Psychological Medicine (2018), **48**, 72–81. © Cambridge University Press 2017
doi:10.1017/S0033291717001271

ORIGINAL ARTICLE

Adjunctive memantine for schizophrenia: a meta-analysis of randomized, double-blind, placebo-controlled trials

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Background. Dysfunction of *N*-methyl-D-aspartate receptor (NMDAR) is involved in the pathophysiology of schizophrenia. A meta-analysis of randomized controlled trials (RCTs) was conducted to examine the efficacy and safety of memantine, a non-competitive NMDAR antagonist, in the treatment of schizophrenia.

Methods. Standardized/weighted mean differences (SMDs/WMDs), risk ratio (RR), and their 95% confidence intervals (CIs) were calculated and analyzed.

Results. Included in the meta-analysis were eight RCTs ($n = 452$) of 11.5 ± 2.6 weeks duration, with 229 patients on memantine (20 mg/day) and 223 patients on placebo. Adjunctive memantine outperformed placebo in the measures of Positive and Negative Syndrome Scale and Brief Psychiatric Rating Scale negative symptoms [SMD: −0.63 (95% CI −1.10 to −0.16), $p = 0.009$, $I^2 = 77\%$], but not in the total, positive and general symptoms [SMD: −0.46 to −0.08 (95% CI −0.93 to 0.22), $p = 0.06$–0.60, $I^2 = 0$–74%] or the Clinical Global Impression Severity Scale [WMD: 0.04 (95% CI −0.24 to 0.32), $p = 0.78$]. The negative symptoms remained significant after excluding one outlying RCT [SMD: −0.41 (95% CI −0.72 to −0.11), $p = 0.008$, $I^2 = 47\%$]. Compared with the placebo group, adjunctive memantine was associated with significant improvement in neurocognitive function using the Mini-Mental State Examination (MMSE) [WMD: 3.09, (95% CI 1.77–4.42), $p < 0.00001$, $I^2 = 22\%$]. There was no significant difference in the discontinuation rate [RR: 1.34 (95% CI 0.76–2.37), $p = 0.31$, $I^2 = 0\%$] and adverse drug reactions between the two groups.

Conclusions. This meta-analysis showed that adjunctive memantine appears to be an efficacious and safe treatment for improving negative symptoms and neurocognitive performance in schizophrenia. Higher quality RCTs with larger samples are warranted to confirm these findings.

Received 9 February 2017; Revised 12 April 2017; Accepted 13 April 2017; First published online 22 May 2017

Key words: Memantine, meta-analysis, negative symptoms, NMDA receptor antagonists, schizophrenia.

Introduction

Schizophrenia is a severe psychiatric disorder affecting approximately 1% of the population worldwide. For instance, the estimated direct and indirect costs amounted to $62.7 billion in the USA in 2002 (Wu *etal.* 2005). Although its etiology is still unclear, glutamate deregulation, mainly through *N*-methyl-D-aspartate receptor (NMDAR) dysfunction, may play an important role in the neurobiology of schizophrenia (Tsai & Lin, 2010; Field *et al.* 2011; Moghaddam & Javitt, 2012). A meta-analysis (Singh & Singh, 2011) of 29 randomized controlled trials (RCTs) found that NMDAR modulators appear to be superior than placebo in improving negative and general symptoms of schizophrenia.

To date, of the NMDAR antagonists, only memantine and amantadine have been approved to use in

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humans (Carroll *et al.* 2007; Kishi & Iwata, 2013). As a non-competitive NMDAR antagonist, memantine has been approved by the Food and Drug Administration (FDA) for treatment of moderate-to-severe Alzheimer's disease (AD) (Koch *et al.* 2005) and has been used off-label for various psychiatric disorders, including schizophrenia (Zdanys & Tampi, 2008). Case series (Gama *et al.* 2005; John *et al.* 2014) and an observational study (Krivoy *et al.* 2008) have found that memantine may be useful as an adjunctive medication in the treatment of schizophrenia. However, the results of published RCTs (de Lucena *et al.* 2009; Lieberman *et al.* 2009; Gu *et al.* 2012; Lee *et al.* 2012; Rezaei *et al.* 2013; Omranifard *et al.* 2015; Veerman *et al.* 2016) focusing on the efficacy and safety of adjunctive memantine for schizophrenia have been conflicting.

