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Adjunctive memantine for major mental disorders: A systematic review and meta-analysis of randomized double-blind controlled trials

Wei Zheng [a,1], Xiao-Min Zhu [b,1], Qing-E Zhang [c,1], Dong-Bin Cai [d], Xin-Hu Yang [a], Yan-Ling Zhou [a], Gabor S. Ungvari [e,f], Chee H. Ng [g], Shu-Hua He [h], Xiao-Jiang Peng [i], Yu-Ping Ning [a,*], Yu-Tao Xiang [j,**]

[a] The Affiliated Brain Hospital of Guangzhou Medical University (Guangzhou Huiai Hospital), Guangzhou, China
[b] Suzhou Guangji Hospital, Affiliated Guangji Hospital of Soochow University, Suzhou, China
[c] The National Clinical Research Center for Mental Disorders & Beijing Key Laboratory of Mental Disorders, Beijing Anding Hospital, Capital Medical University, Beijing, China
[d] Shenzhen Traditional Chinese Medicine Hospital, Shenzhen, China
[e] The University of Notre Dame Australia, Fremantle, Australia
[f] Division of Psychiatry, School of Medicine, University of Western Australia, Perth, Australia
[g] Department of Psychiatry, University of Melbourne, Melbourne, Victoria, Australia
[h] University of California, Davis, USA
[i] Guangzhou Civil Aviation College, Guangzhou, China
[j] Unit of Psychiatry, Institute of Translational Medicine, Faculty of Health Sciences, University of Macau, Macao SAR, China

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ABSTRACT

Objective: As a non-competitive *N*-methyl-D-aspartate receptor antagonist, memantine has been used to treat major mental disorders including schizophrenia, bipolar disorder, and major depressive disorder (MDD). This meta-analysis systematically investigated the effectiveness and tolerability of adjunctive memantine for patients with schizophrenia, bipolar disorder, and MDD.
Methods: Only randomized controlled trials (RCTs) were identified and included in the study. Data of the three disorders were separately synthesized using the RevMan 5.3 software.
Results: Fifteen RCTs (n = 988) examining memantine (5–20 mg/day) as an adjunct treatment for schizophrenia (9 trials with 512 patients), bipolar disorder (3 trials with 319 patients), and MDD (3 trials with 157 patients) were analyzed. Memantine outperformed the comparator regarding total psychopathology with a standardized mean difference (SMD) of −0.56 [95% confidence interval (CI): −1.01, −0.11; $I^2 = 76\%$, P = 0.01] and negative symptoms with an SMD of −0.71 (95% CI: −1.09, −0.33; $I^2 = 74\%$, P = 0.0003) in schizophrenia, but no significant effects were found with regard to positive symptoms and general psychopathology in schizophrenia, or depressive and manic symptoms in bipolar disorder or depressive symptoms in MDD. Memantine outperformed the comparator in improving cognitive performance in schizophrenia with an SMD of 1.07 (95% CI: 0.53, 1.61; $P < 0.0001$, $I^2 = 29\%$). No group differences were found in the rates of adverse drug reactions and discontinuation due to any reason in the three major mental disorders.
Conclusions: Memantine as an adjunct treatment appears to have significant efficacy in improving negative symptoms in schizophrenia. The efficacy and safety of adjunctive memantine for bipolar disorder or MDD needs to be further examined.
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1. Introduction

Patients with major mental disorders have an increased risk of somatic comorbidities and premature death compared to the general population (De Hert et al., 2011; Vancampfort et al., 2015, 2016). Pharmacotherapy is the main treatment modality for major mental disorders, but its overall effectiveness remains unsatisfactory for many patients (Torrey and Davis, 2012). As a result, augmentation strategy is commonly used to improve the effectiveness of pharmacotherapy.

The association between glutamate deregulation in schizophrenia (Hu et al., 2015; Madeira et al., 2018), bipolar disorder (Blacker et al., 2017; Soeiro-de-Souza et al., 2018), and major depressive disorder (MDD) (Inoshita et al., 2018; Shirayama et al., 2017), through *N*-methyl-D-aspartate receptor (NMDAR) dysfunction, has gained

* Corresponding author.
** Correspondence to: Y.-T. Xiang, 3/F, Building E12, Faculty of Health Sciences, University of Macau, Avenida da Universidade, Taipa, Macau SAR, China.
E-mail addresses: ningjeny@126.com (Y.-P. Ning), xyutly@gmail.com (Y.-T. Xiang).
[1] There authors contributed equally to this work.

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increasing attention. For example, patients with schizophrenia (Yamamori et al., 2014), bipolar disorder (Palsson et al., 2015), or MDD (Inoshita et al., 2018; Ogawa et al., 2018) appear to have higher plasma glutamate levels compared to healthy controls. In addition, patients with major mental disorders complicated with catatonia had significantly greater anti-NMDAR antibody response and intensity of anti-NMDAR antibody immunofluorescence than healthy controls (Lin et al., 2017). NMDAR hypofunction in these conditions is possibly the result of the dysregulation of downstream neurons, excitotoxic neurodegeneration and dysfunction of neuroplasticity in response to glutamate release.

