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Mechanistic insights into the efficacy of memantine in treating certain drug addictions

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ABSTRACT

The deleterious effects of the drug addiction epidemic are compounded by treatment strategies that are only marginally efficacious. Memantine is a unique glutamatergic medication with proven ability to attenuate drug addiction in preclinical models. However, clinical translational studies are inconsistent. In this review, we summarize preclinical evidences and clinical trials that investigated the efficacy of memantine in treating patients with alcohol, opiate, cocaine, and nicotine use disorders and discuss the results from a mechanistic point of view. Memantine has shown efficacy in reducing alcohol and opiate craving, consumption, and withdrawal severity. However, in cocaine and nicotine use disorders, memantine did not have significant effect on cravings or consumption. Additionally, memantine was associated with increased subjective effects of alcohol, cocaine, and nicotine. We discuss possible mechanisms behind this variability. Since memantine transiently blocks NMDA receptors and protects neurons from overstimulation by excessive synaptic glutamate, its efficacy should be observed in drug phases that cause hyperglutamatergic states, while hypoglutamatergic drug use states would not resolve with blocking NMDA receptors. Second, memantine pharmacokinetic studies have been done in rodents and healthy volunteers, but not in patients with substance use disorder. Memantine, opiates, cocaine, and nicotine share the same transporter family at the blood brain barrier. This shared transport mechanism could impact brain concentrations of memantine and its effects. In conclusion, memantine remains an intriguing compound in our pharmacopeia with controversial results in treating certain aspects of drug addiction. Further studies are needed to understand the clinical and biological correlates of its efficacy.

1. Introduction

The unprecedented epidemic of drug addiction presents as a real threat to our society (Lund et al., 2013; Murray et al., 2012; Rehm et al., 2009; Roerecke and Rehm, 2013; Samokhvalov et al., 2010; Tetrault and Butner, 2015). Recent data from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) indicated that the prevalence of heroin use and heroin use disorder have significantly increased by 300% and 500%, respectively, from 2001 to 2002 to 2012–2013 (Martins et al., 2017). Additionally, the proportion of individuals reporting initiation of nonmedical use of prescription opioids before initiating heroin use increased across time among Caucasians from 35% in 2001–2002 to 52% in 2012–2013 (Martins et al., 2017). Similarly alarming data from the National Survey on Drug Use and Health have shown that the rates of lifetime and past-year non-medical use of prescription opiates were 13.6% and 5.1%, respectively; among past-year users, 13.2% met criteria for current prescription opiate abuse or dependence (Back et al., 2010). The prevalence rates of other drugs such as alcohol, cocaine, and nicotine are still high despite modest decline in recent years (www.samhsa.gov).

Despite the awareness of this major public health problem and intense research efforts, our current armamentarium has only a few

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marginally effective treatment options for substance abuse (Albanese, 2012; Jonas et al., 2014; Muller et al., 2014). Since a therapeutic breakthrough appears unreachable (Forray and Sofuoglu, 2014; Rezvani et al., 2012; Zindel and Kranzler, 2014), we need to identify the potential utility of promising medications in treating various aspects of drug addiction. Memantine, a candidate for treating substance abuse, is an low-affinity, uncompetitive N-Methyl-D-Aspartate (NMDA) receptor antagonist that transiently blocks the channel without interfering with normal synaptic transmission (Chen and Lipton, 2005). Memantine is approved by the United States Food and Drug Administration (FDA) for the treatment of moderate to severe Alzheimer's Disease (Rogawski and Wenk, 2003). The efficacy of memantine has also been tested as a neuroenhancement compound in healthy individuals (Repantis et al., 2010) and as a treatment for various neuropsychiatric disorders such as primary and migraine headache (Hoffmann and Charles, 2018; Huang et al., 2014), neuropathic pain (Alviar et al., 2016; Collins et al., 2010; Kurian et al., 2019; Loy et al., 2016; Pickering and Morel, 2018), fibromyalgia (Blumenthal and Malemud, 2016; Littlejohn and Guymer, 2017), unipolar depression (Amidfar et al., 2019; Caddy et al., 2015; Jaso et al., 2017; Kishi et al., 2017), schizophrenia (Di Iorio et al., 2017), bipolar disorder (Serra et al., 2014; Veronese et al., 2016), and obsessive compulsive disorder (Marinova et al., 2017; Modarresi et al., 2019; Wu et al., 2012). Within the current literature, the efficacy of memantine in attenuating behavioral manifestations of drug addiction in preclinical models and human studies varies based on the specific drug of abuse. However, there are discrepancies between the results of animal and clinical studies investigating the same substance of abuse. The aim of this review is to present published studies that utilized memantine for the treatment of alcohol, opiate, cocaine, and nicotine use disorders and to discuss the potential mechanistic basis for the drug-specific differential efficacy of memantine for the treatment of substance use disorders.

2. Methods

We conducted a systematic review of the literature by searching MEDLINE to identify original studies about memantine effects in drug addiction. The following search words were used [((("*N*-methyl-D-aspartate" AND "NMDA") AND ("antagonist" OR "antagonism") AND "drugs") OR "memantine") AND ("cocaine" OR "alcohol" OR "opiates" OR "opioid" OR "nicotine" OR "behavioral addiction" OR "gambling" OR "addiction" OR "addictive disorders") AND ("withdrawal" OR "craving" OR "consumption" OR "dependence" OR "subjective effects" OR "severity" OR "cognitive effects") AND "Human"]. The search was conducted on July 8, 2020 and yielded 66 records.

We included all original articles (open label or double-blind trials, and prospective or retrospective observational studies) written in English, in which subjects were drug users and were treated with memantine. We included only studies involving adults (age > 18 years). Reviews, commentaries, letters to the editor, studies enrolling patients with predominant medical comorbidity, and studies not enrolling patients affected by addictive disorders or not including a clinical assessment were excluded. All the authors agreed on inclusion and exclusion criteria.

We excluded 21 records by reading titles and abstracts. By reading the full texts of the 45 remaining articles, we found 19 studies meeting our inclusion/exclusion criteria, and therefore included these studies in the qualitative synthesis (Fig. 1).

The quality of the studies was gauged by considering the 5 items of the Quality Assessment Checklist for Observational Studies (QATSO

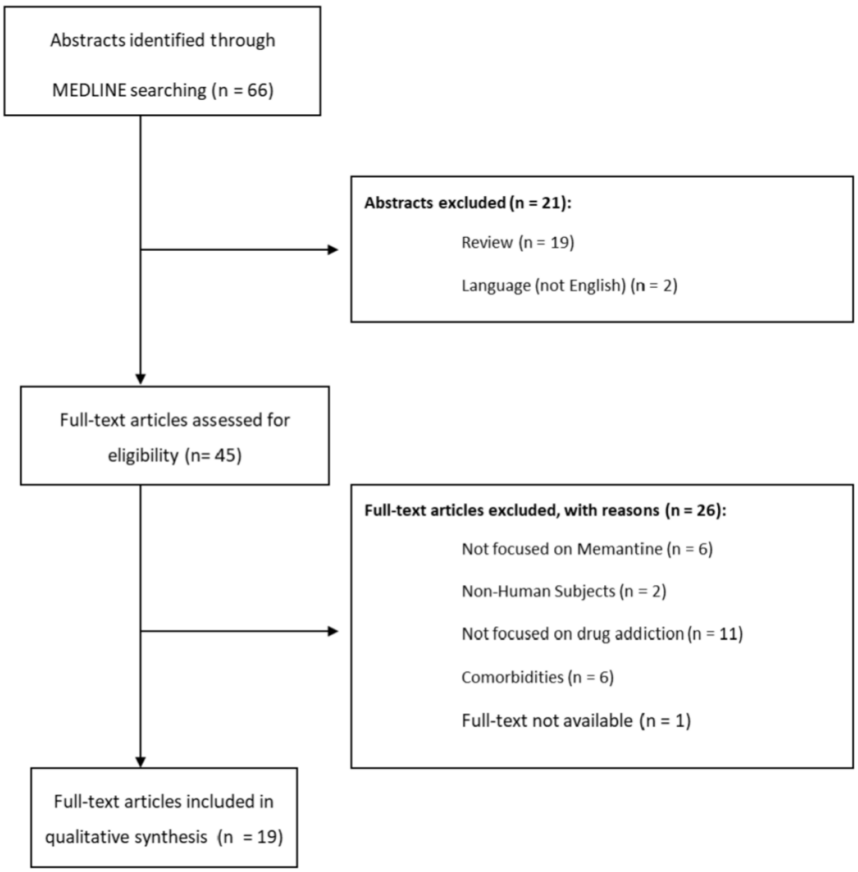

Fig. 1. PRISMA flowchart for articles selection.

Score) (Wong et al., 2008) which was adapted for observational – open trial studies. In particular, the checklist evaluates 5 criteria: 1) sample size and source; 2) use of validated tool; 3) if the study reports response rate; 4) control for confounding factors (e.g. stratification/matching/restriction/adjustment); 5) privacy and ethical aspects considered. The quality of the Randomized Control Trials (RCTs) was assessed using the first 3 items on the Jadad Scale (Moher et al., 1995) which gauge randomization, blinding, and the withdrawal description.

In addition to the clinical studies, we reviewed preclinical evidence for the use of memantine in each of the four drugs of interest.

3. Results

3.1. The efficacy of memantine in alcohol use disorder

3.1.1. Preclinical evidence

We collected 15 studies evaluating memantine treatment for alcohol consumption, self-administration, and withdrawal in mice or rats (Fig. 2). Two studies (Idrus et al., 2014; Idrus et al., 2011) focused on early post-natal alcohol exposure in rats (postnatal day 6, in which brain development corresponds to the human late gestation period). Overall, memantine showed efficacy in reducing voluntary alcohol drinking, self-administration, and withdrawal. Chronic memantine pretreatment attenuated the development of alcohol dependence as quantified by the reduction in withdrawal audiogenic seizures induced during the 12 h after the last ethanol administration in rats (Kotlinska, 2001) and reduced operant responding to alcohol in dependent rats when administered 30 min before sessions (Piasecki et al., 1998). In addition, 25 mg/kg memantine injection reduced alcohol self-administration in dependent rats during early and late withdrawal (6–30 h) (Alaux-Cantin et al., 2015). Furthermore, single dose administration of memantine (1–5–10 mg/kg) reduced voluntary alcohol drinking among alcohol-preferring rats (Malpass et al., 2010) and alcohol-dependent mice (Oberlin et al., 2010) and decreased both self-administration and motivation to consume alcohol in alcohol-preferring rats for at least 30 h (Jeanblanc et al., 2014). However, the reduction in alcohol intake was also associated with a reduction in total fluid drinking in non-dependent mice during induced-polydipsia (Escher et al., 2006), a reduction in both total drinking and food intake in alcohol dependent rats (Piasecki et al., 1998), and increased aggressive behavior in trained mice when administered 30 min prior to instigation sessions (Newman et al., 2012).

