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Adjunctive memantine for opioid use disorder treatment: A systematic review

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ABSTRACT

Memantine is commonly used for the treatment of moderate-to-severe Alzheimer's disease. Due to its antagonism of the *N*-methyl-D-aspartate (NMDA) receptor, which has been shown to block rewarding and reinforcing effects of morphine, memantine has been investigated for potential utilization in opioid use disorder (OUD). The objective of this systematic review is to assess the evidence available to determine the safety and efficacy of memantine as treatment for OUD. Pubmed (1946-August 2019) and Embase (1947-August 2019) were queried using the following search terms: opioid-related disorders, opioids, substance withdrawal syndrome, withdrawal syndrome, opiate addiction, opiate, opiate dependence, opiate substitution treatment, managed opioid withdrawal, or drug withdrawal and memantine. After assessing studies appropriate for the objective, one single-blind and five double-blind, placebo-controlled trials were included. Of the included studies, four demonstrated beneficial effects of memantine either as monotherapy or adjunct to methadone or buprenorphine on reducing opioid cravings and methadone dose, increasing retention rates, and improving cognitive performance in patients with OUD. Two studies did not show benefit on patient retention rates with memantine adjunct to naltrexone. Study durations ranged from 3 to 13 weeks, and memantine dosing ranged from 5 to 60 mg/day. Memantine was well tolerated with similar rates of adverse effects between treatment groups. Based on the reviewed literature, memantine appears most beneficial as an adjunctive treatment for OUD when combined with methadone or buprenorphine, but not naltrexone. Larger studies with longer periods of treatment and follow-up are needed to support the use of memantine in the management of OUD.

1. Introduction

Opioid use disorder (OUD) is characterized as a problematic pattern of opioid use leading to clinically significant impairment or distress (American Psychiatric Association, 2013) and has become an epidemic in many countries. In the United States (US), it is estimated that 130 people per day die from opioid-related drug overdoses (CDC, 2017). In addition to counseling and behavioral therapies, medication-assisted treatment (MAT) can be effective in treating OUD and for helping individuals sustain recovery. To adapt to the growing need for OUD treatment, the number of federally-approved opioid treatment programs offering MAT in the US has increased from about 1100 in 2003 to nearly 1500 at the end of 2016 (Alderks, 2017). There are currently three medications approved by the Food and Drug Administration for opioid dependence: buprenorphine, methadone, and naltrexone (Table 1) (Lexi-Drugs, 2019).

The detoxification process for opioid users involves the administration of supportive medications to ease the symptoms of withdrawal and cravings after a patient has stopped using opioids. Patients are typically inducted onto methadone, a mu-opioid receptor agonist, or buprenorphine, a mu-opioid receptor partial agonist, to stabilize the patient and diminish any euphorigenic effects if illicit opioids are used again in the future. Additionally, an adjunctive medication class that can be used to ameliorate autonomic symptoms of withdrawal are alpha-2 adrenergic agonists (e.g. clonidine or lofexidine) (Ayanga, Shorter, & Kosten, 2016). After initial induction on either methadone or buprenorphine, the dosages of these medications can be gradually tapered down over time as patients become more medically and psychologically stable (Ayanga et al., 2016). Patients may remain on the lowest effective dose of methadone or buprenorphine for years as maintenance treatment to reduce relapse risk. Treatment with a mu-opioid receptor agonist has been shown to at least double the probability of achieving opioid abstinence, and methadone has a higher rate of treatment retention compared to buprenorphine (Connery, 2015). However, discontinuation of mu-opioid receptor agonist therapy results in high rates of opioid relapse due to withdrawal and craving (Connery, 2015). An alternative option for maintenance treatment is transitioning

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Table 1
Current Food and Drug Administration-approved medication assisted treatment for opioid use disorder (Lexi-Drugs, 2019).