The effect of memantine for schizophrenia has been examined in meta-analyses (Singh & Singh, 2011; Kishi & Iwata, 2013; Matsuda *et al.* 2013), but these studies had limited number of RCTs and power. Furthermore, previous meta-analyses did not include non-English databases or the recently published RCTs (Omranifard *et al.* 2015; Mazinani *et al.* 2016; Veerman *et al.* 2016). Thus, we conducted this meta-analysis of RCTs to systematically assess the efficacy and safety of adjunctive memantine for schizophrenia.

Methods

Selection criteria

According to the *PICOS* acronym based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher *et al.* 2009), the following selection criteria were presented: Participants (*P*): adult patients (age $\geqslant$18 years) with schizophrenia based on any diagnostic criteria; Intervention (*I*): memantine plus antipsychotics (APs); Comparison (*C*): APs plus placebo; Outcomes (*O*): efficacy with meta-analyzable data and safety; Study design (*S*): RCTs. Non-blinded studies were excluded because open studies could be biased toward the study sponsors (Leucht *et al.* 2009*a*).

Search strategy

Two reviewers independently searched English (PubMed, PsycINFO, EMBASE, and Cochrane Library databases) and Chinese databases (WanFang, Chinese Biomedical, and China Journal Net databases), from their inception until 15 December 2016 for RCTs examining the efficacy and safety of adjunctive memantine for schizophrenia. The search terms was presented as follows: (memantine OR memantin OR 1, 3-Dimethyl-5-aminoadamantane OR Namenda OR 1-Amino-3, 5-dimethyladamantane OR Ebixa OR Axura) AND (schizophrenic disorder OR disorder, schizophrenic OR schizophrenic disorders OR schizophrenia OR dementia praecox) AND (placebo OR random*). The electronic search was supplemented by hand-searching reference lists of identified RCTs, pertinent reviews, and meta-analyses (Singh & Singh, 2011; Kishi & Iwata, 2013; Matsuda *et al.* 2013).

Outcome measures

Co-primary outcomes were the total score of the Positive and Negative Syndrome Scale (PANSS) (Kay *et al.* 1987) or the Brief Psychiatric Rating Scale (BPRS) (Overall & Gorham, 1962) at endpoint and the negative symptom scores assessed by the PANSS negative symptoms subscale or the BPRS negative symptoms cluster. The key secondary outcomes were as follows: positive symptoms as assessed by the PANSS positive symptoms subscale or the BPRS positive symptoms cluster; general symptoms as assessed by the PANSS general symptoms subscale; global illness severity as assessed by the Clinical Global Impression Severity Scale (CGI-S) (Guy, 1976); neurocognitive symptoms as assessed by the Mini-Mental State Examination (MMSE) (Folstein *et al.* 1975); discontinuation rate; and the frequency of adverse drug reactions (ADRs). Results based on intention-to-treat (ITT) or modified ITT data were preferred to observed cases data.

Data extraction

Data were independently checked, extracted, and analyzed by two reviewers, calculating results from graphs or figures if possible, and if necessary resolving inconsistencies by consensus or involvement of a third reviewer. If the same data were reported in more than one RCT, only the RCT with complete data was included and analyzed. For randomized cross-over studies, only data in the first randomized study phase prior to cross-over were extracted and analyzed (Veerman *et al.* 2016). The first/corresponding authors were contacted for missing data, if necessary.