Furthermore, a single memantine dose (15–30 mg/kg) administered during withdrawal (21–36 h after alcohol exposure) reduced alcohol-related behavioral alterations in early alcohol-exposed rats (Idrus et al., 2014; Idrus et al., 2011) and reduced withdrawal-induced anxiety during early (6 h) withdrawal (rats, 4 mg/kg; (Yuanyuan et al., 2018)), but not during late withdrawal (24 h) (rats, 8–12 mg/kg; (Kotlinska and Bochenski, 2008)). Meanwhile, memantine reduced withdrawal-induced seizures in rats when administered at both 10 and 15–16 h after last ethanol administration (Bienkowski et al., 2001; Stepanyan et al., 2008). However, single-dose memantine increased withdrawal-induced aggressive behaviors in mice when administered 30 min before confrontation task during early withdrawal (Hwa et al., 2015). Memantine chronic administration during alcohol withdrawal (20 mg/kg on the first day of withdrawal +1 mg/kg/day for a 4-week period) has been shown to improve behavioral impairments in rats performing the water maze task: withdrawn rats injected with memantine showed better learning rates and higher numbers of platform crossings and percentages of time spent in the training quadrant compared to those treated with saline or MK-801, and their rates were not statistically different from those of the control (not alcohol dependent/not withdrawn) group (Lukoyanov and Paula-Barbosa, 2001). Moreover, in long-term (10 months) alcohol drinking rats, deprived for two weeks and presented again with alcohol solution after a memantine implantation with a daily memantine dose of 4.8 mg, memantine have been shown to reduce the rise in alcohol intake after re-presentation (Holter et al., 1996).

In summary, several preclinical studies show efficacy for memantine in reducing the development of alcohol dependence, voluntary alcohol drinking, and alcohol withdrawal manifestations in both rats and mice. Few adverse effects were associated with memantine treatment such as increased withdrawal-induced aggressive behavior and reduced total fluid and food intake.

3.1.2. Clinical studies

Our search identified 6 primary studies on the use of memantine for alcohol use disorder (Table 1). Abstinence was not required in 4 of the 6 studies (Bisaga and Evans, 2004; Evans et al., 2007; Krishnan-Sarin et al., 2015; Muhonen et al., 2008b). The remaining 2 studies included only individuals in early withdrawal (abstinence range 8–48 h) (Krupitsky et al., 2007b) or early abstinence (mean sobriety 22 days) (Krupitsky et al., 2007a). The effect of memantine on alcohol craving differed based on memantine dosage. Memantine was reported to significantly reduce cravings for alcohol at moderate doses ranging from 20 to 30 mg (Bisaga and Evans, 2004; Krishnan-Sarin et al., 2015; Krupitsky et al., 2007b; Muhonen et al., 2008a). Bisaga and Evans (Bisaga and Evans, 2004) found that 15 mg of memantine reduced cravings, but the effect did not reach significance ($P = 0.06$). The effects of higher doses of memantine were inconclusive. Two studies found no significant effects of 40 mg doses of memantine on alcohol cravings (Evans et al., 2007; Krishnan-Sarin et al., 2015). However, Krupitsky et al. (Krupitsky et al., 2007a) found that 40 mg of memantine significantly reduced cravings when administered during early abstinence.

Only three of the collected studies reported on the effect of memantine on alcohol consumption levels. The first study (Muhonen et al., 2008a) found that 20 mg of memantine significantly reduced alcohol consumption. Conversely, other studies found no significant effect of memantine on alcohol consumption at 20 mg (Krishnan-Sarin et al., 2015) or 40 mg (Evans et al., 2007; Krishnan-Sarin et al., 2015).

Fewer studies reported other effects of memantine on alcohol measures. Krupitsky et al. (Krupitsky et al., 2007a) found that 20 mg and 40 mg doses of memantine produced dose-related alcohol-like subjective effects. Similarly, Bisaga and Evans (Bisaga and Evans, 2004) reported that 30 mg, but not 15 mg, of memantine increased the subjective effects of alcohol. Finally, Krupitsky et al. (Krupitsky et al., 2007b) the only study including participants in withdrawal, found that 30 mg of memantine reduced the severity of withdrawal symptoms.

In summary, there were conflicting results among the clinical studies investigating the effect of memantine on alcohol use disorder populations. Among the studies showing significant effects of memantine, there was agreement with preclinical evidence, indicating efficacy of memantine in reducing alcohol consumption, craving, and withdrawal manifestations. In addition, memantine was associated with increased subjective effects of alcohol in a few reports.

3.2. The efficacy of memantine in opiate use disorder

3.2.1. Preclinical evidence

We collected 13 studies evaluating memantine in opioid addiction. In seven of the studies, memantine was administered prior to opioid dependence establishment, as chronic or acute pretreatment. Animal studies evaluating memantine efficacy in opioid addiction have been graphically summarized in Fig. 2. Acute memantine pretreatment, described as a single memantine dose administered 30 min prior to morphine, has been shown to reduce both morphine intake in mice during self-administration (Semenova et al., 1999) and morphine stimulus effects in rats receiving 3.2 mg/kg of morphine (Chen et al., 2013). Otherwise, memantine did not show any effects on naloxone-conditioned place aversion in mice receiving 1, 3 or 10 mg/kg of memantine, either 30 ahead of, alongside, 2 or 3.5 h after morphine (Blokhina et al., 2000).

In non-dependent mice, chronic pretreatment with high daily doses

Fig. 2. Characteristics and findings of included opioid, alcohol, and cocaine-related animal studies.

Table 1
Characteristics of included alcohol-related clinical trials.

Study	Total n Age (mean ± SD), years Male (%) Race (%)	Study Duration	Experimental treatment design	Concurrent treatment	Assessments	Primary outcomes	Results	Side Effects
Krishnan-Sarin et al. (2015)	*n* = 90 30.9 ± 8.5 years 71% male 68% Caucasian 26% African American	8 days	1. MEM 20 mg/day 2. MEM 40 mg/day 3. Placebo	Alcohol drinking paradigm	Yale craving scale (YCS) Alcohol urge questionnaire Alcohol consumption BAES BIS-11	Total drinks consumed Alcohol cravings (YCS)	MEM 20 mg reduced craving for alcohol. MEM 40 mg had no effect on cravings MEM had no effect on alcohol consumption	headache (11.6%), dizziness (5.6%), nausea (6.9%), fatigue (6.0%), and nervousness (5.35%) 7 drop out due to side effects MEM 40 mg dose produced greater side effects than MEM 20 mg or placebo
Muhonen et al. (2008b)	*n* = 80 47.7 ± 8.3 years 55% male 100% Caucasian	26 weeks	1. MEM 20 mg/day 2. Escitalopram 20 mg/day	N/A	Obsessive-Compulsive Drinking Scale AUDIT AUDIT-QF AUDIT-3 Drinking diary	alcohol craving mean number of abstinent days per week alcohol consumption (AUDIT)	reduced AUDIT scores for consumption and number of drinking days reduced cravings	No group differences 90% pp. in memantine group reported at least 1 AE Drowsiness and headache most common (1/3 pp)
Evans et al., 2007)	*n* = 34 42.6 years 80% male 44% Caucasian 24% African American	16 weeks	1. MEM 40 mg 2. Placebo	Cognitive Behavioral Therapy	Alcohol consumption OCDS ADS DrinC-2R CGI BDI-II SAFTEE	Average drinks per day average drinks per drinking day percentage heavy drinking days percentage days abstinent	Reduction in alcohol consumption did not differ between groups Craving reduction did not differ between the two groups Percentage of heavy drinking days showed greated reduction in placebo group	significantly higher rate of side effects reported in MEM group vs placebo gastrointestinal disturbance (5), lightheaded/dizziness (5), anxiety (3), and disorientation/difficulty concentrating (3)
Krupitsky et al. (2007b)	*n* = 174 43 years 100% male Race not reported	1 week	1. MEM 30 mg/day 2. Lamotrigine 25 mg/6 h 3. Diazepam 10 mg/8 h 4. Topiramate 25 mg/6 h 5. Placebo	N/A	TLFB CIWA-Ar AWSC MADRS	Alcohol withdrawal (CIWA-Ar, AWSC) MADRS	Efficacy in alcohol detoxification Lamotrigine = memantine = topiramate = diazepam > plabebo Reduction in withdrawal severity Significantly reduced craving compared to placebo	No side effects reported for MEM
Krupitsky et al. (2007a)	*n* = 38 39.2 ± 9 years 100% male Race not reported	3 days	Each patient received a single dose of every drug in a randomized order: 1. MEM 20 mg/day 2. MEM 40 mg/day 3. Placebo	N/A	Verbal fluency test Hopkins Verbal Learning Test Biphasic Alcohol Effects Scale VAS for craving Number of drinks	Subjective effects of alcohol (Biphasic Alcohol Effects Scale and VAS for craving)	MEM produced modest but significant dose-related ethanol-like effects MEM 40 mg significantly reduced craving for alcohol	Not reported
Bisaga and Evans (2004)*	*n* = 18 27.9 years 67% male 67% Caucasian	1 day	Acute MEM administration 1. MEM 15 mg 2. MEM 30 mg 3. Placebo	Four hours after drug administration, alcohol was administered as four 150 ml beverages, spaced 20 min apart. Participants were given 30 s to consume each beverage.	Word Recall and Recognition Tasks (WRRT) Performance task battery (PB) Subjective-effects battery (SEB) Profile of Mood states (POMS)	subjective and behavioral effects of alcohol	MEM 30 mg significantly reduced craving for alcohol MEM increased subjective ratings of the dissociative effects of alcohol	Impairment in balance (MEM 30 > MEM 15 > PBO)

(*continued on next page*)

Table 1 (*continued*)

Study	Total n / Age (mean ± SD), years / Male (%) / Race (%)	Study Duration	Experimental treatment design	Concurrent treatment	Assessments	Primary outcomes	Results	Side Effects
					Alcohol craving scale (ACS) Alcohol-effects battery (AEB)			

* Participants in this study were categorized as moderate drinkers (10–30 drinks per day) and did not meet criteria for alcohol dependence. All other studies included only individuals who met DSM-IV criteria for alcohol dependence.

(20–30 mg/kg/day) of memantine reduced morphine antinociceptive effects in both rats (Chen et al., 2013) and mice (Hosseinzadeh et al., 2012), and morphine tolerance in mice (Dravolina et al., 1999; Hosseinzadeh et al., 2012). Lower memantine doses (0.2–1 mg/kg/day) reduced morphine-induced conditioned place preference and increased BDNF levels in rats (Chen et al., 2012). Meanwhile, memantine chronic pretreatment did not show any effect on methadone dependence and withdrawal .

In six studies, memantine was administered at various dosages ranging from 7.5 to 30 mg/kg to opioid dependent animals and showed positive effects on spontaneous and naloxone-induced withdrawal. Memantine administered 30–45 min before naloxone has been proven to dose-dependently reduce and even block withdrawal signs in mice (Harris et al., 2008; Medvedev et al., 1998; Popik and Skolnick, 1996) During spontaneous withdrawal, memantine administered 48 h after last morphine administration reduced withdrawal-induced aggressive behaviors in mice (Sukhotina and Bespalov, 2000), but did not show any effect on naloxone discrimination in rats when administered 24 h after last morphine administration (Medvedev et al., 1998).

In summary, memantine treatment was not effective for methadone but reduced morphine, dependence, conditioned place preference, self-administration, and naloxone-precipitated withdrawal manifestations.

3.2.2. Clinical studies

We collected 7 publications about the use of memantine for opioid use disorder (Table 2). Two of the 7 publications are based on the same cohort (Chang et al., 2015; Lee et al., 2015), therefore we consider there to be only 6 primary studies regarding the effects of memantine on opioid use disorder.

Memantine was reported to significantly reduce opioid consumption (Comer and Sullivan, 2007; Gonzalez et al., 2015) and relapse rates following treatment with methadone (Chang et al., 2015) and buprenorphine (Gonzalez et al., 2015). Additionally, Lee et al. (Lee et al., 2015) found that memantine reduced the required dose of methadone needed for individuals undergoing methadone maintenance therapy.