Medication	Mechanism of action	Dosage form
Buprenorphine	Partial mu-opioid receptor agonist	Subcutaneous injection, subdermal implant, oral (in combination with naloxone)
Methadone	Full mu-opioid receptor agonist	Oral
Naltrexone	Mu-opioid receptor antagonist	Extended-release intramuscular injection

patients from agonist therapy to a mu-opioid receptor antagonist, such as naltrexone (Ayanga et al., 2016).

Despite the advances in MAT, substance abuse relapse rates are estimated to range from 40 to 60% (National Institute on Drug Abuse, 2018). Thus, there is a need for development of additional therapies for long-term treatment of OUD to improve success rates of treatment. One potential non-opioid receptor treatment is memantine. Memantine is an *N*-methyl-D-aspartate (NMDA) receptor antagonist that is approved by the Food and Drug Administration for the treatment of moderate-to-severe Alzheimer's disease (Namenda [package insert], 2013). The NMDA-receptor is one type of glutamate receptor that, when not functioning normally, has been associated with various disease states including drug addiction (Tomek, Lacrosse, Nemirovsky, & Olive, 2013). The proposed mechanism of this association is due to glutamate, the primary excitatory neurotransmitter in the central nervous system, which is a critical part of the mesolimbic dopamine reward pathway in the brain (Tomek et al., 2013). Previously, NMDA antagonists have been shown to block rewarding and reinforcing effects of morphine in rats, which suggests potential for human use (Tomek et al., 2013). In the study by Popik et al., mice were insensitive to morphine-induced reinstatement of place preference response after being treated with 7.5 mg/kg of memantine. This was observed at 2 days and at 21 days after extinction of place preference (Popik, Wrobel, & Bisaga, 2006). In the study by Chen et al., low dose memantine (1 mg/kg) was also shown to inhibit morphine-induced place preference in rats. Additionally, they found lower levels of inflammatory cytokines and upregulation of brain-derived neurotrophic factor in the serum and brain, hypothesizing that memantine may also curb opioid addiction behavior through anti-inflammatory and neuroprotective effects (Chen et al., 2012).

The immediate-release form of memantine is typically started at 5 mg orally once daily, titrated up to max dose of 20 mg/day in two divided doses when used to treat dementia associated with Alzheimer's disease. It is generally well tolerated, with the most common adverse effects being dizziness (6%), headache (5%), constipation (5%), hypertension (4%), and somnolence (3%) (Kavirajan, 2009).

As there is growing evidence on the potential utilization of memantine in opioid withdrawal and abstinence, the objective of this review is to assess the evidence available to determine the safety and efficacy of memantine as treatment for OUD.

2. Methods

2.1. Literature search

A comprehensive literature search was performed using Pubmed (1946-August 2019) and Embase (1947-August 2019) with the following search terms: opioid-related disorders, opioids, substance withdrawal syndrome, withdrawal syndrome, opiate addiction, opiate, opiate dependence, opiate substitution treatment, managed opioid withdrawal, or drug withdrawal and memantine. References within each article were evaluated for inclusion in the systematic review. This report adheres to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines for conducting a systematic review (Moher et al., 2009).

2.2. Study selection

Studies were included for review if they were a prospective controlled study that utilized memantine in the treatment of OUD. Animal studies, non-English articles, case studies, retrospective trials, incomplete studies, human laboratory studies, and studies with patients who were not seeking treatment or only undergoing acute withdrawal were excluded. The titles and abstracts of articles were initially screened for possible inclusion. Full texts of the remaining reports were then reviewed to determine final eligibility for inclusion in the systematic review. Two authors (AME and JNB) independently performed the literature search and study review for inclusion, and disagreements were resolved by a third author (MJP).

2.3. Data extraction

A standardized data extraction process was used to collect the following information: authors, publication date, study size and duration, patient demographics, memantine and comparator medication treatment regimens, adjunct therapies, clinical outcomes, and reported adverse drug effects. The Jadad scale was used to evaluate each study for quality of evidence and was completed independently by each author, with final scores determined by uniform group consensus. The Jadad scale is a questionnaire assessing if randomized controlled trials are appropriately randomized, appropriately double-blinded, and describe withdrawals and dropouts. A trial can receive a final score between 0 and 5, with higher scores indicating a higher quality of study (Jadad et al., 1996).