Glutamate neurotransmission modulators, such as memantine, may thus have mood stabilizing (Koukopoulos et al., 2012; Lee et al., 2013), antipsychotic (Veerman et al., 2014) and antidepressant properties (Henter et al., 2018; McCloud et al., 2015). Both memantine and selective NMDAR blockers (e.g., IEM-1754, IEM-1755 and IEM-1752) showed anticonvulsant, antioxidant and anti-ischemic effects (Gmiro and Serdiuk, 2000). As a non-competitive NMDAR antagonist, memantine has been approved for moderate to severe Alzheimer's disease (AD) (Koch et al., 2005; Moriguchi et al., 2018; Okada et al., 2019). In clinical practice, memantine has often been prescribed as an off-label drug for major mental disorders (Sani et al., 2012; Zdanys and Tampi, 2008). However, the findings of randomized controlled trials (RCTs) investigating the effectiveness and tolerability of memantine as an adjunct treatment in the above psychiatric disorders have been inconsistent (Amidfar et al., 2017; Anand et al., 2012; de Lucena et al., 2009; Fakhri et al., 2016; Gu et al., 2012; Lee et al., 2012; Lee et al., 2014; Lieberman et al., 2009; Mazinani et al., 2017; Omranifard et al., 2014, 2017; Rezaei et al., 2013; Sahraian et al., 2017; Smith et al., 2013; Veerman et al., 2016). To the best of our knowledge, no systematic review or meta-analysis has been published that systematically evaluated the effectiveness and tolerability of memantine as an adjunct treatment in all three major mental disorders, although meta-analyses and reviews have separately targeted schizophrenia (Kishi and Iwata, 2013; Kishi et al., 2017a; Matsuda et al., 2013; Singh and Singh, 2011; Zheng et al., 2018), bipolar disorder (McCloud et al., 2015) or MDD (Caddy et al., 2015).

In order to provide a comprehensive review of the effectiveness and tolerability of memantine, an updated meta-analysis was conducted to systematically investigate its effectiveness and tolerability when added to a primary psychotropic medication in treating schizophrenia, bipolar disorder and MDD.

2. Methods

2.1. Selection criteria

This meta-analysis has been prepared based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009) and was conducted following the methodology recommended by the Cochrane Collaboration (Higgins and Higgins, 2008).

According to the reporting structure of *PICOS* acronym, the inclusion criteria were: ***P***articipants: adult patients aged between 18 and 65 years diagnosed with schizophrenia, bipolar disorder, or MDD by standardized diagnostic instruments. ***I***ntervention: adjunctive memantine plus primary psychotropic medications. ***C***omparison: primary psychotropic medication plus placebo or primary psychotropic medication monotherapy. ***O***utcomes: primary outcome was clinical efficacy based on the definition of each study. For example, total psychopathology in schizophrenia was assessed with the total score of the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962) or the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Secondary outcomes were psychopathology subscales (positive and negative symptoms and general psychopathology), the Clinical Global Impression

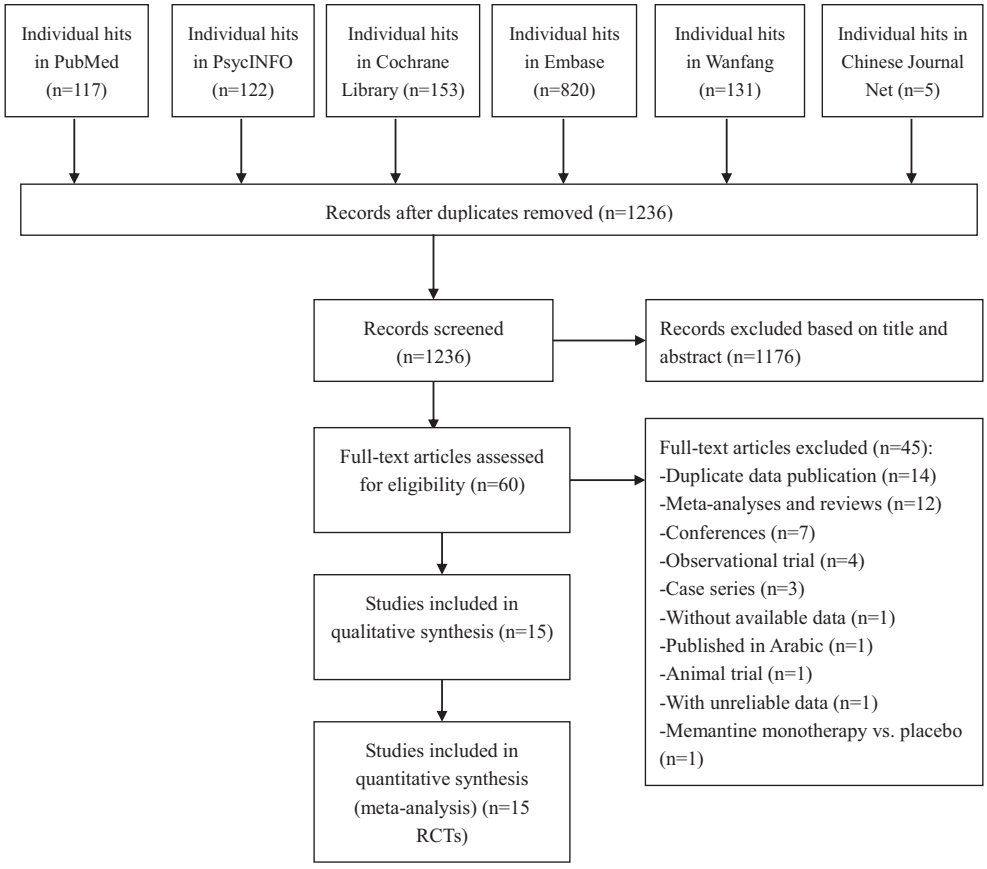

Fig. 1. PRISMA flow diagram.