The effect of memantine on opioid withdrawal was unclear. One study reported a reduction of opioid withdrawal ratings following the administration of memantine (Gonzalez et al., 2015), while another study found no effect of memantine on opioid withdrawal ratings (Bisaga et al., 2011). A third study (Bisaga et al., 2014) found that memantine reduced withdrawal symptoms in the first 2 weeks of naltrexone co-administration, but then was associated with increased withdrawal ratings in the following weeks. Similarly, the effect of memantine on cravings for opioids were inconsistent. Two studies found that 30 mg of memantine significantly reduced cravings . (Gonzalez et al., 2015; Krupitsky et al., 2002), while Bisaga et al. (Bisaga et al., 2011) found no significant effect of memantine on opioid cravings at doses of 30 or 60 mg. Interestingly, memantine had a variety of favorable cognitive effects among individuals with opioid use disorder. For instance, memantine administration was associated with decreases in impulsivity (Gonzalez et al., 2015) and improved performance on cognitive tasks targeting executive functions (Chang et al., 2015). Further, memantine reduced subjective ratings of drug liking, drug quality, and drug potency following opioid detoxification.

In summary, despite some inconsistencies between studies, both preclinical evidence and clinical results document efficacy of memantine in reducing opiate use, craving, and withdrawal manifestations. In addition, memantine showed positive effects on cognitive function. There were no reports of increased subjective feelings for opiates as reported in alcohol treatment studies.

3.3. The efficacy of memantine in cocaine use disorder

3.3.1. Preclinical evidence

We collected 16 preclinical studies evaluating the administration of memantine in animal models of cocaine addiction, with controversial results. Findings and characteristics of the studies cited in this paragraph have been graphically summarized in Fig. 2.When administered before cocaine exposure, medium to low dose memantine decreased drug intake in rats during self-administration and progressive ratio sessions, but results have not been replicated in mice (Blokhina et al., 2005), and opposite results (i.e. increase in self-administration and decrease in cue response) were observed in monkeys (Newman and Beardsley, 2006). At the same time, medium-high dose memantine administration before cocaine exposure decreased both social withdrawal (Lluch et al., 2005) and cocaine-induced seizures (Brackett et al., 2000) in mice. Memantine also seemed to be able to prevent cocaine-induced conditioned place preference and to attenuate conditioned motor activity and reinstatement in both mice (Lin et al., 2011; Maldonado et al., 2007) and rats (Alaghband and Marshall, 2013; Alaghband et al., 2014; Bespalov et al., 2000a; Bespalov et al., 2000b; Kotlinska and Biala, 2000; O'Connor et al., 2015).

Interestingly, memantine was shown to potentiate brain reward function, in both early-adolescence stressed rats and in cocaine/morphine dependent rats (O'Connor et al., 2015; Tzchentke and Schmidt, 2000).

In summary, memantine pretreatment reduced cocaine self-administration, conditioned place preference, and reinstatement and attenuated social withdrawal, cocaine-induced seizure in some, but not all studies. Similar to alcohol studies, memantine increased cocaine self-administration in monkeys (Newman and Beardsley, 2006) and potentiated reward function (O'Connor et al., 2015) in a few studies.

3.3.2. Clinical studies

Our search identified 4 papers on the efficacy of memantine for cocaine use disorder (Table 3). Across these studies, memantine was administered in doses ranging from 10 to 60 mg (Bisaga et al., 2010; Collins et al., 2007; Collins et al., 2006; Vosburg et al., 2005). Collectively, these studies found no evidence that memantine is effective in treating cocaine use disorder. Memantine had no effect on cocaine consumption or cravings (Bisaga et al., 2010; Collins et al., 2006). At doses of 20 mg and 60 mg, memantine was found to increase the

Table 2
Characteristics of included cocaine-related clinical trials.

Study	Total n Age (mean ± SD), years Male (%) Race (%)	Study Duration	Experimental treatment design	Concurrent treatment	Assessments	Primary outcomes	Results	Side Effects
Bisaga et al. (2010)	*n* = 81 40 ± 8 years 79% male 41% Caucasian 37% African American	12 weeks	1. Memantine 40 mg 2. Placebo	Contingency Management therapy (3w) Motivational Enhancement Therapy Cognitive Behavioral Treatment-Relapse Prevention	Urine drug screening Self-reported measures of drug use, craving, and mood	Proportion of days per week with cocaine use	No significant effects of MEM on proportion of days with cocaine use or proportion of days with cravings.	No significant group differences in frequency of AEs. Only 1 of 9 moderate AEs reported by the memantine-treated patients were considered to be definitely related to memantine.
Collins et al. (2007)	n = 6 38 100% male 100% African American	11 days	Pretreatment: 1. Memantine 60 mg (2 days) 2. Placebo (7 days)	N/A	VAS Assessment for mental acuity, learning and memory Laboratory choice session	Cocaine self-administration Subjective effects (VAS) Cardiovascular effects	MEM was associated with an increase in feeling of stimulation and anxiety MEM produced a significant decrease in feeling of depression MEM may increase some subjective and cardiovascular cocaine effects	Not reported
Collins et al. (2006)	n = 8 37 88% male Race data not provided	47 days	1. Memantine 20 mg 2. Placebo	Alternating inpatient and outpatient periods. Methadone maintenance (mean 86.3 mg/day)	Laboratory choice session VAS (18) Opiate symptoms checklist SOWS OOWS Blood pressure	Cocaine self-administration Subjective effects (VAS)	MEM was associated with an increase in blood pressure following cocaine administration MEM had no effect on the number of times subjects chose cocaine over the alternative MEM had no effect on cocaine consumption MEM had no effect on cocaine craving but reduced craving for heroin	Not reported
Vosburg et al. (2005)	n = 8 38 75% male 88% African American	7 weeks	1. Memantine 10 mg 2. Memantine 20 mg 3. Memantine 30 mg 4. Placebo Blocks of 7 sessions, 1 session per visit. Each block tested one dose of memantine, each block consisted of two "sample" sessions, where participants received one active and one placebo dose and five "choice" sessions, where participants selected between the two options	N/A	VAS DEQ	Choice of placebo or MEM (distinguished by color) subjective effects	MEM was chosen less than placebo MEM did not produce reinforcing effects	Not reported

cardiovascular effects of cocaine (Collins et al., 2007; Collins et al., 2006). Finally, co-administration of cocaine and memantine resulted in increased subjective feelings of "stimulation" and "anxiety" and decreased subjective feelings of "depression" (Collins et al., 2007; Vosburg et al., 2005) (Collins et al., 2007). Vosbourg et al. (2005) reported that, when given the choice, participants chose placebo over memantine, suggesting that memantine did not enhance the subjective effects of cocaine in a way that would create abuse potential for memantine among individuals with cocaine use disorder.

In summary, memantine treatment did not reduce cocaine consumption or cravings, but increased subjective feelings of stimulation and anxiety.

Table 3
Characteristics of included opioid-related clinical trials.

Study	Total n Age (mean ± SD), years Male (%) Race (%)	Study Duration	Primary treatment	Experimental treatment design	Assessments	Primary outcomes	Results	Side Effects
Gonzalez et al. (2015)	n = 80 22 ± 1.9 years 66% male 91% Caucasian	13 weeks	Buprenorphine (16 mg/day) + Naloxone (4 mg/day), discontinued on week 9 of study	Add-on: 1. MEM 15 mg/day 2. MEM 30 mg/day 3. placebo	Urine drug screen TLFB COWS OWS HCQ-SF-14 VAS CES-D BIS Anti-saccade test	mean proportion of opioid use Cumulative abstinence rates after rapid buprenorphine discontinuation on week 9	MEM 30 mg/day: 1. Improvement in short-term treatment with buprenorphine/naloxone; 2. Craving reduction 3. Lower rate of relapses 4. Opioid use reduction 5. Reduction is COWS scores 6. Reduction in BIS	Most commonly reported side effects: pain 21%, upper respiratory infection 9.3%, nausea 7.6%, vivid dreams 6.7%, constipation 5.9%, headaches 5%, and drowsiness 5%. No significant differences between placebo, MEM 15 mg and MEM 30 mg
Chang et al. (2015)	*n* = 134 36.24 ± 7.48 years 83% male 100% Asian	12 weeks	Methadone-maintenance therapy (MMT)	Add-on: 1. MEM 5 mg 2. Placebo	Urine drug screen Wisconsin Card Sort Task (WCST) Continuous performance test (CPT) Opiate Treatment Index (OTI) Schedule of Affective Disorders and Schizophrenia-Lifetime (SADS-L)	Cognitive performance on WCST and CPT	MEM 5 mg/day: 1. Improvement in cognitive tasks, frontal and executive functions 2. Lower rate of relapses	Not reported
Lee et al. (2015)	n = 134 36.24 ± 7.48 years 83% male 100% Asian	12 weeks	Methadone-maintenance therapy (MMT)	Add-on: 1. MEM 5 mg 2. Placebo	Methadone dose required OTI TNF-α CRP IL-6 IL-8 TGF-β1 plasma BDNF	Methadone dose required Retention rates Participants' opioid use	MEM 5 mg/day: 1. Reduction in required methadone dose 2. Lower TNF-α level 3. Higher TGF-β1 level	Urogenital system side effects in MEM group
Bisaga et al. (2014)	*n* = 82 42 ± 17 years 81% male 48% Caucasian 33% Hispanic	12 weeks	Buprenorphine (2 days), followed by washout period (1 day), then naltrexone (slow induction procedure; 3.125 mg, 6.25 mg, 25 mg)	Starting on day 2 of naltrexone, add-on: 1. MEM (40 mg or max tolerated dose) 2. placebo	Clinical global impression severity score (CGI) Hamilton rating scale for depression (HAM-D) Subjective opiate withdrawal scale (SOWS) Heroin consumption	Retention rates	MEM 1. Lower withdrawal scores (first 2 weeks) 2. Higher withdrawal scores (remaining weeks)	At least one adverse event among insomnia, fatigue, headaches and dizziness, in 98% MEM and 71% PBO.
Bisaga et al. (2011)	n = 81 41 ± 10.1 years 81% male 48% Caucasian 30% Hispanic	12 weeks	Buprenorphine (1 day), followed by washout period (1–2 days), then naltrexone (rapid induction procedure; 12.5 mg, 25 mg, 50 mg, 100 mg)	On day 2 of naltrexone induction; add-on: 1. MEM 30 mg 2. MEM 60 mg 3. placebo	Weekly proportion of group using opiates Weekly average CGI Weekly CGI improvement score Weekly craving scores Hamilton rating scale for depression (HAM-D) Subjective opiate	Retention rates	No significant difference across groups	Adverse events reported in 59% PBO, 37% MEM 30 mg, and 63% MEM 60 mg. No significant group difference in adverse events. 1 SAE in MEM 30 mg (relapse, overdose, and hostpialization)

(*continued on next page*)

Table 3 (*continued*)

Study	Total n Age (mean ± SD), years Male (%) Race (%)	Study Duration	Primary treatment	Experimental treatment design	Assessments	Primary outcomes	Results	Side Effects
					withdrawal scale (SOWS)			
Comer and Sullivan (2007)*	$n = 12$ 34 years 75% male 50% Hispanic	8 weeks	1 week detox	Following detox, ppts received 2 weeks of each treatment: 1. placebo (MEM 0 mg) 2. MEM 30 mg 3. MEM 60 mg	SOWS Drug effects questionnaire (DEQ) Heroin craving questionnaire (HCQ) Visual analog scale (VAS; 26 items) Cognitive tasks	VAS ratings for heroin	MEM: Lower VAS rates in drug liking, potency and quality MEM 30 mg: Lower amount of self-administered drug	Not reported
Krupitsky et al. (2002)*	$n = 67$ 22 years 91% male race data not provided	3 weeks	7–10 day detox standard psychotherapy and counseling	Following detox 1. MEM 30 mg 2. amitriptyline 75 mg 3. placebo	Treatment retention Visual analog scale (VAS) Zung's depression scale Spielberger's anxiety scale Anhedonia syndrome scale	Reduced symptoms of protracted withdrawal (depression, anxiety, and craving)	By the end of the study, MEM and amitriptyline reduced anxiety, depression, and cravings. MEM reduced cravings faster and with fewer side effects than amitriptyline.	Side effects of MEM not significantly different from placebo

* This study is a single blind placebo-controlled study. All other opiate studies were double blind randomized controlled trials.