3. Results

3.1. Study selection (Fig. 1)

Initially, 1242 studies were identified upon preliminary search. After removal of duplications, 1153 unique studies remained. Titles and abstracts were screened, and 1142 studies were excluded due to irrelevance. The remaining 11 full-text articles were read to determine eligibility and 5 were excluded (Bisaga et al., 2001; Comer & Sullivan, 2007; Denio, West, & Stock, 2013; Gonzalez, DiGirolamo, Kolodziej, Smelson, & Romero-Gonzalez, 2015; Jain, Jain, & Dhawan, 2011). Ultimately 6 randomized controlled trials, one with memantine monotherapy and five with memantine adjunct to either naltrexone, buprenorphine, or methadone, were included for analysis in this review. Fig. 1 describes the study selection process, with a summary of included studies shown in Table 2.

3.2. Memantine monotherapy

Krupitsky et al. evaluated the effect of memantine versus amitriptyline and placebo on protracted withdrawal (syndrome of anhedonia) and cravings in recently detoxified heroin addicts. In this single-blind, randomized, placebo-controlled trial, 67 inpatients were randomly assigned to receive either memantine 30 mg/day, amitriptyline 75 mg/day, or placebo after withdrawing from heroin and confirmed to be opiate free. Memantine was started at 10 mg/day and gradually titrated to goal dose over one week. At the end of the three-week study, cravings for heroin measured using the Visual Analogue Scale were significantly decreased by both memantine and amitriptyline compared to baseline. Additionally, the significant difference from baseline was measured at day 7 for memantine, but not until day 21 for amitriptyline. Both the amitriptyline and memantine groups also had a significant reduction in the affective, cognitive, and behavioral components of the anhedonia scale compared to baseline. Compared to placebo, only the memantine group had a significantly lower severity of the affective and cognitive components of syndrome of