Table 1
Patient and treatment characteristics of the included studies.

Study (country)	Number of patients	Blinding	Analyses	Trial duration (weeks)	Setting (%)	Diagnosis (%)	Diagnostic criteria	Duration	Age[a]: yrs (range)	Sex[a]: male (%)	Control-group: dose (mg/d): mean (range)	Intervention-group: dose (mg/d): mean (range)		Jadad score
Schizophrenia (9RCTs, n = 512)														
de Lucena et al., 2009 (Brazil)	T: 22 C: 11 I: 11	DB	ITT	12	Outpatients (100)	SCZ (100)	DSM-IV	−17.8 yrs	34.7 (18–65)	90.5	CLZ: Ø = 659 (NR)	CLZ: Ø = 540 (NR)	MEM: Ø = 20 (5–20)	3
Fakhri et al., 2016 (Iran)	T: 60 C: 30 I: 30	DB	ITT	6	Inpatients (100)	SCZ (100)	DSM-IV-TR	-NR	37.0 (18–60)	50.0	OLA: Ø = NR (15–20)	OLA: Ø = NR (15–20)	MEM: Ø = 20 (10−20)	3
Gu et al., 2012 (China)	T: 64 C: 32 I: 32	DB	ITT	12	Inpatients (100)	SCZ (100)	CCMD-3	−15.7 yrs	42.7 (20–60)	54.7	CLZ: Ø = 254 (125–450)	CLZ: Ø = 223 (100–375)	MEM: Ø = 20 (5–20)	3
Lee et al., 2012 (Korea)	T: 26 C: 11 I: 15	DB	ITT	12	Inpatients (100)	SCZ (100)	DSM-IV	−13.0 yrs	43.9 (18–50)	61.5	CPZ-eq[b]: Ø = 986.4 (NR)	CPZ-eq[b]: Ø = 1261.7 (NR)	MEM: Ø = 20 (5–20)	5
Lieberman et al., 2009 (USA)	T: 138 C: 68 I: 70	DB	ITT	8	Outpatients (100)	SCZ (99), SzA (1)	DSM-IV	−16.5 yrs	40.5 (18–65)	69.1	APs[c]: Ø = NR (NR)	APs[c]: Ø = NR (NR)	MEM: Ø = 20 (5–20)	3
Mazinani et al., 2017 (Iran)	T: 46 C: 23 I: 23	DB	ITT	16	Inpatients (100)	SCZ (100)	DSM-IV	−24.6 yrs	45.1 (18–55)	100.0	RIS: Ø = NR (4–6)	RIS: Ø = NR (4–6)	MEM: Ø = 20 (5–20)	5
Omranifard et al., 2015 (Iran)	T: 64 C: 32 I: 32	DB	OC	12	Inpatients (100)	SCZ (100)	DSM-IV-TR	−9.0 yrs	33.3 (18–65)	53.3	APs[d]: Ø = NR (NR)	APs[d]: Ø = NR (NR)	MEM: Ø = 20 (5–20)	5
Rezaei et al., 2013 (Iran)	T: 40 C: 20 I: 20	DB	ITT	8	Outpatients (100)	SCZ (100)	DSM-IV-TR	−10.9 yrs	33.3 (18–50)	57.5	RIS: Ø = 6 (FD)	RIS: Ø = 6 (FD)	MEM: Ø = 20 (10–20)	4
Veerman et al., 2016 (Netherlands)	T: 52 C: 26 I: 26	DB, crossover[e]	ITT	12	In- (12) and outpatients (88)	SCZ (100)	DSM-IV	−22.9 yrs	42.4 (18–60)	75.0	CLZ[f]: Ø = NR (NR)	CLZ[f]: Ø = NR (NR)	MEM: Ø = 20 (10–20)	5
Bipolar disorder (3 RCTs, n = 319)														
Anand et al., 2012 (USA)	T: 29 C: 15	DB	ITT	8	Outpatients (100)	BP-I (62); BP-II (38)	DSM-IV-TR	−21.5 yrs	39.6 (18–65)	41.4	LAM: Ø = 182 (>100)	LAM: Ø = 221 (>100)	MEM: Ø = 20	5

	I: 14												(5–20)	
Lee et al., 2014 (China)	T: 232 C: 117 I: 115	DB	OC	12	In- (NR) and outpatients (NR)	BP-II (100)	DSM-IV	-NR	31.8 (NR)	50.9	VPA: Ø = NR (500–1000)	VPA: Ø = NR (500–1000)	MEM: Ø = 5 (FD)	3
Sahraian et al., 2017 (Iran)	T: 58 C: 29 I: 29	DB	ITT	16	NR	BP-I (100)	DSM-IV	−10 yrs	33.2 (18–60)	34.5	Medication[g]: Ø = NR (NR)	Medication[g]: Ø = NR (NR)	MEM: Ø = NR (5–20)	5
Major depressive disorder (3 RCTs, n = 157)														
Amidfar et al., 2017 (Iran)	T: 66 C: 33 I: 33	DB	OC	6	Outpatients (100)	MDD (100)	DSM-V	−0.2 yrs	33.9 (18–50)	64.5	SER: Ø = 200 (100−200)	SER: Ø = 200 (100–200)	MEM: Ø = 20 (10–20)	5
Omranifard et al., 2014 (Iran)	T: 60 C: 30 I: 30	DB	OC	8	NR	MDD (100)	DSM-IV-TR	-NR	68.2 (>60)	40.4	CIT: Ø = 20 (10–20)	CIT: Ø = 20 (10–20)	MEM: Ø = 20 (5–20)	5
Smith et al., 2013 (USA)	T: 31 C: 16 I: 15	DB	ITT	8	Outpatients (100)	MDD (100)	DSM-IV-TR	-NR	52.2 (18–85)	38.7	Medication[h]: Ø = NR (NR)	Medication[h]:Ø = NR (NR)	MEM: Ø = 20 (5–20)	5