3.4. The efficacy of memantine in nicotine use disorder

3.4.1. Preclinical evidence

Only one study investigated the effects of memantine on nicotine addiction. Low dosage memantine (1–10 mg/kg) reduced nicotine discriminative-stimulus effects when co-administered with nicotine in rats trained to discriminate nicotine from saline (Zakharova et al., 2005).

3.4.2. Clinical studies

Only two studies have been published on the effects of memantine for nicotine use disorder in humans (Table 4). Thuerauf et al. (Thuerauf et al., 2007) reported that 20 mg of memantine had no effect on cigarette cravings, olfactory nicotine discrimination, or cigarette consumption. Jackson et al. (Jackson et al., 2009) found that 40 mg of memantine had no effect on nicotine cravings or the cognitive enhancement associated with smoking cigarettes. On the contrary, there were reports of increases in the subjective effects of smoking, specifically the feelings of being "buzzed" and "dizzy" (Jackson et al., 2009).

In summary, neither of the two available studies show efficacy of memantine in reducing nicotine smoking or craving. However, memantine seemed to increase subjective feelings of being buzzed or dizzy.

4. Mechanisms of action

Memantine's clinical effects are generally attributed to its ability to transiently block NMDA receptors and reduce glutamatergic overstimulation (Chen and Lipton, 2005). While this mechanism could be effective in relieving drug-induced hyperglutamatergic states such as acute alcohol withdrawal (Tsai et al., 1998), it may not be effective in hypoglutamatergic conditions such as cocaine (Miguéns et al., 2008) or nicotine withdrawal (Abulseoud et al., 2020). Thus, this mechanism can account for the differential efficacy of memantine when used to treat different types of substance use disorders. However, the variability in the efficacy of memantine as a substance use disorder treatment does not differ only based on the particular drug of abuse. In addition to the observed discrepancy between the results of preclinical and clinical studies, specifically for cocaine and nicotine use disorders, the clinical literature reveals a memantine-associated enhancement of the subjective effects of alcohol, cocaine, and nicotine. Therefore, here we explore the NMDA receptor mechanism as well as two other potential mechanisms of action for memantine that could account for the observed effects of memantine among substance use disorder populations. Specifically, we consider how the presence of certain drugs could impact the bioavailability of memantine, for example by altering its ability to penetrate or clear the blood brain barrier. Additionally, we discuss potential pharmacokinetic interactions between memantine and drugs of abuse that could facilitate the transport these substances into the brain, thus increasing subjective effects of the drug. Finally, we explore the effect of memantine on other factors such as modulation of BDNF signaling pathways (Jeanblanc et al., 2014) or balancing the neuroimmune response triggered by substances of abuse.

4.1. The efficacy of memantine through regaining glutamatergic homeostasis

The well-established dopamine hypothesis for drug addiction has been challenged since it does not provide an explanation for the long-lasting behavioral abnormalities like craving or relapse (Marquez et al., 2017) and also because dopaminergic medications show only marginal efficacy in reducing addiction severity (Indave et al., 2016; Swift, 2010). The emerging glutamate hypothesis proposes that pervasive drug-related behavioral manifestations stem from persistent alterations in synaptic plasticity, which is largely influenced by glutamatergic mechanisms (Kalivas and Volkow, 2011). Indeed, glutamate is the major excitatory neurotransmitter in the brain and is intimately involved in energy homeostasis, synaptic integrity, overall network functionality, and, ultimately, behavioral manifestations. As such, glutamatergic dysregulations are in the core pathology of various neuropsychiatric disorders, specifically addiction (Kalivas, 2009).

Table 4
Characteristics of included nicotine-related clinical trials.

Study	Total n Age (mean ± SD), years Male (%) Race (%)	Study Duration	Experimental treatment design	Concurrent treatment	Assessments	Primary outcomes	Results	Side Effects
Thuerauf et al. (2007)	$n = 40$ 26.47 ± 5.21 47.5% male Race not reported	2 weeks	Memantine 10 mg/day for 3 days, then 20 mg/day Placebo	N/A	Nicotine discrimination Hedonic and intensity ratings for nicotine Cigarette consumption VAS for craving	Smoking reduction Perception of nicotine	Memantine 20 mg: No effect on smoking reduction No effect on olfactory nicotine discrimination No effect on craving	Headache (2/20 in MEM group) Dizziness (1/20 in MEM group)
Jackson et al. (2009)	$n = 60$ 23.5 years 50% male Race not reported	1 day	1. MEM 40 mg 2. Mecamylamine 10 mg 3. Placebo	N/A	Rapid Visual Information Processing Task (RVIP) Digit Symbol Substitution Test (DSST) nicotine-VAS Questionnaire of Smoking Urges (QSU) Spatial Recognition Memory (SRM) Word Recall Profile of Mood States Questionnaire (POMS) NMDA-related Visual Analog Scales (NMDA-VAS) Paired Associates Learning (PAL) Affective Go/No Go (AGNG)	Impact of MEM on cognitive and subjective effects of cigarette smoking	MEM increased subjective effects of smoking: buzzed, dizzy MEM had no effect on the cognitive benefit of smoking MEM had no effect on nicotine cravings	Anxiety (1) MEM induced NDMA-related subjective effects: lightheaded, detached, slow motion, unreal

Memantine presents as an attractive treatment option for substance use disorders based on its ability to regulate the glutamatergic over-stimulation of NMDA receptors (Chen and Lipton, 2005). Maintaining a proper balance between synaptic and peri-synaptic glutamate concentrations is essential for maintaining synaptic plasticity and strength (Gass and Olive, 2008). This glutamatergic homeostasis is disrupted differently during different stages of drug addiction (Koob and Volkow, 2010). For instance, the use of cocaine, nicotine, or low doses of alcohol causes an increase in synaptic glutamate and an inhibition of NMDA function; conversely, the use of opiates or high doses of alcohol causes a reduction in glutamate and an upregulation in NMDA function in certain brain regions (reviewed in Olive et al., 2012a). In contrast, withdrawal from alcohol is associated with a marked increase in synaptic glutamate, possibly due to reduced glutamate uptake (Abulseoud et al., 2014). Further, long-lasting increases in NMDA receptor activity are observed post withdrawal (Steven Rosenzweig Haugbøl and Ulrichsen, 2005). On the other hand, during cocaine and opiate withdrawal, extracellular glutamate levels are decreased and we have recently reported reduced total glutamate in dorsal anterior cingulate in smokers during nicotine withdrawal (Abulseoud et al., 2020). Furthermore, relapse to alcohol and opiate and cocaine reinstatement are triggered by high glutamate concentrations in limbic brain regions and while NMDA antagonists attenuate morphine reinstatement, they can induce cocaine reinstatement [reviewed in (Alasmari et al., 2018; Goldstein and Volkow, 2002; Kalivas et al., 2009; Marquez et al., 2017; Olive et al., 2012b; Reissner and Kalivas, 2010; Scofield et al., 2016; Spencer et al., 2016)].

Based on this brief overview, one can observe two glutamate concentration-based categories. First a hyperglutamatergic group where we observe markedly high glutamate in alcohol withdrawal, and moderately high glutamate during low dose alcohol consumption, cocaine administration, or nicotine administration. The persistence of this high glutamate during abstinence triggers relapse to alcohol, cocaine, and opiates. In this category, competitive antagonism of NMDA receptors by memantine protects the neurons from over stimulation in the presence of high synaptic glutamate. Indeed, clinical trials have shown efficacy for memantine in reducing alcohol and opiate craving, consumption, and withdrawal severity.

The other category is the hypoglutamatergic group which includes high dose alcohol and opiate use and withdrawal states for cocaine, opiate, and nicotine use disorders. In all of these conditions, glutamate concentrations are reportedly low in one or more brain regions. Here, we see that memantine does not have a significant effect on cocaine craving or consumption. However, this categorization does not explain the efficacy of memantine in reducing high dose alcohol consumption, a hypoglutamatergic state, and does not provide an answer for why memantine increased subjective effects of alcohol, cocaine, and nicotine. One way to explore this apparent discrepancy is to examine the pharmacokinetic interaction between memantine and substances of abuse at the kidney and blood brain barrier (BBB).

4.2. The efficacy of memantine depends on achieving adequate blood and brain concentration

Shared pharmacokinetic properties among drugs of abuse and

memantine offer a potential explanation for the effects of memantine observed in substance use disorder treatment trials. Orally administered memantine has excellent bioavailability and plasma levels correlate well with daily dose; however, plasma levels do not correlate well with clinical efficacy due to the wide interindividual variability (Kornhuber et al., 2007). This interindividual variability could be attributed to variability in renal excretion which takes place via renal tubular organic cation transporter family (OCT) (Busch et al., 1998). Renal excretion of memantine is significantly affected by urine PH (Noetzli and Eap, 2013). Memantine clearance is 7–10 times greater in alkaline (PH 8) than in acidic (PH 5) urine (Freudenthaler et al., 1998). Given that alcohol intake is associated with urine acidity (Eggleton, 1946) while alcohol withdrawal causes urine alkalinity (Sereny et al., 1966), it is possible that the efficacy of memantine is affected by the stage of alcohol use disorder in which it is administered. However, the few studies that have reported efficacy for memantine in reducing alcohol consumption and withdrawal manifestations did not report plasma concentrations or whether alcohol use or early abstinence altered urine PH or renal clearance of memantine. Further studies are required to assess memantine bioavailability in relation to its efficacy for reducing alcohol consumption and withdrawal severity.

In addition to requiring adequate blood concentrations to achieve efficacy, it is equally important for memantine to achieve adequate brain concentrations under drug use conditions. Since levels of memantine in the CSF correlate with plasma levels (Kornhuber and Quack, 1995), alterations in renal excretion is expected to be associated with changes in brain concentrations and hence efficacy of memantine. An additional consideration of the ability to establish a sufficient brain concentration of memantine is the transportation of memantine across the BBB. The BBB keeps strict control over the brain environment through tight junctions between adjacent endothelial cells while allowing specific molecules to be actively transported across the BBB. Memantine is transported across the BBB by organic cation transporter (OCT) (Higuchi et al., 2015; Koepsell et al., 2007; Mehta et al., 2013) in a concentration dependent manner (Higuchi et al., 2015). OCTs also transport several other substances such as nicotine (Cisternino et al., 2013; Tega et al., 2013), codeine (Fischer et al., 2010), oxycodone (Okura et al., 2008), tramadol (Kitamura et al., 2014), and cocaine (Chapy et al., 2014) across the BBB. Since OCTs are saturable, co-administration of memantine and these substances could results in competition over the transporter which, in turn, could lead to reduced brain uptake of memantine (Mehta et al., 2013). The competitive or facilitative interactions between addictive substances and memantine at the BBB might also affect the speed at which these substances cross into the brain. It is known that rapid influx of substances of abuse such as cocaine and alcohol is associated with more rewarding effects (Volkow et al., 2012). Interestingly, a few clinical studies reported increased subjective feelings for cocaine (Collins et al., 2010) and alcohol (Evans et al., 2007; Krupitsky et al., 2007a) in patients pretreated with memantine. Whether memantine causes upregulation of OCTs and facilitates the quick delivery of these drugs into the brain remains to be investigated.