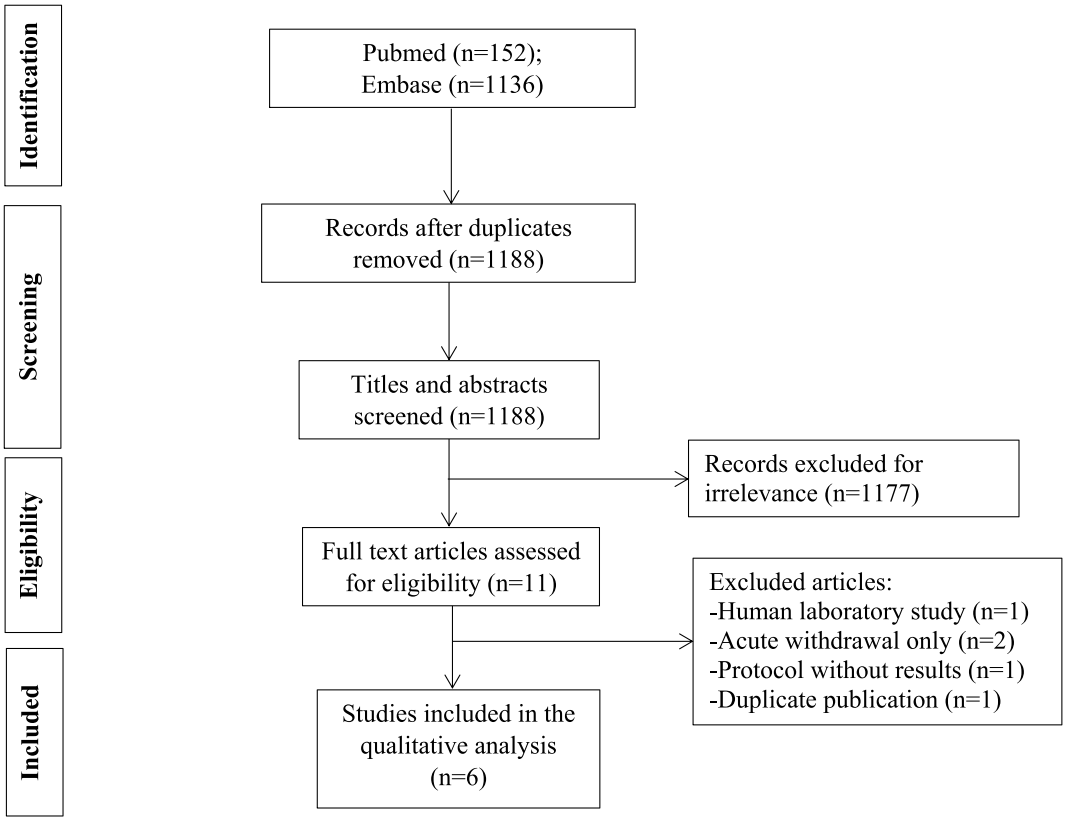

Fig. 1. Literature evaluation process.

anhedonia at the end of the study. Additionally, there was statistically significant reduction in symptoms of depression, measured using Zung's scale, in both treatment groups compared to baseline and placebo (memantine: 52.3 ± 1.8 vs 36.8 ± 2.5; amitriptyline: 53.8 ± 1.7 vs 36.7 ± 2.0; placebo: 54.5 ± 1.4 vs 48.5 ± 2.9). The memantine group also had a significant reduction in state anxiety scores, measured using Spielberger's scale, at the end of the study compared to placebo (32.7 ± 2.6 in memantine vs 45.6 ± 2.4 in placebo). In terms of the dropout rate, 2/21 patients (9.5%) in the memantine group withdrew from the study due to relapse and acute hepatitis, respectively. Comparatively, 6/24 patients (25%) in the amitriptyline group and 8/22 patients (36.4%) in the placebo group withdrew due to relapse. The number of adverse drug reactions reported by patients in the memantine group was similar to the number reported in the placebo group, and was significantly lower than the number reported in the amitriptyline group (Krupitsky et al., 2002).

3.3. Adjunctive memantine

Bisaga et al. conducted a randomized, double-blind, placebo-controlled trial of 81 detoxified opioid dependent inpatients receiving naltrexone and being discharged to outpatient care. Patients in the study were randomized to receive memantine 30 mg/day, 60 mg/day, or placebo in addition to naltrexone for 12 weeks. Naltrexone was administered to patients at doses of 100 mg on Mondays and Wednesdays, and 150 mg on Fridays. Randomization was stratified based on age and amount of heroin use prior to detoxification. Memantine was titrated to the target dose over 1 to 2 weeks. Only 24% (n = 20) of patients completed all 12 weeks of the trial, with the most significant dropout occurring during the first week after inpatient discharge. Of those who did not complete the trial, 10 were removed before completing detoxification, 32 did not continue attending clinic appointments to receive naltrexone, 6 continued to use heroin, 5 stopped citing medical reasons, 4 moved to a different state, 3 had work requirements that interfered, and 1 had accidental overdose. There was no statistically significant difference in the primary outcome of retention rates between any of the three groups. Secondary outcomes assessed showed a significant time effect in all treatment groups of reduction in opiate use (p = 0.008), reduction in Clinical Global Impression severity and improvement scores (p < 0.001), and reduction in Subjective Opiate Withdrawal Scale scores (p < 0.001). However, these changes were not significantly different when compared between the three treatment groups. Adverse drug reactions were similar between memantine and placebo groups, and there were no serious adverse reactions related to memantine (Bisaga et al., 2011).