Ø = mean.

Abbreviations: APs = antipsychotics; BP-I=Bipolar I disorder; BP-II=Bipolar II disorder; C = control; CCMD-3 = China's Mental Disorder Classification and Diagnosis Standard 3th edition; CIT = citalopram; CLZ = clozapine; CPZ-eq = chlorpromazine equivalent; DB = double blind; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders 4th edition; DSM-IV-TR = Diagnostic and Statistical Manual of Mental Disorders 4th edition, Text Revision; DSM-V = Diagnostic and Statistical Manual of Mental Disorders 5th edition; FD = fixed dosage; LAM = Lamotrigine; I = intervention; ITT = intent to treat; MDD = Major depressive disorder; MEM = memantine; NR = not reported; OC = observed cases; OLA = Olanzapine; RCT = randomized controlled trial; RIS = risperidone; SCZ = schizophrenia; SER = Sertraline; SzA = schizoaffective disorders; T = total; VPA = Valproic acid; yrs. = years.

[a] Data were extracted based on mean baseline value of each included trials.

[b] Did not report the use of APs.

[c] Including olanzapine, aripiprazole, risperidone, ziprasidone, and quetiapine.

[d] Including olanzapine, aripiprazole, risperidone, and clozapine.

[e] Only data with the first randomized study phase were extracted and analyzed.

[f] Including clozapine monotherapy or clozapine combined with other drugs including APs, antidepressants, mood stabilizers, and benzodiazepines.

[g] Including lithium, olanzapine, and clonazepam.

[h] Patients continued taking the same doses of psychotropic agents.

Severity Scale (CGI-S) scores (Guy, 1976), cognitive functions measured by the Mini-Mental State Examination (MMSE) (Folstein et al., 1975), rates of adverse drug reactions (ADRs) and/or discontinuation due to any reason. ***S***tudy design: double-blind RCTs published in Chinese or English language and examined the effectiveness and tolerability of memantine as an adjunct treatment for schizophrenia, bipolar disorder or MDD.

2.2. Search strategy

Chinese and English databases including China Journal Net (CJN), WanFang database, EMBASE, PsycINFO, Cochrane Library, and PubMed were systematically and dependently searched by 2 reviewers (WZ and D-BC) from their inception until May 27, 2018 for publications on adjunctive memantine in the above psychiatric disorders in Chinese or English language. The search terms are listed in the Supplemental Methods. Additionally, bibliographies of the included studies and reviews (Caddy et al., 2015; Kishi and Iwata, 2013; Kishi et al., 2017a, 2017b; Matsuda et al., 2013; McCloud et al., 2015; Singh and Singh, 2011; Zheng et al., 2018) were scrutinized for further, potentially eligible studies. If there were overlapping data in studies (e.g., Omranifard et al., 2015 and Omranifard et al., 2017), only the study with complete data was included for analyses.

2.3. Data extraction

Data of each selected study were independently extracted and checked by 2 reviewers (X-HY and D-BC) using a standardized Microsoft Excel sheet. Inconsistencies during this process were resolved by consensus. Only data in the first phase (before crossover) were extracted for randomized cross-over studies (Veerman et al., 2016). Missing information was obtained by contacting the first or corresponding authors, or extracted from graphs or figures of the included RCTs using The WebPlotDigitizer 4.1 version (https://automeris.io/WebPlotDigitizer/) if necessary.

2.4. Data analysis

The RevMan 5.3 software was used to pool all meta-analyzable data. A random effects model by DerSimonian and Laird (DerSimonian and Laird, 1986) was applied to all meta-analyzable outcomes given the likely heterogeneity across studies. Summary statistics of continuous outcomes are presented by calculating standardized mean difference (SMD) with their 95% confidence intervals (CIs). Similarly, for meta-analytic pooling of dichotomous outcomes, risk ratios (RR) with their CIs are reported. In cases of unavailability of the standard deviations (SDs) values, the average SDs of other studies (using the same drug and metrics) were applied following recommendations (Leucht et al., 2009). The heterogeneity between studies was measured using I^2 statistics or Q test, with $I^2 \geq 50\%$ and P value<0.1 in Q test indicating heterogeneity of significance.