Statistical methods

Continuous and dichotomous data were analyzed using weighted/standardized mean differences (WMDs/SMDs) and risk ratio (RR) with their 95% confidence interval (CI). Number needed to harm was calculated as the inverse of the risk difference (RD) where appropriate. All meta-analyzable outcome measures were pooled with the random-effect model of DerSimonian and Laird (DerSimonian & Laird, 1986). For missing standard deviations (S.D.), the average S.D. of other RCTs with the same medication and metrics were used (Leucht *et al.* 2009*b*). Study heterogeneity was

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explored using I^2 statistics and Q test of homogeneity, with $I^2 > 50\%$ and $p < 0.1$ indicating significant heterogeneity. In order to examine the credibility of co-primary outcomes, a sensitivity analysis was performed by removing one study (de Lucena *et al.* 2009) with an outlying effect size of <−1.5 (i.e. more than one and a half S.D. superiority of memantine). Furthermore, six subgroup analyses were conducted to explain the heterogeneity of negative symptoms: (1) Chinese *v.* non-Chinese; (2) clozapine *v.* other than clozapine; (3) trial duration (weeks): 8 *v.* 12 *v.* 16; (4) male predominance (⩾60%) *v.* no sex predominance; (5) age (years): ⩾39.5 *v.* <39.5 (using the mean split of age); and (6) Jadad score ⩾4 *v.* <4 (using the mean split of Jadad score). In addition, meta-regression analyses of three continuous variables with available data were conducted for negative symptoms to examine the potential mediating effect: (1) baseline total psychopathology scores, (2) baseline positive symptom scores, and (3) baseline negative symptom scores.

Funnel plots and Egger's intercept (Egger *et al.* 1997) were conducted to investigate whether publication bias existed using the Comprehensive Meta-Analysis, Version 2 (www.meta-analysis.com) whenever possible. All meta-analyzable data were analyzed with the RevMan (Version 5.3) software (http://www.cochrane.org) according to the recommendations of the Cochrane Collaboration (Higgins & Higgins, 2008), which were considered significant at the level of 0.05 (two sided).

Assessment of study quality

The Cochrane risk of bias (Higgins & Higgins, 2008) and the Jadad scale (Jadad *et al.* 1996) were used to assess the quality of RCTs by two independent reviewers according to the Cochrane Handbook for Systematic Reviews (Higgins & Higgins, 2008). The latter was used to define the quality of included RCTs as either high or low quality based on Jadad score ⩾3 and <3, respectively. Additionally, the grading of recommendations assessment, development, and evaluation (GRADE) system (Atkins *et al.* 2004; Balshem *et al.* 2011) was used to assess the quality of evidence of all meta-analyzable outcomes, being rated as 'very low', 'low', 'moderate', or 'high' (online Supplementary Table S1).

Results

Results of the search

The original search yielded 200 hits. After excluding duplicate articles (26 trials), and reviewing the titles or abstracts (147 trials) and full texts (19 trials), eight RCTs (de Lucena *et al.* 2009; Lieberman *et al.* 2009; Gu *et al.* 2012; Lee *et al.* 2012; Rezaei *et al.* 2013; Omranifard *et al.* 2015; Mazinani *et al.* 2016; Veerman *et al.* 2016) with meta-analyzable data were eligible and included in the meta-analysis (Fig. 1).

Study, patient, and treatment characteristics

Included in the above eight RCTs of 8–16 (mean = 11.5 ± 2.6, median = 12.0) weeks duration were 452 randomized patients, including 229 patients on memantine and 223 patients on placebo (Table 1). The patients were 39.5 ± 4.9 years old, 70.2 ± 17.3% were male, and 51.4 ± 52.1% were inpatients. Almost all patients had a diagnosis of schizophrenia ($n = 451$, 99.8%) and only 1 (0.2%) had schizoaffective disorder. Two RCTs (de Lucena *et al.* 2009; Veerman *et al.* 2016) were conducted in treatment-refractory schizophrenia, while the remaining RCTs were conducted in chronic patients. Of the eight RCTs, three were conducted in Iran ($n = 150$), and one each in Brazil ($n = 22$), USA ($n = 138$), Korea ($n = 26$), China ($n = 64$), and the Netherlands ($n = 52$). Memantine was typically started at a low dose and titrated to 20 mg/day as the target dose in all RCTs (Table 1).