Bisaga et al. also conducted a follow up randomized, double-blind, placebo-controlled trial to assess memantine compared to placebo as adjunctive treatment to injectable naltrexone. Inpatients were assisted with opioid withdrawal with 1–2 days of buprenorphine followed by a gradual naltrexone induction. Patients were then randomized to receive either memantine 20 mg twice daily or placebo starting on the second day of naltrexone induction and followed for 12 weeks as outpatients. On the fourth day of naltrexone induction, week 4, and week 8, patients were given an IM injection of naltrexone XR 380 mg. In total, 55 patients were randomized for inclusion and were stratified based on age and baseline opioid use. Only 56% (n = 31) of patients completed all 12 weeks of the trial. Of those who dropped out, one left before complete detoxification, 18 did not continue to attend clinic appointments, 3 continued to use heroin, 1 stopped the study medication due to withdrawal symptoms, 1 moved to a different state, and 1 was hospitalized for psychiatric worsening. The primary outcome of retention rate until the end of the trial was higher in the placebo group compared to the memantine group. Secondary outcomes assessed showed a significant time effect in both treatment groups of reduction in opiate use (p = 0.002), reduction in Clinical Global Impression severity scores (p = 0.002), reduction in craving intensity (p = 0.007), and reduction in depression as measured using HAM-D (p < 0.0001). However, there was no significant difference in these outcomes when compared between the two treatment groups. The severity of opioid withdrawal,

Table 2
Summary of studies evaluating safety and efficacy of memantine for opioid use disorder.

Author, year	Study design	Study duration, sample size	Intervention (s)	Adjunct therapy	Outcome(s)	Results	Memantine adverse drug reactions ≥5%, (%)	Quality assessment[d]
Krupitsky et al., 2002	RCT, single-blind	21 days *N* = 67	Memantine: 30 mg/day Amitriptyline: 75 mg/day Placebo	None	Craving visual analogue scale	Memantine: 5.7[a] Amitriptyline: 7.3[a] Placebo: 30.0	Not reported	3/5
Bisaga et al., 2011	RCT, double-blind	12 weeks *N* = 94	Memantine: 30 mg/day Memantine: 60 mg/day Placebo	Naltrexone oral	Retention rate	Memantine 30 mg: 19% Memantine 60 mg: 22% Placebo: 26%	Memantine 30 mg: insomnia (29.6); weakness (11.1); headache (7.4); dizziness (7.4); diarrhea (7.4) Memantine 60 mg: insomnia (33.3); GI distress (25.9); nausea/vomiting (18.5); diarrhea (14.8); headache (11.1); body aches (7.4); dizziness (7.4)	5/5
Bisaga et al., 2014	RCT, double-blind	12 weeks *N* = 55	Memantine: 40 mg/day Placebo	Naltrexone intramuscular	Retention rate	Memantine: 43%[b] Placebo: 70%	Memantine 40 mg: insomnia (77.2); fatigue/drowsiness (31.8); mood changes (31.8); changes in appetite (25); body aches (18.1); gastrointestinal distress (18.1); diarrhea (13.6); headache (9.1); sweating/chills (9.1); faintness/dizziness (9.1)	5/5
Gonzalez, DiGirolamo, Romero-Gonzalez, et al., 2015	RCT, double-blind	13 weeks *N* = 80	Memantine: 15 mg/day Memantine: 30 mg/day Placebo	Buprenorphine/naloxone	Proportion of weekly opioid use, mean	Memantine 15 mg: 27% Memantine 30 mg: 0%[b,c] Placebo: 39%	Memantine 15 & 30 mg: pain (21); upper respiratory infection (9.3); nausea (7.6); vivid dreams (6.7); constipation (5.9); headaches (5); drowsiness (5)	5/5
Lee et al., 2015	RCT, double-blind	12 weeks *N* = 128	Memantine: 5 mg/day Placebo	Methadone	Methadone dose Methadone dose, percent change Participant retention rates	Memantine: +1.52 mg[b] Placebo: +8.07 mg Memantine: 4.4%[b] Placebo: 22.4% Memantine: 84.9% Placebo: 76.3%	Not reported	5/5
Chang et al., 2015	RCT, double-blind	12 weeks *N* = 81	Memantine: 5 mg/day Placebo	Methadone	Wisconsin Card Sorting Test subscores	Memantine: TNE: −15.46[b] PE: −9.24 CLR: +16.48[b] NCC: +1.96[b] TCC: −3.44[b] Placebo: TNE: −3.49 PE: −5.3 CLR: +5.33 NCC: +0.31 TCC: +4.54	Not reported	5/5

CLR = conceptual level responses; NCC = number of completed categories; PE = perseverative errors; RCT = randomized controlled trial; TCC = trials to complete the first category; TNE = total number of errors.