In case of $I^2 \geq 50\%$ for the efficacy of adjunctive memantine for schizophrenia on symptomatic improvement in total psychopathology, sensitivity analysis was conducted by repeating the analyses after excluding one study that reported an outlying effect size of less than −1.2 (de Lucena et al., 2009). Furthermore, in order to identify the sources of heterogeneity of the primary outcome (total psychopathology) and two key secondary outcomes with clinical relevance (positive and negative symptoms measured with the subscales of the BPRS or the PANSS or the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1983) and/or the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984)), the following subgroup analyses were performed: (i) Chinese vs. non-Chinese studies; (ii) studies with clozapine vs. studies that did not use clozapine; (iii) trial duration (weeks): ≥12 vs. <12; (iv) no sex predominance vs. male predominance (≥60%); (v) Jadad score ≥ 4 vs. Jadad score < 4 (using the weighted mean split of Jadad score); (vi) age (years): ≥39.4 vs. <39.4 (using the weighted mean split of age); and (vii) inpatients vs. outpatients vs. mixed. The following 3 meta-regression analyses for the primary outcome and the two key secondary outcomes were performed to evaluate the moderating effects based on the following continuous variables: (i) PANSS total score at baseline or converted PANSS total score from BPRS total score at baseline (Leucht et al., 2013); (ii) PANSS positive symptom scores at baseline; and (iii) PANSS negative symptom scores at baseline. Publication bias was detected by running an Egger's regression (Egger et al., 1997) and performing a funnel plot if necessary. Statistical differences for all analyses were considered significant when $P < 0.05$ (two-sided).

2.5. Quality assessment

The Jadad scale (Jadad et al., 1996) and the Cochrane risk of bias (Higgins and Higgins, 2008) were administered to assess methodological quality. Jadad total score of 3 or higher was considered as high-quality. Moreover, the grading of recommendations assessment, development, and evaluation (GRADE) was used to evaluate the overall evidence levels for all meta-analyzable outcome measures (Atkins et al., 2004; Balshem et al., 2011).

3. Results

3.1. Search results

The literature search yielded 1348 potentially relevant articles (Fig. 1). Fifteen RCTs comprising 988 patients met the inclusion criteria. In one RCT (Tavakoli-Ardakani et al., 2018) the results presented in the text and tables were different, therefore this study was excluded from the meta-analysis.

3.2. Study characteristics

Fifteen RCTs (schizophrenia: 9 RCTs, n = 512; bipolar disorder: 3 RCTs, n = 319; MDD: 3 RCTs, n = 157) involved 495 patients in the memantine (5–20 mg/day) and 493 patients in the control groups.

3.2.1. Schizophrenia

Of the 512 patients in the 9 RCTs, 259 were on memantine and 253 were controls (Table 1). The weighted mean illness duration was 16.3 years in 8 RCTs with available data; mean age was 39.4 years and 33.8% of the patients were women.

3.2.2. Bipolar disorder

In the 3 RCTs with 319 patients, 158 received memantine and 161 were controls (Table 1). The weighted mean illness duration was 13.8 years in 2 RCTs with available data; mean age was 32.8 years, and 52.9% of the patients were women.

3.2.3. Major depressive disorder

In the 3 RCTs involving 157 patients, 78 were on memantine and 79 were controls (Table 1). The weighted mean illness duration was 0.2 years in the one RCT that had data; mean age was 50.6 years, and 49.8% of the participants were women.

3.3. Quality assessment

The Cochrane risk of bias found that 7 studies (46.7%, 7/15) were considered as low risk regarding allocation concealment, while 10 studies (66.7%, 10/15) described an adequate method of random sequence generation (Supplemental Fig. 1). The weighted mean Jadad scores were 3.9; all RCTs were classified as high-quality. Altogether, the quality of evidence for 27 meta-analyzable outcome measures based on the

GRADE approach ranged from "low" (7.4%, 2/27), via "moderate" (70.4%, 19/27) to "high" (22.2%, 6/27) (Supplemental Table 1).

3.4. Primary and secondary outcomes

3.4.1. Schizophrenia

Nine RCTs investigated the effectiveness and tolerability of memantine as an adjunct treatment for schizophrenia. Memantine co-treatment outperformed the control group regarding total psychopathology with an SMD of −0.56, (95% CI: −1.01, −0.11; $I^2 = 76\%$, P = 0.01) (Supplemental Fig. 2 and Table 2), positive symptoms with an SMD of −0.32 (95% CI: −0.64, 0.00; $I^2 = 66\%$, P = 0.05; Table 2), negative symptoms with an SMD of −0.71 (95% CI: −1.09, −0.33; $I^2 = 74\%$, P = 0.0003; Table 2), but not general psychopathology (P > 0.05). The superiority of memantine remained after removing one RCT with outlying effect size (de Lucena et al., 2009) with respect to total psychopathology with an SMD of −0.38 (95% CI:-0.72, −0.04; $I^2 = 58\%$,P = 0.03) and negative symptoms with an SMD of −0.57 (95% CI: −0.86, −0.28; $I^2 = 57\%$, P = 0.0001), but not positive symptoms (P= 0.12).

Six of the 15 subgroup analyses confirmed the significant superiority of adjunctive memantine for total psychopathology (Table 3). In an exploratory meta-regression analysis, higher PANSS negative symptom scores at baseline (slope = −0.038, P = 0.027) were significantly associated with greater efficacy of adjunctive memantine for total psychopathology, but baseline PANSS total and positive symptom scores were not (P > 0.05).