Taken together, pharmacokinetic studies suggest that renal excretion and brain influx of memantine share the same OCT family of transporters with several substances of abuse. This evidence suggests that memantine efficacy could be reduced by the presence or withdrawal of these substances. Furthermore, the possibility that memantine could enhance the rapid passage of specific drugs into the brain and increase rewarding effects should be examined as this may be an obstacle for the use of memantine as a treatment for substance use disorders.

4.3. The efficacy of memantine is related to balancing neuroinflammatory response

For memantine to block NMDA receptors, a minimum dose is needed to achieve a concentration of at least 2–3 μM at the receptor site (Parsons et al., 1999). However, despite that this minimum concentration is not reached at 0.1 mg/kg or lower doses, studies have shown that very low dose memantine (0.02–0.1 mg/kg) could abolish the acquisition of cocaine- (Lin et al., 2011) and morphine- induced conditioned place preference (Chen et al., 2012). Since the concentration of memantine is not reaching the minimum level needed to block NMDA receptors, it is likely that these effect of memantine occur through NMDA-independent mechanisms (Wu et al., 2009). Indeed, in both of the aforementioned studies on conditioned place preference, memantine reversed immune responses that were enhanced by cocaine and morphine (i.e. high proinflammatory cytokines interleukin-6 (IL-6), interleukin 1-β, and brain-derived neurotrophic factor (BDNF) in the medial prefrontal cortex and nucleus accumbens) (Chen et al., 2012; Lin et al., 2011). Based on these observations and the known effects of substances of abuse on neuroinflammatory pathways (Bachtell et al., 2017; Erickson et al., 2019; Hofford et al., 2019), it is plausible to hypothesize that memantine's efficacy is related to an immune modulation mechanism. Studies on low dose memantine and association between immune markers in patients with addiction are scarce. We found only one study using low dose memantine: patients with opioid dependence undergoing methadone maintenance therapy (MMT) were treated with add-on low dose memantine (5 mg/day) in a randomized, double-blind, controlled 12-week study (Chang et al., 2015; Lee et al., 2015); this study was included in our discussion of clinical trials for memantine in opioid use disorder. The results showed that low dose memantine may significantly reduce the required methadone dose and lower plasma tumor necrosis factor (TNF)-α and higher transforming growth factor (TGF)-β1 levels (Lee et al., 2015). In cognitive function, add-on low dose memantine may also improve performance on the Wisconsin Card Sorting Test in opioid dependent patients undergoing MMT (Chang et al., 2015). However, the results did not show significant improvements in heroin use behaviors whether in urine drug toxicology tests or in self-report questionnaires (Chang et al., 2015; Lee et al., 2015). In summary, although few preclinical data showed immune modulatory effects and neuroprotective effects of low dose memantine, translational human studies delineating this aspect of memantine's action are still required.

5. Concluding remarks and future directions

The solid evidence for direct relationships between glutamatergic signaling and the perpetuation of substance use disorders brings glutamate-modulating medications such as memantine to the focus of addiction treatment research. However, the apparent inconsistency between preclinical and clinical results calls for a better understanding of memantine's mechanism of action. Since the effect of substance abuse on glutamatergic homeostasis varies based on the stage of addiction and the particular substance of abuse, it is critically important to examine the utility of memantine with a more precise focus on glutamatergic state (hyperglutamatergic vs hypoglutamatergic) regardless to individual substances and stage of use. This concept brings several challenges such as the variations in glutamate level changes between different brain regions and the difficulty in measuring subtle changes in glutamate in human subjects. However, such a pathophysiology-based treatment approach will bring us closer to an individualized treatment approach with potential imaging biomarkers for medication selection and treatment outcome prediction. Moreover, the pharmacokinetic interactions between memantine and various drugs of abuse at clearance sites and the BBB could possibly explain some of the observed inefficacy and, more importantly, some of the accentuation of subjective drug feelings reported in several studies. Preclinical studies could inform whether concomitant administration of memantine and substances of abuse enhances the transportation of substances of abuse across the BBB and hence increases the reward-like effects of substance use. If indeed memantine alters BBB permeability to certain drugs, we could envision benefiting from this property by modulating BBB carrier to attenuate drug entry to the brain. Finally, the fact that memantine has shown

unique ability to reverse substance-induced neuroinflammatory response highlights the long-ignored role of microglia in addiction and calls for further research to explore non-neuronal mechanisms for drug addiction. Overall, the current, controversial results of clinical trials should not discourage the use of memantine as a substance use disorder treatment; rather, the variety of clinical results calls for further research into memantine's mechanism of action.

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Authors' contributions

All authors reviewed and contributed to the intellectual content of the manuscript and approved the final version to be published. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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References

Abulseoud, O.A., Camsari, U.M., Ruby, C.L., Kasasbeh, A., Choi, S., Choi, D.S., 2014. Attenuation of ethanol withdrawal by ceftriaxone-induced upregulation of glutamate transporter EAAT2. Neuropsychopharmacology 39, 1674–1684.

Abulseoud, O.A., Ross, T.J., Nam, H.W., Caparelli, E.C., Tennekoon, M., Schleyer, B., Castillo, J., Fedota, J., Gu, H., Yang, Y., Stein, E., 2020. Short-term nicotine deprivation alters dorsal anterior cingulate glutamate concentration and concomitant cingulate-cortical functional connectivity. Neuropsychopharmacology. 45 (11), 1920–1930.

Alaghband, Y., Marshall, J.F., 2013. Common influences of non-competitive NMDA receptor antagonists on the consolidation and reconsolidation of cocaine-cue memory. Psychopharmacology 226, 707–719.

Alaghband, Y., O'Dell, S.J., Azarnia, S., Khalaj, A.J., Guzowski, J.F., Marshall, J.F., 2014. Retrieval-induced NMDA receptor-dependent Arc expression in two models of cocaine-cue memory. Neurobiol. Learn. Mem. 116, 79–89.

Alasmari, F., Goodwani, S., McCullumsmith, R.E., Sari, Y., 2018. Role of glutamatergic system and mesocorticolimbic circuits in alcohol dependence. Prog. Neurobiol. 171, 32–49.

Alaux-Cantin, S., Buttolo, R., Houchi, H., Jeanblanc, J., Naassila, M., 2015. Memantine reduces alcohol drinking but not relapse in alcohol-dependent rats. Addict. Biol. 20, 890–901.

Albanese, A.P., 2012. Management of alcohol abuse. Clin. Liver Dis. 16, 737–762.

Alviar, M.J., Hale, T., Dungca, M., 2016. Pharmacologic interventions for treating phantom limb pain. Cochrane Database Syst. Rev. 10, CD006380.

Amidfar, M., Woelfer, M., Reus, G.Z., Quevedo, J., Walter, M., Kim, Y.K., 2019. The role of NMDA receptor in neurobiology and treatment of major depressive disorder: evidence from translational research. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 94, 109668.

Bachtell, R.K., Jones, J.D., Heinzerling, K.G., Beardsley, P.M., Comer, S.D., 2017. Glial and neuroinflammatory targets for treating substance use disorders. Drug Alcohol Depend. 180, 156–170.

Back, S.E., Payne, R.L., Simpson, A.N., Brady, K.T., 2010. Gender and prescription opioids: findings from the National Survey on Drug Use and Health. Addict. Behav. 35, 1001–1007.

Bespalov, A.Y., Dravolina, O.A., Zvartau, E.E., Beardsley, P.M., Balster, R.L., 2000a. Effects of NMDA receptor antagonists on cocaine-conditioned motor activity in rats. Eur. J. Pharmacol. 390, 303–311.

Bespalov, A.Y., Zvartau, E.E., Balster, R.L., Beardsley, P.M., 2000b. Effects of N-methyl-D-aspartate receptor antagonists on reinstatement of cocaine-seeking behavior by priming injections of cocaine or exposures to cocaine-associated cues in rats. Behav. Pharmacol. 11, 37–44.

Bienkowski, P., Krzascik, P., Koros, E., Kostowski, W., Scinska, A., Danysz, W., 2001. Effects of a novel uncompetitive NMDA receptor antagonist, MRZ 2/579 on ethanol self-administration and ethanol withdrawal seizures in the rat. Eur. J. Pharmacol. 413, 81–89.

Bisaga, A., Evans, S.M., 2004. Acute effects of memantine in combination with alcohol in moderate drinkers. Psychopharmacology 172, 16–24.

Bisaga, A., Aharonovich, E., Cheng, W.Y., Levin, F.R., Mariani, J.J., Raby, W.N., Nunes, E.V., 2010. A placebo-controlled trial of memantine for cocaine dependence with high-value voucher incentives during a pre-randomization lead-in period. Drug Alcohol Depend. 111, 97–104.

Bisaga, A., Sullivan, M.A., Cheng, W.Y., Carpenter, K.M., Mariani, J.J., Levin, F.R., Raby, W.N., Nunes, E.V., 2011. A placebo controlled trial of memantine as an adjunct to oral naltrexone for opioid dependence. Drug Alcohol Depend. 119, e23–e29.

Bisaga, A., Sullivan, M.A., Glass, A., Mishlen, K., Carpenter, K.M., Mariani, J.J., Levin, F. R., Nunes, E.V., 2014. A placebo-controlled trial of memantine as an adjunct to injectable extended-release naltrexone for opioid dependence. J. Subst. Abus. Treat. 46, 546–552.

Blokhina, E.A., Sukhotina, I.A., Bespalov, A.Y., 2000. Pretreatment with morphine potentiates naloxone-conditioned place aversion in mice: effects of NMDA receptor antagonists. Eur. J. Pharmacol. 406, 227–232.

Blokhina, E.A., Kashkin, V.A., Zvartau, E.E., Danysz, W., Bespalov, A.Y., 2005. Effects of nicotinic and NMDA receptor channel blockers on intravenous cocaine and nicotine self-administration in mice. Eur. Neuropsychopharmacol. 15, 219–225.

Blumenthal, D.E., Malemud, C.J., 2016. Recent strategies for drug development in fibromyalgia syndrome. Expert. Rev. Neurother. 16, 1407–1411.

Brackett, R.L., Pouw, B., Blyden, J.F., Nour, M., Matsumoto, R.R., 2000. Prevention of cocaine-induced convulsions and lethality in mice: effectiveness of targeting different sites on the NMDA receptor complex. Neuropharmacology 39, 407–418.

Busch, A.E., Karbach, U., Miska, D., Gorboulev, V., Akhoundova, A., Volk, C., Arndt, P., Ulzheimer, J.C., Sonders, M.S., Baumann, C., Waldegger, S., Lang, F., Koepsell, H., 1998. Human neurons express the polyspecific cation transporter hOCT2, which translocates monoamine neurotransmitters, amantadine, and memantine. Mol. Pharmacol. 54, 342–352.

Caddy, C., Amit, B.H., McCloud, T.L., Rendell, J.M., Furukawa, T.A., McShane, R., Hawton, K., Cipriani, A., 2015. Ketamine and other glutamate receptor modulators for depression in adults. Cochrane Database Syst. Rev. 9, CD011612.

Chang, Y.H., Chen, S.L., Lee, S.Y., Chen, P.S., Wang, T.Y., Lee, I.H., Chen, K.C., Yang, Y. K., Hong, J.S., Lu, R.B., 2015. Low-dose add-on memantine treatment may improve cognitive performance and self-reported health conditions in opioid-dependent patients undergoing methadone-maintenance-therapy. Sci. Rep. 5, 9708.

Chapy, H., Smirnova, M., Andre, P., Schlatter, J., Chiadmi, F., Couraud, P.O., Scherrmann, J.M., Decleves, X., Cisternino, S., 2014. Carrier-mediated cocaine transport at the blood-brain barrier as a putative mechanism in addiction liability. Int. J. Neuropsychopharmacol. 18.