[a] Statistically significant vs. baseline.

[b] Statistically significant vs. placebo.

[c] Statistically significant vs. active comparator.

[d] Based on Jadad criteria.

measured using the Subjective Opiate Withdrawal Scale, was lower in the memantine group during the first three weeks of the trial, but did not reach significance ($p = 0.07$). There were no significant differences in the incidence of adverse events between the two groups, although one serious adverse drug reaction of psychiatric worsening occurred in a memantine patient (Bisaga et al., 2014).

In the randomized, double-blind, placebo-controlled trial by Gonzalez et al., 80 patients actively using either heroin or opioid analgesics were initiated on buprenorphine 16 mg/naloxone 4 mg per day after stopping opioid use. Buprenorphine-naloxone was continued for 8 weeks and discontinued during week 9 of the study. Patients were randomly assigned to receive either memantine 15 mg/day, memantine 30 mg/day, or placebo starting on week 2 of the study while also receiving buprenorphine-naloxone. Memantine was gradually titrated to target dose and continued through week 12 and discontinued on week 13. Only 21 subjects (25%) completed the study through week 13, although there was no significant difference in retention rates between the treatment groups. In the primary outcome, patients in the memantine 30 mg group had significantly reduced weekly mean proportion of opioid use over time compared to both the memantine 15 mg group and the placebo group. The memantine 30 mg group had the most significant reduction in opioid use after discontinuing buprenorphine compared to the other groups ($p < 0.009$). The change in weekly scores for opioid cravings, measured by Heroin Craving Questionnaire-Short Form-14, was significantly reduced in the memantine 30 mg group after buprenorphine continuation compared to memantine 15 mg and placebo (2.7 ± 0.25 vs 3.2 ± 0.69 vs 3.46 ± 0.32 respectively, $p < 0.009$). There was also a significant reduction in weekly scores for opioid withdrawal symptoms measured by the Clinical Opiate Withdrawal Scale in the memantine 30 mg group compared to memantine 15 mg and placebo at week 13 (1.4 ± 0.6 vs 1.5 ± 0.6 vs 2.17 ± 1 respectively, $p < 0.05$). The memantine 30 mg group had a reduction in the Barratt Impulsivity Scale from baseline to week 8, although it did not reach significance (-5.9%, $p = 0.06$), whereas memantine 15 mg and placebo resulted in a slight worsening of scores (5% and 6.5%, respectively). Memantine was well tolerated and no serious adverse events occurred during the study (Gonzalez et al., 2015).

In the randomized, double-blind, placebo-controlled study by Lee et al., the benefit of low-dose memantine adjunct to methadone maintenance therapy was assessed to determine if memantine would lower methadone requirements. A total of 128 opioid-dependent patients were inducted onto methadone therapy and then randomly assigned to receive either memantine 5 mg/day or placebo. After 12 weeks, the methadone requirements in the memantine group were significantly lower both before and after normalization ($p = 0.034$ and $p = 0.025$, respectively). There was no statistically significant difference in retention rates between the two groups. In the memantine group, 8/45 patients (15.1%) withdrew from the study due to loss of follow-up ($n = 2$), refusal of treatment ($n = 5$), and violation of protocol ($n = 1$). There were no significant differences between adverse events reported in either group (Lee et al., 2015).