Similarly, 12 of the 15 subgroup analyses found significant superiority of adjunctive memantine for negative symptoms (Table 3). In an exploratory meta-regression analysis, no significant findings were related to negative symptom change (P > 0.05). However, 13.3% (2/15) of the subgroups (Table 3) showed an advantage of adjunctive memantine over controls for positive symptoms, including studies with non-Chinese patients and with a mean age of <39.4 years. In an exploratory meta-regression analysis, higher baseline PANSS negative symptom scores (slope = −0.055, P = 0.001) were significantly related to greater efficacy of adjunctive memantine for positive symptoms, but baseline PANSS total and positive symptom scores were not (P > 0.05).

The advantage of adjunctive memantine over controls was also found with regard to MMSE with an SMD of 1.07 (CI: 0.53, 1.61; P < 0.0001, $I^2 = 29\%$), but not to CGI-S scores (P > 0.05) (Table 3).

Rates of discontinuation (RR = 1.34, P > 0.05) and ADRs including fatigue, nausea, diarrhea, dizziness, insomnia, headache, anxiety, and constipation (RR = 0.98 to 1.86, P > 0.05) were similar between the memantine and control groups (Table 2).

3.4.2. Bipolar disorder

Three RCTs of the effectiveness and tolerability of adjunctive memantine were conducted in bipolar disorder. One RCT (Sahraian

Table 2
Primary and secondary outcomes.

Variables	Studies (no. of subjects)	SMDs/RRs (95%CI)	I^2 (%)	P
Schizophrenia				
Clinical efficacy:				
Total psychopathology score	7 (395)	−0.56 (−1.01, −0.11)	76	**0.01**
Positive symptom score	9 (501)	−0.32 (−0.64, 0.00)	66	0.05
Negative symptom score	9 (501)	−0.71 (−1.09, −0.33)	74	**0.0003**
General psychopathology score	5 (236)	−0.27 (−0.64, 0.09)	49	0.14
MMSE	3 (93)	1.07 (0.53, 1.61)	29	<**0.0001**
CGI-S	3 (205)	0.05 (−0.25, 0.34)	8	0.76
Discontinuation rate:				
Discontinuation due to any reason	6 (362)	1.34 (0.76, 2.37)	0	0.31
ADRs:				
Fatigue	3 (236)	1.86 (0.83, 4.15)	0	0.13
Dizziness	5 (283)	1.34 (0.66, 2.73)	0	0.42
Insomnia	2 (196)	0.98 (0.41, 2.37)	0	0.97
Anxiety	2 (176)	1.27 (0.47, 3.42)	0	0.64
Headache	5 (322)	1.48 (0.82, 2.68)	0	0.19
Constipation	5 (326)	1.64 (0.82, 3.28)	0	0.16
Diarrhea	2 (162)	1.20 (0.40, 3.62)	0	0.74
Nausea	5 (317)	1.14 (0.53, 2.43)	0	0.74
Bipolar disorder				
Clinical efficacy:				
HAMD total scores	2 (186)	−0.13 (−0.42, 0.16)	0	0.37
YMRS total scores	1 (157)	−0.27 (−0.58, 0.05)	N/A	0.09
Discontinuation rate:				
Discontinuation for any reason	3 (319)	0.87 (0.63, 1.20)	0	0.40
ADRs:				
Dizziness	2 (290)	1.02 (0.11, 9.62)	0	0.99
Major depressive disorder				
Clinical efficacy:				
HAMD total scores	3 (150)	−0.09 (−0.67, 0.48)	67	0.75
Discontinuation rate:				
Discontinuation for any reason	3 (157)	0.77 (0.23, 2.56)	0	0.67
ADRs:				
Dizziness	3 (150)	0.61 (0.23, 1.65)	0	0.33
Insomnia	2 (93)	0.77 (0.28, 2.11)	0	0.62
Sedation	2 (93)	0.92 (0.34, 2.44)	0	0.86
Headache	3 (150)	1.29 (0.62, 2.68)	0	0.50
Nausea	3 (150)	0.82 (0.23, 2.88)	40	0.76
Skin rash	3 (150)	1.43 (0.27, 7.59)	13	0.67

Abbreviations: ADRs = adverse drug reactions; CI = confidence intervals; CGI-S=Clinical Global Impression of Severity; HAMD = Hamilton Depression Scale; MMSE = Mini-mental State Examination; N/A = Not applicable; RRs = risk ratio; SMDs = standardized mean differences; YMRS=Young Manic Rating Scale; RCT = randomized controlled trial.
Bolded values: P< 0.05.

Table 3
Subgroup analyses of the clinical efficacy of memantine in schizophrenia.