Quality assessment

While all included RCTs were double-blinded studies (online Supplementary Fig. S1), only five RCTs (63%) reported randomization methods based on a specific description. Moreover, all RCTs were rated as unclear with respect to other sources of bias. The Jadad scores ranged from 3 to 5 (mean = 4.1 ± 1.0, median = 4.5), and all RCTs were rated as high quality (Table 1). According to the GRADE approach, the quality of evidence of 14 meta-analyzable outcome measures were rated as 'low' (7.1%), 'moderate' (71.5%), and 'high' (21.4%) (online Supplementary Table S1).

Primary outcomes

There were no significant differences between adjunctive memantine and placebo groups at endpoint in terms of total psychopathology scores [six RCTs, $n = 335$; SMD: −0.46 (95% CI −0.93 to 0.01), $p = 0.06$, $I^2 = 74\%$; Fig. 2]. The result remained not significant after one outlying study (de Lucena *et al.* 2009) was removed [five RCTs, $n = 314$; SMD: −0.23 (95% CI −0.48 to 0.01), $p = 0.07$, $I^2 = 12\%$].

Adjunctive memantine however outperformed placebo at endpoint in terms of negative symptoms [seven RCTs, $n = 381$; SMD: −0.63 (95% CI −1.10 to −0.16), $p = 0.009$, $I^2 = 77\%$; Fig. 2]. The result remained significant after excluding the one outlying RCT (de Lucena *et al.* 2009) [six RCTs, $n = 360$; SMD: −0.41 (95% CI −0.72 to −0.11), $p = 0.008$, $I^2 = 47\%$].

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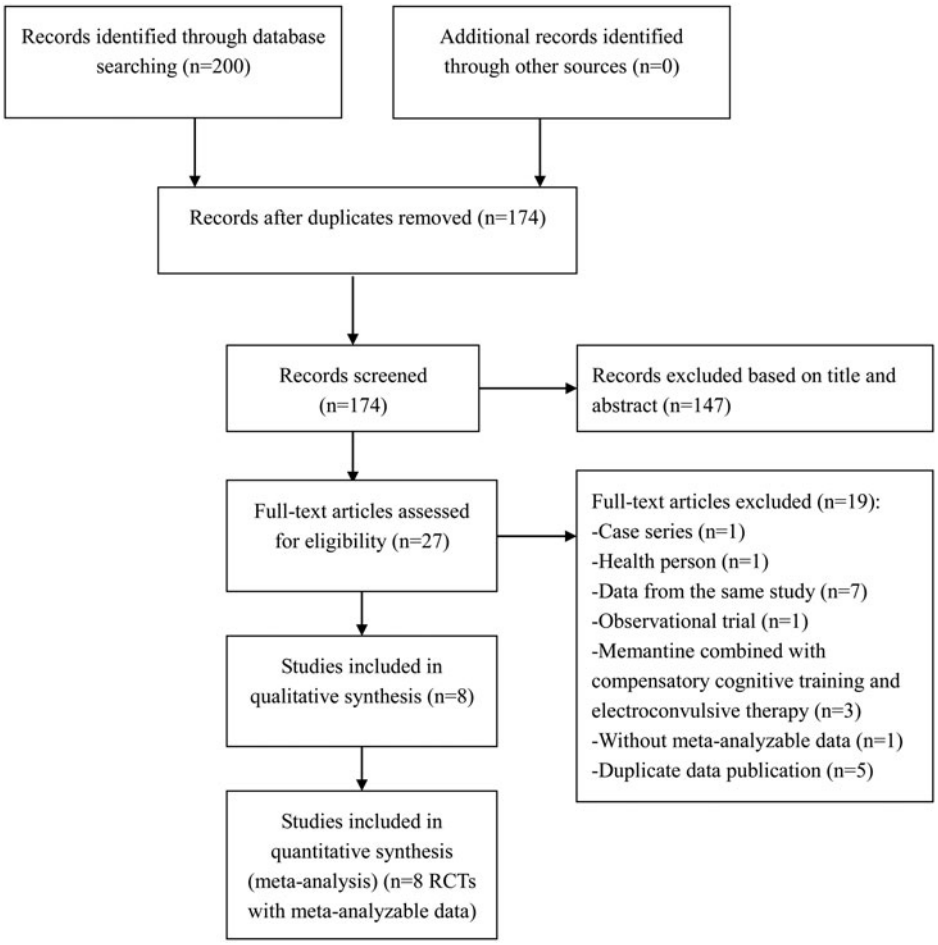