Chang et al. conducted a double-blind, randomized, placebo-controlled trial assessing the effect of low dose memantine on cognitive performance in opioid-dependent patients on methadone maintenance therapy. Patients on methadone were randomly assigned to receive either memantine 5 mg or placebo and were compared to healthy controls. Cognitive performance was assessed using the Wisconsin Card Sorting Test and the Continuous Performance Test, which assesses the ability to maintain focused attention. Compared to both treatment groups, the healthy controls performed significantly better on cognitive tasks at baseline. After 12 weeks of treatment, both treatment groups improved in cognitive performance. However, there was a significant improvement over time in cognitive performance and executive function in the memantine group compared to the placebo group. Specifically, in the Continuous Performance Test, the hit reaction time by block change was significantly reduced in the memantine group (-5.35 ms for memantine vs. $+4.14$ ms for placebo, $p = 0.02$). In the Wisconsin Card Sorting Test, there was a significant reduction in the total number of errors ($p = 0.04$) and in the trials to complete the first category ($p = 0.04$), and a significant increase in the number of completed categories ($p = 0.03$) and the conceptual level responses ($p = 0.04$). The dropout rate of the memantine group was lower (26.3%) compared to in the placebo group (49.4%). Adverse events were not reported (Chang et al., 2015).

4. Discussion

A total of six randomized, placebo-controlled trials were identified analyzing the safety and efficacy of memantine for treatment of OUD. Trial design and outcomes varied, which limits the ability to compare results across studies. However, the beneficial effect seen and measured by different methods may represent a multimodal effect of memantine in OUD treatment.

Out of the six studies included in this review, four studies showed beneficial effects of memantine when used for OUD and two studies did not show benefit (Bisaga et al., 2011; Bisaga et al., 2014; Chang et al., 2015; Gonzalez, DiGirolamo, Kolodziej, et al., 2015; Krupitsky et al., 2002; Lee et al., 2015). The two studies that did not show benefit both evaluated memantine in conjunction with a mu-opioid receptor antagonist, naltrexone (Bisaga et al., 2011; Bisaga et al., 2014). One study (Krupitsky et al., 2002) showed benefit of memantine monotherapy, and three studies (Lee et al., 2015; Gonzalez, DiGirolamo, Kolodziej, et al., 2015; Chang et al., 2015) showed benefit of memantine adjunct to partial and full mu-agonist therapy. This suggests, in addition to previous studies conducted in murine models, that memantine may have synergistic effects when combined with mu-opioid receptor agonists and that when combined with mu-opioid receptor antagonists, this beneficial synergy is not observed (Gonzalez, DiGirolamo, Romero-Gonzalez, et al., 2015). All of the included studies assessed patient retention rate, and both studies by Bisaga et al. assessed this as a primary outcome (Bisaga et al., 2011; Bisaga et al., 2014). While the studies by Bisaga et al. showed less retention in the memantine group, the other studies either showed increased retention or no difference between treatment groups (Bisaga et al., 2011; Bisaga et al., 2014; Chang et al., 2015; Gonzalez, DiGirolamo, Romero-Gonzalez, et al., 2015; Krupitsky et al., 2002; Lee et al., 2015). As multiple factors may contribute to patients discontinuing treatment, there may likely be several confounding factors that were not fully explored in these studies to assess this outcome. Additionally, in the 2011 trial by Bisaga et al., the large dropout rate of patients in the beginning of the study resulted in a very limited exposure to memantine, and in the 2014 study by Bisaga et al., there was a large variation in memantine blood levels in the treatment group, suggesting varying rates of adherence to the intervention (Bisaga et al., 2011; Bisaga et al., 2014). Lack of sufficient exposure to memantine may have contributed to the lack of significant results in these trials.