Variables		Studies (subjects)	SMDs (95%CI)	I^2 (%)	P
Total psychopathology scores					
1.	Chinese	1 (64)	−0.67 (−1.17, −0.16)	N/A	**0.009**
	Non-Chinese	6 (331)	−0.56 (−1.09, −0.02)	79	**0.04**
2.	Antipsychotic class: clozapine	3 (134)	−0.95 (−2.04, 0.14)	87	0.09
	Other than clozapine	4 (261)	−0.40 (−0.87, 0.08)	67	0.10
3.	Trial duration (weeks): ≥ 12	5 (220)	−0.75 (−1.40, −0.10)	80	**0.02**
	Trial duration (weeks): < 12	2 (175)	−0.16 (−0.46, 0.13)	0	0.28
4.	Male predominance (≥ 60%)	4 (231)	−0.50 (−1.24, 0.24)	81	0.19
	No sex predominance	3 (164)	−0.72 (−1.08, −0.36)	19	<**0.0001**
5.	Jadad score[a] ≥ 4	4 (175)	−0.39 (−0.90, 0.12)	63	0.13
	Jadad score < 4	3 (220)	−0.94 (−1.91, 0.04)	88	0.06
6.	Age (years)[a]: ≥ 39.4	4 (274)	−0.21 (−0.52, 0.09)	30	0.17
	Age (years): < 39.4	3 (121)	−1.21 (−2.19, −0.23)	81	**0.02**
7.	Inpatients	3 (196)	−0.86 (−1.90, 0.18)	87	0.11
	Outpatients	3 (150)	−0.65 (−1.15, −0.14)	53	**0.01**
	Mixed	1 (49)	−0.00 (−0.56, 0.56)	N/A	1.00
Positive symptom scores					
1.	Chinese	1 (64)	0.11 (−0.38, 0.60)	N/A	0.66
	Non-Chinese	8 (437)	−0.38 (−0.73, −0.03)	67	**0.03**
2.	Antipsychotic class: clozapine	3 (134)	−0.28 (−0.94, 0.38)	69	0.41
	Other than clozapine	6 (367)	−0.35 (−0.75, 0.05)	69	0.09
3.	Trial duration (weeks): ≥ 12	6 (261)	−0.32 (−0.68, 0.05)	52	0.09
	Trial duration (weeks): < 12	3 (235)	−0.32 (−1.04, 0.40)	84	0.38
4.	Male predominance (≥60%)	5 (277)	−0.22 (−0.62, 0.18)	56	0.29
	No sex predominance	4 (224)	−0.41 (−0.94, 0.11)	74	0.13
5.	Jadad score[a] ≥ 4	5 (221)	−0.28 (−0.56, −0.00)	7	0.05
	Jadad score < 4	4 (280)	−0.45 (−1.11, 0.22)	84	0.19
6.	Age (years)[a]: ≥ 39.4	5 (320)	0.00 (−0.22, 0.22)	0	1.00
	Age (years): < 39.4	4 (181)	−0.71 (−1.19, −0.23)	56	**0.004**
7.	Inpatients	5 (256)	−0.42 (−0.86, 0.02)	66	0.06
	Outpatients	3 (196)	−0.28 (−0.94, 0.38)	72	0.41
	Mixed	1 (49)	−0.04 (−0.60, 0.52)	N/A	0.89
Negative symptom scores					
1.	Chinese	1 (64)	−0.67 (−1.18, −0.17)	N/A	**0.009**
	Non-Chinese	8 (437)	−0.73 (−1.17, −0.29)	77	**0.001**
2.	Antipsychotic class: clozapine	3 (134)	−1.13 (−2.39, 0.14)	90	0.08
	Other than clozapine	6 (367)	−0.65 (−1.00, −0.30)	58	**0.0003**
3.	Trial duration (weeks): ≥ 12	6 (266)	−0.85 (−1.46, −0.25)	80	**0.006**
	Trial duration (weeks): < 12	3 (235)	−0.54 (−0.95, −0.12)	53	**0.01**
4.	Male predominance (≥ 60%)	5 (277)	−0.72 (−1.42, −0.02)	84	**0.04**
	No sex predominance	4 (224)	−0.80 (−1.08, −0.53)	0	<**0.00001**
5.	Jadad score[a] ≥ 4	5 (221)	−0.54 (−1.01, −0.07)	65	**0.02**
	Jadad score < 4	4 (280)	−1.02 (−1.73, −0.30)	85	**0.006**
6.	Age (years)[a]: ≥ 39.4	5 (320)	−0.41 (−0.78, −0.05)	56	**0.02**
	Age (years): < 39.4	4 (181)	−1.20 (−1.92, −0.48)	77	**0.001**
7.	Inpatients	5 (256)	−0.81 (−1.12, −0.50)	31	<**0.00001**
	Outpatients	3 (196)	−1.11 (−2.25, 0.02)	88	0.05
	Mixed	1 (49)	0.01 (−0.55,0.57)	N/A	0.96

Abbreviations: CI = confidence interval; N/A = Not applicable; SMDs = Standard mean differences.
Bolded values: P< 0.05.
[a] Analyzed using a mean split.

et al., 2017) examining bipolar mania found memantine advantageous in reducing obsessive compulsive symptoms. Two RCTs (Anand et al., 2012; Lee et al., 2014) of bipolar depression found no group differences regarding depressive and manic symptoms (P > 0.05, Table 2). Rates of discontinuation (RR = 0.87, P > 0.05) and ADRs (dizziness; RR = 1.02, P > 0.05) did not show any group differences (Table 2).

3.4.3. Major depressive disorder

Three RCTs investigated the efficacy and tolerability of adjunct memantine for MDD. No significant group difference was found regarding the improvement of depressive symptoms (P > 0.05, Table 2). Only one study (Omranifard et al., 2014) examined neurocognitive performance using the MMSE and reported no significant group difference (Supplemental Table 2). Rates of discontinuation (RR = 0.77, P > 0.05) and ADRs (dizziness, insomnia, sedation, headache, nausea, and skin rash; RR = 0.61 to 1.43, P > 0.05) were similar between the memantine and control groups (Table 2).

3.4.4. Publication bias

Publication bias for primary and secondary outcomes could not be assessed by performing a funnel plot graph or running Egger's regression because the number of RCTs in each disorder was <10.

