an explosive growth of preclinical research suggesting the role of glutamatergic, in particular NMDA receptor neurotransmission, in mediating the behavioural effects of alcohol and other drugs of abuse. At the present time there are no systematic studies across all models and all classes of substances that produce dependence to sufficiently verify the hypothesis that NMDA receptor antagonists may be effective pharmacotherapies across all classes of abused substances. However, there are numerous studies, as presented in this review, that would support such a notion. Similar hypotheses, linking all of the abused substances to a common neural circuit and dopaminergic neurotransmitter system, have been posed previously [e.g., 91].
<table>
<thead>
<tr>
<th>Agent</th>
<th>Mode of action</th>
<th>Company</th>
<th>Indication</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADD-234037 (Harkoseride)</td>
<td>GlyB A</td>
<td>Res. Corp. Techn.</td>
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<tr>
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<td>Hoechst Marion Roussel</td>
<td>Neuroprotection</td>
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<td>P</td>
</tr>
<tr>
<td>ACPC</td>
<td>GlyB PA</td>
<td>Symphony</td>
<td>Stroke</td>
<td>I</td>
</tr>
<tr>
<td>MRZ 2/576</td>
<td>GlyB A</td>
<td>Merz+Co + Grunenthal</td>
<td>Neuroprotection, Pain</td>
<td>P</td>
</tr>
<tr>
<td>SM 18400</td>
<td>GlyB A</td>
<td>Sumitomo</td>
<td>Stroke, Epilepsy</td>
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<tr>
<td>Parkinsonan (Budipine)</td>
<td>ChB</td>
<td>Byk Gulden</td>
<td>Parkinson</td>
<td>L</td>
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<tr>
<td>Felbamate</td>
<td>ChB</td>
<td>Carter Wallace</td>
<td>Stroke</td>
<td>P</td>
</tr>
<tr>
<td>Memantine (Akatinol)</td>
<td>ChB</td>
<td>e.g., Merz + Co.</td>
<td>Dementia</td>
<td>I/III</td>
</tr>
<tr>
<td></td>
<td></td>
<td>+ NTI</td>
<td>Neuropathic pain</td>
<td>II</td>
</tr>
<tr>
<td></td>
<td></td>
<td>+NTI</td>
<td>AIDS-Dementia</td>
<td>II</td>
</tr>
<tr>
<td></td>
<td></td>
<td>+Allergan</td>
<td>Glaucoma</td>
<td>II</td>
</tr>
<tr>
<td>Dextromethorphan</td>
<td>ChB</td>
<td>Roche</td>
<td>Antitussive</td>
<td>L</td>
</tr>
<tr>
<td>CNS-1102 (Cerestat)</td>
<td>ChB</td>
<td>Cambridge Neurosci.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>+Allergan</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dextromethorphan + morphine (MorphiDex)</td>
<td>ChB</td>
<td>Algos</td>
<td>Pain (cancer patients)</td>
<td>III (2)</td>
</tr>
<tr>
<td>Remacemide (FPL 12924AA)</td>
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<td>Astra Charnwood /Merck</td>
<td>Epilepsy</td>
<td>II/III</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Astra Charnwood</td>
<td>Stroke</td>
<td>IIa</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Astra Merck</td>
<td>Parkinson’s</td>
<td>II</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Astra Charnwood</td>
<td>Huntington’s</td>
<td>III</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Astra Arcus</td>
<td>Alzheimer’s</td>
<td>Ia</td>
</tr>
<tr>
<td>ARL 15896AR</td>
<td>ChB</td>
<td>Astra Charnwood</td>
<td>Stroke</td>
<td>Ia</td>
</tr>
<tr>
<td>HU-211 (Dexanabinol)</td>
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<td>Cambridge Neurosci.</td>
<td>Stroke, TBI</td>
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<tr>
<td></td>
<td></td>
<td>+Allergan</td>
<td>Spinal cord injury</td>
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<tr>
<td>ADCI</td>
<td>ChB</td>
<td>NIH, Neurogen</td>
<td>Epilepsy</td>
<td>Ia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>+Wyet-Ayerst</td>
<td>Stroke</td>
<td></td>
</tr>
<tr>
<td>Araxins (NPS-1506)</td>
<td>ChB</td>
<td>NPS</td>
<td>Neuroprotection</td>
<td>I/IIa</td>
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<tr>
<td>CNS 5101</td>
<td>ChB</td>
<td>Cambridge Neurosci.</td>
<td>Neuropathic pain</td>
<td>I</td>
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<tr>
<td>CNS 5161</td>
<td>ChB</td>
<td>Merz + Co.</td>
<td>Neurogenic pain</td>
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</tr>
<tr>
<td>MRZ 2/579</td>
<td>ChB</td>
<td>Merz + Co.</td>
<td>Drug and alcohol dependence, Chronic pain</td>
<td>I</td>
</tr>
<tr>
<td>CNS-1102 (Cerestat)</td>
<td>ChB</td>
<td>Cambridge Neurosci.</td>
<td>Neuroprotection</td>
<td></td>
</tr>
<tr>
<td>Dextromethorphan</td>
<td>ChB</td>
<td>Algos + Interneuron</td>
<td>Migraine</td>
<td>P</td>
</tr>
<tr>
<td>Dextromethorphan + morphine (MorphiDex)</td>
<td>ChB</td>
<td>Algos</td>
<td>Opioid dependence</td>
<td>P</td>
</tr>
</tbody>
</table>
is possible that NMDA receptor neurotransmission interacts with these dopaminergic pathways. Therefore, both systems play a role in mediating the CNS effects of a variety of substances of abuse.