Chen, H.S., Lipton, S.A., 2005. Pharmacological implications of two distinct mechanisms of interaction of memantine with N-methyl-D-aspartate-gated channels. J. Pharmacol. Exp. Ther. 314, 961–971.

Chen, S.L., Tao, P.L., Chu, C.H., Chen, S.H., Wu, H.E., Tseng, L.F., Hong, J.S., Lu, R.B., 2012. Low-dose memantine attenuated morphine addictive behavior through its anti-inflammation and neurotrophic effects in rats. J. NeuroImmune Pharmacol. 7, 444–453.

Chen, Y., Evola, M., Young, A.M., 2013. Memantine and dizocilpine interactions with antinociceptive or discriminative stimulus effects of morphine in rats after acute or chronic treatment with morphine. Psychopharmacology 225, 187–199.

Cisternino, S., Chapy, H., Andre, P., Smirnova, M., Debray, M., Scherrmann, J.M., 2013. Coexistence of passive and proton antiporter-mediated processes in nicotine transport at the mouse blood-brain barrier. AAPS J. 15, 299–307.

Collins, E.D., Vosburg, S.K., Ward, A.S., Haney, M., Foltin, R.W., 2006. Memantine increases cardiovascular but not behavioral effects of cocaine in methadone-maintained humans. Pharmacol. Biochem. Behav. 83, 47–55.

Collins, E.D., Vosberg, S.K., Ward, A.S., Haney, M., Foltin, R.W., 2007. The effects of acute pretreatment with high-dose memantine on the cardiovascular and behavioral effects of cocaine in humans. Exp. Clin. Psychopharmacol. 15, 228–237.

Collins, S., Sigtermans, M.J., Dahan, A., Zuurmond, W.W., Perez, R.S., 2010. NMDA receptor antagonists for the treatment of neuropathic pain. Pain Med. 11, 1726–1742.

Comer, S.D., Sullivan, M.A., 2007. Memantine produces modest reductions in heroin-induced subjective responses in human research volunteers. Psychopharmacology 193, 235–245.

Di Iorio, G., Baroni, G., Lorusso, M., Montemitro, C., Spano, M.C., di Giannantonio, M., 2017. Efficacy of Memantine in schizophrenic patients: a systematic review. J. Amino Acids 2017, 7021071.

Dravolina, O.A., Belozertseva, I.V., Sukhotina, I.A., Bespalov, A.Y., 1999. Morphine tolerance and dependence in mice with history of repeated exposures to NMDA receptor channel blockers. Pharmacol. Biochem. Behav. 63, 613–619.
Eggleton, M.G., 1946. Urine acidity in alcohol diuresis in man. J. Physiol. 104, 312–320.
Erickson, E.K., Grantham, E.K., Warden, A.S., Harris, R.A., 2019. Neuroimmune signaling in alcohol use disorder. Pharmacol. Biochem. Behav. 177, 34–60.
Escher, T., Call, S.B., Blaha, C.D., Mittleman, G., 2006. Behavioral effects of aminoadamantane class NMDA receptor antagonists on schedule-induced alcohol and self-administration of water in mice. Psychopharmacology 187, 424–434.
Evans, S.M., Levin, F.R., Brooks, D.J., Garawi, F., 2007. A pilot double-blind treatment trial of memantine for alcohol dependence. Alcohol. Clin. Exp. Res. 31, 775–782.
Fischer, W., Bernhagen, J., Neubert, R.H., Brandsch, M., 2010. Uptake of codeine into intestinal epithelial (Caco-2) and brain endothelial (RBE4) cells. Eur. J. Pharm. Sci. 41, 31–42.
Forray, A., Sofuoglu, M., 2014. Future pharmacological treatments for substance use disorders. Br. J. Clin. Pharmacol. 77, 382–400.
Freudenthaler, S., Meineke, I., Schreeb, K.H., Boakye, E., Gundert-Remy, U., Gleiter, C. H., 1998. Influence of urine pH and urinary flow on the renal excretion of memantine. Br. J. Clin. Pharmacol. 46, 541–546.
Gass, J.T., Olive, M.F., 2008. Glutamatergic substrates of drug addiction and alcoholism. Biochem. Pharmacol. 75, 218–265.
Goldstein, R.Z., Volkow, N.D., 2002. Drug addiction and its underlying neurobiological basis: neuroimaging evidence for the involvement of the frontal cortex. Am. J. Psychiatry 159, 1642–1652.
Gonzalez, G., DiGirolamo, G., Romero-Gonzalez, M., Smelson, D., Ziedonis, D., Kolodziej, M., 2015. Memantine improves buprenorphine/naloxone treatment for opioid dependent young adults. Drug Alcohol Depend. 156, 243–253.
Harris, A.C., Rothwell, P.E., Gewirtz, J.C., 2008. Effects of the NMDA receptor antagonist memantine on the expression and development of acute opiate dependence as assessed by withdrawal-potentiated startle and hyperalgesia. Psychopharmacology 196, 649–660.
Higuchi, K., Kitamura, A., Okura, T., Deguchi, Y., 2015. Memantine transport by a proton-coupled organic cation antiporter in hCMEC/D3 cells, an in vitro human blood-brain barrier model. Drug Metab. Pharmacokinet 30, 182–187.
Hoffmann, J., Charles, A., 2018. Glutamate and its receptors as therapeutic targets for migraine. Neurotherapeutics 15, 361–370.
Hofford, R.S., Russo, S.J., Kiraly, D.D., 2019. Neuroimmune mechanisms of psychostimulant and opioid use disorders. Eur. J. Neurosci. 50, 2562–2573.
Holter, S.M., Danysz, W., Spanagel, R., 1996. Evidence for alcohol anti-craving properties of memantine. Eur. J. Pharmacol. 314, R1–R2.
Hosseinzadeh, H., Imenshahidi, M., Hosseini, M., Razavi, B.M., 2012. Effect of linalool on morphine tolerance and dependence in mice. Phytother. Res. 26, 1399–1404.
Huang, L., Bocek, M., Jordan, J.K., Sheehan, A.H., 2014. Memantine for the prevention of primary headache disorders. Ann. Pharmacother. 48, 1507–1511.
Hwa, L.S., Nathanson, A.J., Shimamoto, A., Tayeh, J.K., Wilens, A.R., Holly, E.N., Newman, E.L., DeBold, J.F., Miczek, K.A., 2015. Aggression and increased glutamate in the mPFC during withdrawal from intermittent alcohol in outbred mice. Psychopharmacology 232, 2889–2902.
Idrus, N.M., McGough, N.N., Spinetta, M.J., Thomas, J.D., Riley, E.P., 2011. The effects of a single memantine treatment on behavioral alterations associated with binge alcohol exposure in neonatal rats. Neurotoxicol. Teratol. 33, 444–450.
Idrus, N.M., McGough, N.N., Riley, E.P., Thomas, J.D., 2014. Administration of memantine during withdrawal mitigates overactivity and spatial learning impairments associated with neonatal alcohol exposure in rats. Alcohol. Clin. Exp. Res. 38, 529–537.
Indave, B.I., Minozzi, S., Pani, P.P., Amato, L., 2016. Antipsychotic medications for cocaine dependence. Cochrane Database Syst. Rev. 3, CD006306.
Jackson, A., Nesic, J., Groombridge, C., Clowry, O., Rusted, J., Duka, T., 2009. Differential involvement of glutamatergic mechanisms in the cognitive and subjective effects of smoking. Neuropsychopharmacology 34, 257–265.
Jaso, B.A., Niciu, M.J., Iadarola, N.D., Lally, N., Richards, E.M., Park, M., Ballard, E.D., Nugent, A.C., Machado-Vieira, R., Zarate, C.A., 2017. Therapeutic modulation of glutamate receptors in major depressive disorder. Curr. Neuropharmacol. 15, 57–70.
Jeanblanc, J., Coune, F., Botia, B., Naassila, M., 2014. Brain-derived neurotrophic factor mediates the suppression of alcohol self-administration by memantine. Addict. Biol. 19, 758–769.
Jonas, D.E., Amick, H.R., Feltner, C., Bobashev, G., Thomas, K., Wines, R., Kim, M.M., Shanahan, E., Gass, C.E., Rowe, C.J., Garbutt, J.C., 2014. Pharmacotherapy for adults with alcohol use disorders in outpatient settings: a systematic review and meta-analysis. JAMA 311, 1889–1900.
Kalivas, P., 2009. The glutamate homeostasis hypothesis of addiction. Nat. Rev. Neurosci. 10, 561–572.
Kalivas, P., Volkow, N., 2011. New medications for drug addiction hiding in glutamatergic neuroplasticity. Mol. Psychiatry 16, 974–986.
Kalivas, P.W., Lalumiere, R.T., Knackstedt, L., Shen, H., 2009. Glutamate transmission in addiction. Neuropharmacology 56 (Suppl. 1), 169–173.
Kishi, T., Matsunaga, S., Iwata, N., 2017. A meta-analysis of Memantine for depression. J. Alzheimers Dis. 57, 113–121.
Kitamura, A., Higuchi, K., Okura, T., Deguchi, Y., 2014. Transport characteristics of tramadol in the blood-brain barrier. J. Pharm. Sci. 103, 3335–3341.
Koepsell, H., Lips, K., Volk, C., 2007. Polyspecific organic cation transporters: structure, function, physiological roles, and biopharmaceutical implications. Pharm. Res. 24, 1227–1251.
Koob, G., Volkow, N., 2010. Neurocircuitry of addiction. Neuropsychopharmacol 35, 217–238.
Kornhuber, J., Quack, G., 1995. Cerebrospinal fluid and serum concentrations of the N-methyl-D-aspartate (NMDA) receptor antagonist memantine in man. Neurosci. Lett. 195, 137–139.
Kornhuber, J., Kennepohl, E.M., Bleich, S., Wiltfang, J., Kraus, T., Reulbach, U., Meineke, I., 2007. Memantine pharmacotherapy: a naturalistic study using a population pharmacokinetic approach. Clin. Pharmacokinet. 46, 599–612.
Kotlinska, J., 2001. NMDA antagonists inhibit the development of ethanol dependence in rats. Pol. J. Pharmacol. 53, 47–50.
Kotlinska, J., Biala, G., 2000. Memantine and ACPC affect conditioned place preference induced by cocaine in rats. Pol. J. Pharmacol. 52, 179–185.
Kotlinska, J., Bochenski, M., 2008. The influence of various glutamate receptors antagonists on anxiety-like effect of ethanol withdrawal in a plus-maze test in rats. Eur. J. Pharmacol. 598, 57–63.
Krishnan-Sarin, S., O'Malley, S.S., Franco, N., Cavallo, D.A., Morean, M., Shi, J., Pittman, B., Krystal, J.H., 2015. N-methyl-D-aspartate receptor antagonism has differential effects on alcohol craving and drinking in heavy drinkers. Alcohol. Clin. Exp. Res. 39, 300–307.
Krupitsky, E.M., Masalov, D.V., Burakov, A.M., Didenko, T.Y., Romanova, T.N., Bespalov, A.Y., Neznanova, O.N., Grinenko, N.I., Grinenko, A.Y., Slavina, T.Y., Tcheremissine, O.V., Zvartau, E.E., 2002. A pilot study of Memantine effects on protracted withdrawal (syndrome of Anhedonia) in heroin addicts. Addict. Disord. Treat. 1.
Krupitsky, E.M., Neznanova, O., Masalov, D., Burakov, A.M., Didenko, T., Romanova, T., Tsoy, M., Bespalov, A., Slavina, T.Y., Grinenko, A.A., Petrakis, I.L., Pittman, B., Gueorguieva, R., Zvartau, E.E., Krystal, J.H., 2007a. Effect of memantine on cue-induced alcohol craving in recovering alcohol-dependent patients. Am. J. Psychiatry 164, 519–523.
Krupitsky, E.M., Rudenko, A.A., Burakov, A.M., Slavina, T.Y., Grinenko, A.A., Pittman, B., Gueorguieva, R., Petrakis, I.L., Zvartau, E.E., Krystal, J.H., 2007b. Antiglutamatergic strategies for ethanol detoxification: comparison with placebo and diazepam. Alcohol. Clin. Exp. Res. 31, 604–611.
Kurian, R., Raza, K., Shanthanna, H., 2019. A systematic review and meta-analysis of memantine for the prevention or treatment of chronic pain. Eur. J. Pain 23, 1234–1250.
Lee, S.Y., Chen, S.L., Chang, Y.H., Chen, P.S., Huang, S.Y., Tzeng, N.S., Wang, L.J., Lee, I. H., Wang, T.Y., Chen, K.C., Yang, Y.K., Hong, J.S., Lu, R.B., 2015. Low-dose memantine attenuated methadone dose in opioid-dependent patients: a 12-week double-blind randomized controlled trial. Sci. Rep. 5, 10140.
Lin, K.Y., Cherng, C.G., Yang, F.R., Lin, L.C., Lu, R.B., Yu, L., 2011. Memantine abolishes the formation of cocaine-induced conditioned place preference possibly via its IL-6-modulating effect in medial prefrontal cortex. Behav. Brain Res. 220, 126–131.
Littlejohn, G., Guymer, E., 2017. Modulation of NMDA receptor activity in fibromyalgia. Biomedicines 5.
Lluch, J., Rodriguez-Arias, M., Aguilar, M.A., Minarro, J., 2005. Role of dopamine and glutamate receptors in cocaine-induced social effects in isolated and grouped male OF1 mice. Pharmacol. Biochem. Behav. 82, 478–487.
Loy, B.M., Britt, R.B., Brown, J.N., 2016. Memantine for the treatment of phantom limb pain: a systematic review. J. Pain Palliat. Care Pharmacother. 30, 276–283.
Lukoyanov, N.V., Paula-Barbosa, M.M., 2001. Memantine, but not dizocilpine, ameliorates cognitive deficits in adult rats withdrawn from chronic ingestion of alcohol. Neurosci. Lett. 309, 45–48.
Lund, I.O., Skurtveit, S., Engeland, A., Furu, K., Ravndal, E., Handal, M., 2013. Prescription drug use among pregnant women in opioid Maintenance Treatment. Addiction 108, 367–376.
Maldonado, C., Rodriguez-Arias, M., Castillo, A., Aguilar, M.A., Minarro, J., 2007. Effect of memantine and CNQX in the acquisition, expression and reinstatement of cocaine-induced conditioned place preference. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 31, 932–939.
Malpass, G.E., Williams, H.L., McMillen, B.A., 2010. Effects of the non-competitive NMDA receptor antagonist memantine on the volitional consumption of ethanol by alcohol-preferring rats. Basic Clin. Pharmacol. Toxicol. 106, 435–444.
Marinova, Z., Chuang, D.M., Fineberg, N., 2017. Glutamate-modulating drugs as a potential therapeutic strategy in obsessive-compulsive disorder. Curr. Neuropharmacol. 15, 977–995.
Marquez, J., Campos-Sandoval, J.A., Penalver, A., Mates, J.M., Segura, J.A., Blanco, E., Alonso, F.J., de Fonseca, F.R., 2017. Glutamate and brain Glutaminases in drug addiction. Neurochem. Res. 42, 846–857.
Martins, S.S., Sarvet, A., Santaella-Tenorio, J., Saha, T., Grant, B.F., Hasin, D.S., 2017. Changes in US lifetime heroin use and heroin use disorder: prevalence from the 2001–2002 to 2012–2013 National Epidemiologic Survey on alcohol and related conditions. JAMA Psychiatry 74, 445–455.
Medvedev, I.O., Dravolina, O.A., Bespalov, A.Y., 1998. Effects of N-methyl-D-aspartate receptor antagonists on discriminative stimulus effects of naloxone in morphine-dependent rats using the Y-maze drug discrimination paradigm. J. Pharmacol. Exp. Ther. 286, 1260–1268.
Mehta, D.C., Short, J.L., Nicolazzo, J.A., 2013. Memantine transport across the mouse blood-brain barrier is mediated by a cationic influx H+ antiporter. Mol. Pharm. 10, 4491–4498.
Miguéns, M., Del Olmo, N., Higuera-Matas, A., et al., 2008. Glutamate and aspartate levels in the nucleus accumbens during cocaine self-administration and extinction: a time course microdialysis study. Psychopharmacology 196, 303–313.
Modarresi, A., Chaibakhsh, S., Koulaeinejad, N., Koupaei, S.R., 2019. A systematic review and meta-analysis: Memantine augmentation in moderate to severe obsessive-compulsive disorder. Psychiatry Res. 282, 112602.