4. Discussion

This meta-analysis of 15 RCTs that targeted the efficacy and tolerability of memantine as an adjunct treatment covered three major mental disorders. The results supported the partial efficacy of adjunctive memantine for schizophrenia, but not for bipolar disorder and MDD. These results are in line with the findings of meta-analyses on schizophrenia (Kishi and Iwata, 2013; Matsuda et al., 2013; Singh and Singh, 2011; Zheng et al., 2018), bipolar disorder (McCloud et al., 2015), MDD (Caddy et al., 2015) and mood disorders (Kishi et al., 2017b).

Studies using combination of memantine and antipsychotics and those using memantine monotherapy (Zarate Jr. et al., 2006) were

directly pooled in the two meta-analyses (Caddy et al., 2015; Kishi et al., 2017b), which increases heterogeneity caused by different study designs. Memantine also appeared safe and well-tolerated without significant group differences across the three disorders.

The superiority of memantine co-treatment over comparator was found in the improvement of total psychopathology with a moderate effect size (SMD = -0.56) and negative symptoms with a moderate effect size (SMD = -0.71) in schizophrenia, but not regarding positive symptoms and general psychopathology in schizophrenia, or mood symptoms in both bipolar disorder and MDD. The overall quality levels of negative symptoms and total psychopathology were "moderate" and "low" according to the GARDE approach, which reduces the confidence of the findings. The therapeutic effect of memantine as an adjunct treatment for schizophrenia may be related to its role in the improvement of glutamatergic tonus (de Lucena et al., 2009), enhancing neuroprotective effects (Krebs et al., 2006), and reducing activation of the NMDAR subtype (Tsai and Coyle, 2002). The reason why memantine as an adjunct treatment was only superior to comparator in improving negative symptoms in schizophrenia but not in bipolar disorder and MDD is not clear. It may be due to the small number of studies on bipolar disorder and MDD that limited the statistical power of the findings.

Memantine may also improve neurocognitive dysfunction in patients with moderate to severe AD (Puangthong and Hsiung, 2009; Rogawski and Wenk, 2010). Galantamine-memantine combination could improve neurocognitive impairment caused by traumatic brain injury (Koola, 2018). In this meta-analysis, only 40% (6/15) of RCTs examined the effects of memantine on neurocognitive functions administering various instruments. In 4 of these RCTs where the MMSE was the measurement, memantine was superior for schizophrenia based on 3 RCTs with meta-analytic result, but not for MDD (1 RCT). The improvement of neurocognitive performance owing to memantine as an adjunct treatment for schizophrenia supported previous findings (Kishi and Iwata, 2013; Kishi et al., 2017a; Matsuda et al., 2013; Zheng et al., 2018). The beneficial effects of memantine on cognitive functions may be the result of the reduction of NMDAR overactivity (Zhang et al., 2018) and neuronal oxidative stress (Gama et al., 2007; Gama et al., 2005). However, the MMSE is not a specific instrument to evaluate neurocognitive performance, and these results should be interpreted with caution. Future studies should consider more sophisticated, disease-specific measures on cognition, such as the MATRICS Consensus Cognitive Battery (MCCB) for schizophrenia. Furthermore, aspects pertaining to cognitive performance (Bailey et al., 2017), such as genetic factors, were not examined.

Compared to other NMDA receptor antagonists, such as ketamine that may have adverse cardiovascular and respiratory effects (e.g., hypertension and respiratory depression) (Dunn et al., 2016), memantine seems to be safe, although it is pharmacologically classified as a NMDAR partial antagonist. The possible reason for memantine's safety maybe be due to its low occupancy (around 30%) only of NMDA receptors in the brain (Kantrowitz, 2019; More et al., 2008). Moreover, memantine at therapeutic doses may exert its therapeutic effect in neurological disorders by stimulating dopaminergic transmission (Mazinani et al., 2017) but not acting primarily as an NMDAR antagonist (Periclou et al., 2006).

The following limitations of the study should be acknowledged. First, the number of RCTs examining the effectiveness and tolerability of memantine for bipolar disorder (3 RCTs) and MDD (3 RCTs) were relatively small, which could increase the type II error (Lelorier et al., 1997) and preclude more sophisticated analyses. Second, superiority of memantine as an adjunct treatment for negative symptoms was only reported in one RCT over sixteen weeks of treatment (Mazinani et al., 2017), but not observed in other RCTs (14/15, 93.3%) that had shorter duration (6–12 weeks). It may well be that a robust therapeutic effect of memantine needs relatively longer treatment duration than 12 weeks (Puangthong and Hsiung, 2009). Third, as the memantine dose varied from 5 to 20 mg/day, the relationship between efficacy and doses could not be evaluated. Fourth, studies had a variety of co-prescribed antipsychotics, mood stabilizers, and antidepressants, which could account, in part, for the highly heterogeneous results. Finally, all selected RCTs in the meta-analysis were conducted in physically healthy patients, thus limiting the generalizability of the findings to real-world clinical populations.

5. Conclusion

Adjunctive memantine appears to be partially effective for schizophrenia while the results of its efficacy and safety for bipolar disorder and MDD are preliminary due to the small number of studies. The long-term benefits and safety of memantine as an adjunct treatment in major mental disorders require further investigations.

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Declaration of Competing Interest

The authors declare that they have no conflicts of interest concerning this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2019.05.019.

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