Results of preclinical research conducted so far suggests the therapeutic potential of NMDA receptor antagonists in AOD dependence. Unfortunately, there has been a limited effort aimed at the clinical development of these agents despite supportive preclinical data. Preliminary clinical data, however limited, have been encouraging and we believe that developments in this field will slowly continue. Several possibilities exist for the ‘low popularity’ of these indications. First, the few NMDA receptor antagonists available are being developed for conditions other than alcohol and drug abuse despite the fact that AOD disorders are much more prevalent and costly to society. This is most likely a result of a perception that for marketing purposes, the attachment of the label ‘abuse’ to any drug, no matter whether in a positive or negative sense, can be devastating for further development of the medication for other indications. As a result, all other indications are explored first. Second, might be a belief that alcohol and other drugs users lack health insurance. Hence, it might be doubtful whether any company investing in a medication would be able to obtain sufficient sales. To our knowledge, none of these assumptions have been tested directly but they are consistent with the widely recognised prejudicial attitudes towards alcoholics and drug abusers that exist in society and even in the medical profession. On the other hand, sales and marketing efforts for products to treat dependence on the legal and socially acceptable nicotine are substantial and this have stimulated development of a variety of smoking cessation products.

We predict that a medication that has NMDA receptor antagonist properties might be useful pharmacotherapy for problems resulting from the use of a variety of substances including nicotine, alcohol and illicit drugs. These medications can be promoted as a treatment for nicotine dependence and therefore gain greater social acceptability. At the same time the medication would also be prescribed for a large number of patients who abuse other drugs, providing the potential for an enormous social utility and substantial number of sales.

Table 1: NMDA receptor antagonists currently in development. (cont.)

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mode of action</th>
<th>Company</th>
<th>Indication</th>
<th>Phase</th>
</tr>
</thead>
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<td>Ro 24-6173</td>
<td>ChB</td>
<td>Roche</td>
<td>Stroke</td>
<td>P</td>
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<td>ES 242S</td>
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<td>ES-242-1</td>
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<td>FR 115427</td>
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<td>Fujisawa</td>
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<td>Epilepsy, stroke NeuroPATHy</td>
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<tr>
<td>WAY 126090</td>
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<td>Wyeth-Ayerst</td>
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<td>WAY-126090</td>
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<td>Wyeth-Ayerst</td>
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<td>EAA-090</td>
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</tr>
<tr>
<td>N7</td>
<td>CA</td>
<td>Pfizer</td>
<td>Neuropathy</td>
<td>P</td>
</tr>
<tr>
<td>NPC 17742</td>
<td>CA</td>
<td>Guilford +Scios</td>
<td>Stroke</td>
<td>P</td>
</tr>
<tr>
<td>(GPI-3000)</td>
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<td></td>
</tr>
<tr>
<td>SYM-2351</td>
<td>PA</td>
<td>Symphony</td>
<td>Stroke</td>
<td>P</td>
</tr>
<tr>
<td>Ifenprodyl</td>
<td>NCA, NR2B</td>
<td>Synthelabo</td>
<td>Cerebrovascular diseases</td>
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<td>(Vadilex)</td>
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<td>EMD 95885</td>
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<td>Merck</td>
<td>?</td>
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<td>Ro 25-6981</td>
<td>NCA, NR2B</td>
<td>Roche</td>
<td>Stroke</td>
<td>P</td>
</tr>
</tbody>
</table>

ChB: Channel blocker; GlyB A: Antagonist acting at the glycine site of the NMDA receptors; NCA: Non-competitive antagonist PA: Partial agonist; Phase: P: Preclinical, L: Launched, D: Discontinued.
The most likely scenario is that medications with good safety profiles but without sufficient efficacy for other indications will be tested for AOD dependence. We predict that over the next four years, several of such compounds will be tested for AOD dependence. The most likely indications include smoking cessation, alcohol dependence and cocaine dependence. The most promising candidates for such development in the near future include low affinity uncompetitive antagonists like memantine, dextromethorphan and MRZ 2/579. Others include glycine site antagonists and other non-competitive antagonists. Although the need is great and much preclinical data are available we believe that it will be at least seven years before a medication from this class of agents will be available.

Acknowledgement

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<< Excellent review article from the perspective of analgesics development that includes discussion of cellular mechanisms. >>


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