Moher, D., Jadad, A.R., Nichol, G., Penman, M., Tugwell, P., Walsh, S., 1995. Assessing the quality of randomized controlled trials: an annotated bibliography of scales and checklists. Control. Clin. Trials 16, 62–73.
Muhonen, L.H., Lahti, J., Sinclair, D., Lonnqvist, J., Alho, H., 2008a. Treatment of alcohol dependence in patients with co-morbid major depressive disorder–predictors for the outcomes with memantine and escitalopram medication. Subst Abuse Treat. Prev. Policy 3, 20.
Muhonen, L.H., Lonnqvist, J., Juva, K., Alho, H., 2008b. Double-blind, randomized comparison of memantine and escitalopram for the treatment of major depressive disorder comorbid with alcohol dependence. J. Clin. Psychiatry 69, 392–399.
Muller, C.A., Geisel, O., Banas, R., Heinz, A., 2014. Current pharmacological treatment approaches for alcohol dependence. Expert. Opin. Pharmacother. 15, 471–481.
Murray, C.J., Vos, T., Lozano, R., Naghavi, M., Flaxman, A.D., Michaud, C., Ezzati, M., Shibuya, K., Salomon, J.A., Abdalla, S., Aboyans, V., Abraham, J., Ackerman, I., Aggarwal, R., Ahn, S.Y., Ali, M.K., Alvarado, M., Anderson, H.R., Anderson, L.M., Andrews, K.G., Atkinson, C., Baddour, L.M., Bahalim, A.N., Barker-Collo, S., Barrero, L.H., Bartels, D.H., Basanez, M.G., Baxter, A., Bell, M.L., Benjamin, E.J., Bennett, D., Bernabe, E., Bhalla, K., Bhandari, B., Bikbov, B., Bin Abdulhak, A., Birbeck, G., Black, J.A., Blencowe, H., Blore, J.D., Blyth, F., Bolliger, I., Bonaventure, A., Boufous, S., Bourne, R., Boussinesq, M., Braithwaite, T., Brayne, C., Bridgett, L., Brooker, S., Brooks, P., Brugha, T.S., Bryan-Hancock, C., Bucello, C., Buchbinder, R., Buckle, G., Budke, C.M., Burch, M., Burney, P., Burstein, R., Calabria, B., Campbell, B., Canter, C.E., Carabin, H., Carapetis, J., Carmona, L., Cella, C., Charlson, F., Chen, H., Cheng, A.T., Chou, D., Chugh, S.S., Coffeng, L.E., Colan, S.D., Colquhoun, S., Colson, K.E., Condon, J., Connor, M.D., Cooper, L.T., Corriere, M., Cortinovis, M., de Vaccaro, K.C., Couser, W., Cowie, B.C., Criqui, M.H., Cross, M., Dabhadkar, K.C., Dahiya, M., Dahodwala, N., Damsere-Derry, J., Danaei, G., Davis, A., De Leo, D., Degenhardt, L., Dellavalle, R., Delossantos, A., Denenberg, J., Derrett, S., Des Jarlais, D.C., Dharmaratne, S.D., Dherani, M., Diaz-Torne, C., Dolk, H., Dorsey, E.R., Driscoll, T., Duber, H., Ebel, B., Edmond, K., Elbaz, A., Ali, S.E., Erskine, H., Erwin, P.J., Espindola, P., Ewoigbokhan, S.E., Farzadfar, F., Feigin, V., Felson, D.T., Ferrari, A., Ferri, C.P., Fevre, E.M., Finucane, M.M., Flaxman, S., Flood, L., Foreman, K., Forouzanfar, M.H., Fowkes, F. G., Fransen, M., Freeman, M.K., Gabbe, B.J., Gabriel, S.E., Gakidou, E., Ganatra, H. A., Garcia, B., Gaspari, F., Gillum, R.F., Gmel, G., Gonzalez-Medina, D., Gosselin, R., Grainger, R., Grant, B., Groeger, J., Guillemin, F., Gunnell, D., Gupta, R., Haagsma, J., Hagan, H., Halasa, Y.A., Hall, W., Haring, D., Haro, J.M., Harrison, J.E., Havmoeller, R., Hay, R.J., Higashi, H., Hill, C., Hoen, B., Hoffman, H., Hotez, P.J., Hoy, D., Huang, J.J., Ibeanusi, S.E., Jacobsen, K.H., James, S.L., Jarvis, D., Jasrasaria, R., Jayaraman, S., Johns, N., Jonas, J.B., Karthikeyan, G., Kassebaum, N., Kawakami, N., Keren, A., Khoo, J.P., King, C.H., Knowlton, L.M., Kobusingye, O., Koranteng, A., Krishnamurthi, R., Laden, F., Lalloo, R., Laslett, L.L., Lathlean, T., Leasher, J.L., Lee, Y.Y., Leigh, J., Levinson, D., Lim, S.S., Limb, E., Lin, J.K., Lipnick, M., Lipshultz, S.E., Liu, W., Loane, M., Ohno, S.L., Lyons, R., Mabweijano, J., MF, MacIntyre, Malekzadeh, R., Mallinger, L., Manivannan, S., Marcenes, W., March, L., Margolis, D.J., Marks, G.B., Marks, R., Matsumori, A., Matzopoulos, R., Mayosi, B.M., McAnulty, J.H., McDermott, M.M., McGill, N., McGrath, J., Medina-Mora, M.E., Meltzer, M., Mensah, G.A., Merriman, T.R., Meyer, A.C., Miglioli, V., Miller, M., Miller, T.R., Mitchell, P.B., Mock, C., Mocumbi, A.O., Moffitt, T.E., Mokdad, A.A., Monasta, L., Montico, M., Moradi-Lakeh, M., Moran, A., Morawska, L., Mori, R., Murdoch, M.E., Mwaniki, M.K., Naidoo, K., Nair, M.N., Naldi, L., Narayan, K.M., Nelson, P.K., Nelson, R.G., Nevitt, M.C., Newton, C.R., Nolte, S., Norman, P., Norman, R., O'Donnell, M., O'Hanlon, S., Olives, C., Omer, S.B., Ortblad, K., Osborne, R., Ozgediz, D., Page, A., Pahari, B., Pandian, J.D., Rivero, A.P., Patten, S.B., Pearce, N., Padilla, R.P., Perez-Ruiz, F., Perico, N., Pesudovs, K., Phillips, D., Phillips, M.R., Pierce, K., Pion, S., Polanczyk, G.V., Polinder, S., Pope 3rd, C.A., Popova, S., Porrini, E., Pourmalek, F., Prince, M., Pullan, R.L., Ramaiah, K.D., Ranganathan, D., Razavi, H., Regan, M., Rehm, J.T., Rein, D.B., Remuzzi, G., Richardson, K., Rivara, F.P., Roberts, T., Robinson, C., De Leon, F.R., Ronfani, L., Room, R., Rosenfeld, L.C., Rushton, L., Sacco, R.L., Saha, S., Sampson, U., Sanchez-Riera, L., Sanman, E., Schwebel, D.C., Scott, J.G., Segui-Gomez, M., Shahraz, S., Shepard, D.S., Shin, H., Shivakoti, R., Singh, D., Singh, G.M., Singh, J.A., Singleton, J., Sleet, D.A., Sliwa, K., Smith, E., Smith, J.L., Stapelberg, N.J., Steer, A., Steiner, T., Stolk, W.A., Stovner, L.J., Sudfeld, C., Syed, S., Tamburlini, G., Tavakkoli, M., Taylor, H.R., Taylor, J.A., Taylor, W.J., Thomas, B., Thomson, W.M., Thurston, G.D., Tleyjeh, I.M., Tonelli, M., Towbin, J.A., Truelsen, T., Tsilimbaris, M.K., Ubeda, C., Undurraga, E.A., van der Werf, M.J., van Os, J., Vavilala, M.S., Venketasubramanian, N., Wang, M., Wang, W., Watt, K., Weatherall, D.J., Weinstock, M.A., Weintraub, R., Weisskopf, M.G., Weissman, M.M., White, R.A., Whiteford, H., Wiebe, N., Wiersma, S.T., Wilkinson, J. D., Williams, H.C., Williams, S.R., Witt, E., Wolfe, F., Woolf, A.D., Wulf, S., Yeh, P.H., Zaidi, A.K., Zheng, Z.J., Zonies, D., Lopez, A.D., MA, AlMazroa, Memish, Z.A., 2012. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 380, 2197–2223.
Newman, E.L., Chu, A., Bahamon, B., Takahashi, A., Debold, J.F., Miczek, K.A., 2012. NMDA receptor antagonism: escalation of aggressive behavior in alcohol-drinking mice. Psychopharmacology 224, 167–177.
Newman, J.L., Beardsley, P.M., 2006. Effects of memantine, haloperidol, and cocaine on primary and conditioned reinforcement associated with cocaine in rhesus monkeys. Psychopharmacology 185, 142–149.
Noetzli, M., Eap, C.B., 2013. Pharmacodynamic, pharmacokinetic and pharmacogenetic aspects of drugs used in the treatment of Alzheimer's disease. Clin. Pharmacokinet. 52, 225–241.
Oberlin, B.G., Bristow, R.E., Heighton, M.E., Grahame, N.J., 2010. Pharmacologic dissociation between impulsivity and alcohol drinking in high alcohol preferring mice. Alcohol. Clin. Exp. Res. 34, 1363–1375.
O'Connor, R.M., Moloney, R.D., Glennon, J., Vlachou, S., Cryan, J.F., 2015. Enhancing glutamatergic transmission during adolescence reverses early-life stress-induced deficits in the rewarding effects of cocaine in rats. Neuropharmacology 99, 168–176.
Okura, T., Hattori, A., Takano, Y., Sato, T., Hammarlund-Udenaes, M., Terasaki, T., Deguchi, Y., 2008. Involvement of the pyrilamine transporter, a putative organic cation transporter, in blood-brain barrier transport of oxycodone. Drug Metab. Dispos. 36, 2005–2013.
Olive, M.F., Cleva, R.M., Kalivas, P.W., Malcolm, R.J., 2012a. Glutamatergic medications for the treatment of drug and behavioral addictions. Pharmacol. Biochem. Behav. 100, 801–810.
Olive, M.F.C.R., Kalivas, P.W., Malcolm, R.J., 2012b. Glutamatergic medications for the treatment of drug and behavioral addictions. Pharmacol. Biochem. Behav. 100, 801–810.
Parsons, C.G., Danysz, W., Quack, G., 1999. Memantine is a clinically well tolerated N-methyl-D-aspartate (NMDA) receptor antagonist–a review of preclinical data. Neuropharmacology 38, 735–767.
Piasecki, J., Koros, E., Dyr, W., Kostowski, W., Danysz, W., Bienkowski, P., 1998. Ethanol-reinforced behaviour in the rat: effects of uncompetitive NMDA receptor antagonist, memantine. Eur. J. Pharmacol. 354, 135–143.
Pickering, G., Morel, V., 2018. Memantine for the treatment of general neuropathic pain: a narrative review. Fundam. Clin. Pharmacol. 32, 4–13.
Popik, P., Skolnick, P., 1996. The NMDA antagonist memantine blocks the expression and maintenance of morphine dependence. Pharmacol. Biochem. Behav. 53, 791–797.
Rehm, J., Mathers, C., Popova, S., Thavorncharoensap, M., Teerawattananon, Y., Patra, J., 2009. Global burden of disease and injury and economic cost attributable to alcohol use and alcohol-use disorders. Lancet 373, 2223–2233.
Reissner, K.J., Kalivas, P.W., 2010. Using glutamate homeostasis as a target for treating addictive disorders. Behav. Pharmacol. 21, 514–522.
Repantis, D., Laisney, O., Heuser, I., 2010. Acetylcholinesterase inhibitors and memantine for neuroenhancement in healthy individuals: a systematic review. Pharmacol. Res. 61, 473–481.
Rezvani, A.H., Lawrence, A.J., Arolfo, M.P., Levin, E.D., Overstreet, D.H., 2012. Novel medication targets for the treatment of alcoholism: preclinical studies. Recent Pat. CNS Drug Discov. 7, 151–162.
Roerecke, M., Rehm, J., 2013. Alcohol use disorders and mortality: a systematic review and meta-analysis. Addiction 108, 1562–1578.
Rogawski, M.A., Wenk, G.L., 2003. The neuropharmacological basis for the use of memantine in the treatment of Alzheimer's disease. CNS Drug. Rev. 9, 275–308.
Samokhvalov, A.V., Popova, S., Room, R., Ramonas, M., Rehm, J., 2010. Disability associated with alcohol abuse and dependence. Alcohol. Clin. Exp. Res. 34, 1871–1878.
Scofield, M.D., Heinsbroek, J.A., Gipson, C.D., Kupchik, Y.M., Spencer, S., Smith, A.C., Roberts-Wolfe, D., Kalivas, P.W., 2016. The nucleus Accumbens: mechanisms of addiction across drug classes reflect the importance of glutamate homeostasis. Pharmacol. Rev. 68, 816–871.
Semenova, S., Danysz, W., Bespalov, A., 1999. Low-affinity NMDA receptor channel blockers inhibit acquisition of intravenous morphine self-administration in naive mice. Eur. J. Pharmacol. 378, 1–8.
Sereny, G., Rapoport, A., Husdan, H., 1966. The effect of alcohol withdrawal on electrolyte and acid-base balance. Metabolism 15, 896–904.
Serra, G., Demontis, F., Serra, F., De Chiara, L., Spoto, A., Girardi, P., Vidotto, G., Serra, G., 2014. Memantine: new prospective in bipolar disorder treatment. World J. Psychiatry 4, 80–90.
Spencer, S., Scofield, M., Kalivas, P.W., 2016. The good and bad news about glutamate in drug addiction. J. Psychopharmacol. 30 (11), 1095–1098.
Stepanyan, T.D., Farook, J.M., Kowalski, A., Kaplan, E., Barron, S., Littleton, J.M., 2008. Alcohol withdrawal-induced hippocampal neurotoxicity in vitro and seizures in vivo are both reduced by memantine. Alcohol. Clin. Exp. Res. 32, 2128–2135.
Steven Rosenzweig Haugbøl, B.E., Ulrichsen, Jakob, 2005. Upregulation of glutamate receptor subtypes during alcohol withdrawal in rats. Alcohol Alcohol. 40, 89–95.
Sukhotina, I.A., Bespalov, A.Y., 2000. Effects of the NMDA receptor channel blockers memantine and MRZ 2/579 on morphine withdrawal-facilitated aggression in mice. Psychopharmacology 149, 345–350.
Swift, R., 2010. Medications acting on the dopaminergic system in the treatment of alcoholic patients. Curr. Pharm. Des. 16, 2136–2140.
Tega, Y., Akanuma, S., Kubo, Y., Terasaki, T., Hosoya, K., 2013. Blood-to-brain influx transport of nicotine at the rat blood-brain barrier: involvement of a pyrilamine-sensitive organic cation transport process. Neurochem. Int. 62, 173–181.
Tetrault, J.M., Butner, J.L., 2015. Non-medical prescription opioid use and prescription opioid use disorder: a review. Yale J. Biol. Med. 88, 227–233.
Thuerauf, N., Lunkenheimer, J., Lunkenheimer, B., Sperling, W., Bleich, S., Schlabeck, M., Wiltfang, J., Kornhuber, J., 2007. Memantine fails to facilitate partial cigarette deprivation in smokers–no role of Memantine in the treatment of nicotine dependency? J. Neural Transm. (Vienna) 114, 351–357.
Tsai, G.E.R.P., Chang, R., Chen, S., Linnoila, V.M., Coyle, J.T., 1998. Increased glutamatergic neurotransmission and oxidative stress after alcohol withdrawal. Am. J. Psychiatry 155, 726–732.
Tzchentke, T.M., Schmidt, W.J., 2000. Effects of the non-competitive NMDA-receptor antagonist memantine on morphine- and cocaine-induced potentiation of lateral hypothalamic brain stimulation reward. Psychopharmacology 149, 225–234.
Veronese, N., Solmi, M., Luchini, C., Lu, R.B., Stubbs, B., Zaninotto, L., Correll, C.U., 2016. Acetylcholinesterase inhibitors and memantine in bipolar disorder: a