The doses of memantine used in these studies ranged from 5 mg/day to 60 mg/day, with 60 mg/day being triple the FDA-approved maximum dose of memantine for treatment of Alzheimer's dementia (Namenda [package insert], 2013). Despite the use of doses above 20 mg/day in four of the six studies, memantine was well tolerated and the rate of side effects experienced in patients receiving memantine was not significantly different than the comparator drugs or placebo in any of the studies (Bisaga et al., 2011; Bisaga et al., 2014; Gonzalez, DiGirolamo, Kolodziej, et al., 2015; Krupitsky et al., 2002). The most common adverse drug reactions reported were insomnia (29.6%–77.2%), mood changes (31.8%), fatigue/drowsiness (31.8%), and changes in appetite (25%) (Bisaga et al., 2011; Bisaga et al., 2014; Gonzalez, DiGirolamo, Romero-Gonzalez, et al., 2015). Due to the small number of patients in these trials, incidence of adverse events may be overrepresented compared to if memantine was administered to a larger patient population. In three of the included studies, memantine was titrated to goal dose over one to two weeks, which is considered a rapid titration schedule in comparison to titration in dementia patients (Krupitsky et al., 2002; Bisaga et al., 2011; Gonzalez, DiGirolamo, Kolodziej, et al., 2015; Loy, Britt, & Brown,

2016). Likely, the reason for more rapid titration in these studies was due to wanting to reduce cravings for opioids and have patients discharged home as quickly as possible. A slower dose titration, though, may increase tolerance and warrants exploration in future studies. Memantine's general tolerability may improve medication adherence rates in patients, which is important for maintaining sobriety and would be an important factor to consider in any drug that may be used for long-term treatment.

Opioid withdrawal and cravings were assessed in four of the included studies, with three studies showing a reduction in symptoms with memantine use (Krupitsky et al., 2002; Bisaga et al., 2014; Gonzalez, DiGirolamo, Romero-Gonzalez, et al., 2015). As the symptoms of withdrawal and opioid cravings are a large factor leading patients to relapse, improvement in this may be of large clinical significance. Also of note, in the study by Krupitsky et al., patients treated with memantine had the largest reduction in withdrawal symptoms and craving during the first week of memantine exposure (Krupitsky et al., 2002). This rapid reduction of what are typically distressing physical and emotional symptoms may be a key to preventing early relapse and patient dropout. One study assessed the effect of memantine on cognitive performance as a primary outcome, with memantine demonstrating significant improvement in multiple assessment scales (Chang et al., 2015). Improvement in cognition is an important factor in quality of life and may be a unique benefit of the addition of memantine to an OUD treatment regimen.

It is important to note that in four of the studies included, patients received psychotherapy in addition to medication-assisted treatment (Bisaga et al., 2011; Bisaga et al., 2014; Gonzalez, DiGirolamo, Kolodziej, et al., 2015; Krupitsky et al., 2002). Research has shown that psychotherapy in combination with MAT is more successful at preventing relapse than MAT alone (National Institute on Drug Abuse, 2018). Therefore, memantine use as part of MAT would likely be more efficacious in addition to psychotherapy for OUD treatment.

This analysis has several limitations to consider. There was a wide variety in primary and secondary outcomes assessed, making comparisons between studies difficult. The studies were relatively small and took place over a short duration of time, which may underestimate the effects of memantine on the studied outcomes and does not inform the long-term efficacy of memantine for OUD. As pharmacologic treatment of OUD may be continued for years, it is important to know if any beneficial effects of memantine are maintained. Studies with longer treatment periods in larger patient populations are needed to address this gap in knowledge. When assessing safety and tolerability, three studies did not report rates of adverse drug reactions (Chang et al., 2015; Krupitsky et al., 2002; Lee et al., 2015). Additionally, as OUD is a very complex and not fully understood disease, there may be several confounding factors that were not accounted for affecting the results in these studies.

5. Conclusion

Memantine appears to be most beneficial as an adjunctive treatment for OUD when combined with psychotherapy and methadone or buprenorphine, demonstrating improvement in cognitive performance, patient retention rate, opioid withdrawal, and craving. Memantine use with naltrexone was not shown to be beneficial. Dosing in the included studies that showed benefit ranged from 5 mg to 30 mg/day and was well-tolerated by patients. Larger studies with longer periods of treatment and follow-up are needed to support the use of memantine in the management of OUD.

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