systematic review and best evidence synthesis of the efficacy and safety for multiple disease dimensions. J. Affect. Disord. 197, 268–280.
Volkow, N.D., Wang, G.J., Fowler, J.S., Tomasi, D., 2012. Addiction circuitry in the human brain. Annu. Rev. Pharmacol. Toxicol. 52, 321–336.
Vosburg, S.K., Hart, C.L., Haney, M., Foltin, R.W., 2005. An evaluation of the reinforcing effects of memantine in cocaine-dependent humans. Drug Alcohol Depend. 79, 257–260.
Wong, W.C., Cheung, C.S., Hart, G.J., 2008. Development of a quality assessment tool for systematic reviews of observational studies (QATSO) of HIV prevalence in men having sex with men and associated risk behaviours. Emerg Themes Epidemiol. 5, 23.
Wu, H.M., Tzeng, N.S., Qian, L., Wei, S.J., Hu, X., Chen, S.H., Rawls, S.M., Flood, P., Hong, J.S., Lu, R.B., 2009. Novel neuroprotective mechanisms of memantine: increase in neurotrophic factor release from astroglia and anti-inflammation by preventing microglial activation. Neuropsychopharmacology 34, 2344–2357.
Wu, K., Hanna, G.L., Rosenberg, D.R., Arnold, P.D., 2012. The role of glutamate signaling in the pathogenesis and treatment of obsessive-compulsive disorder. Pharmacol. Biochem. Behav. 100, 726–735.
Yuanyuan, J., Junyan, Z., Cuola, D., Jingjing, C., Yuhui, S., Dan, X., Wei, D., Yongsheng, Z., 2018. Memantine attenuated alcohol withdrawal-induced anxiety-like behaviors through down-regulating NR1-CaMKII-ERK signaling pathway. Neurosci. Lett. 686, 133–139.
Zakharova, E.S., Danysz, W., Bespalov, A.Y., 2005. Drug discrimination analysis of NMDA receptor channel blockers as nicotinic receptor antagonists in rats. Psychopharmacology 179, 128–135.
Zindel, L.R., Kranzler, H.R., 2014. Pharmacotherapy of alcohol use disorders: seventy-five years of progress. J. Stud. Alcohol Drugs Suppl. 75 (Suppl. 17), 79–88.