Fig. 1. PRISMA flow diagram.

Superiority of adjunctive memantine for negative symptoms was confirmed in eight out of the 13 subgroups (Table 2). Significance diminished to a trend in studies lasting 8 weeks (two RCTs, $p = 0.05$). Significance was absent in studies using clozapine treatment (three RCTs, $p = 0.08$), lasting 12 weeks (four RCTs, $p = 0.09$), and having a mean age younger than 39.5 years (two RCTs, $p = 0.21$) and Jadad scores more than 4 (four RCTs, $p = 0.13$) (Table 2). In meta-regression analyses, lower baseline total psychopathology scores [missing data in one RCT (Mazinani *et al.* 2016), slope = 0.019, $p = 0.037$, online Supplementary Fig. S2] and lower baseline positive symptom scores (slope = 0.116, $p = 0.0003$, online Supplementary Fig. S3) predicted greater efficacy of adjunctive memantine on negative symptom scores. However, baseline negative symptom scores did not show any association with the efficacy of adjunctive memantine on negative symptom scores (slope = −0.002, $p = 0.891$).

Due to the limited number of RCTs for co-primary outcomes (<10 trials), the funnel plot or Egger's test could not be used to judge publication bias of total psychopathology and negative symptoms according to Sterne *et al.*'s suggestion (Sterne *et al.* 2011).

Secondary outcomes

There was no significant difference between adjunctive memantine and placebo groups in terms of positive symptoms [seven RCTs, $n = 381$; SMD: −0.12 (95% CI −0.39 to 0.16), $p = 0.40$, $I^2 = 38\%$; Fig. 2] and general psychopathology scores [four RCTs, $n = 176$; SMD: −0.08 (95% CI −0.37 to 0.22), $p = 0.60$, $I^2 = 0\%$; Fig. 2] at endpoint.

Adjunctive memantine outperformed placebo in the MMSE [three RCTs, $n = 93$; WMD: 3.09 (95% CI 1.77–4.42), $p < 0.00001$, $I^2 = 22\%$; Fig. 3], but not with respect to CGI-S scores [three RCTs, $n = 205$; WMD: 0.04 (95% CI −0.24 to 0.32), $p = 0.78$, $I^2 = 10\%$; online Supplementary Fig. S4].

Treatment discontinuation and ADRs

All-cause discontinuation [six RCTs, $n = 362$; RR: 1.34 (95% CI 0.76–2.37), $p = 0.31$, $I^2 = 0\%$; online Supplementary

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Table 1. *Patient and treatment characteristics of the included studies*

Study (Country)	Number of patients	Blinding	Analyses	Trial duration (weeks)	Setting (%)	Diagnosis (%)	Diagnostic criteria	Illness severity (PANSS/BPRS)[a]/ duration	Age[a]: years (range)	Sex[a]: male (%)	Control-group: dose (mg/day): mean (range)	Intervention-group: dose (mg/day): mean (range)		Jadad score
de Lucena *et al.* (2009) (Brazil)	T: 22 C: 11 I: 11	DB	ITT	12	Outpatients (100)	SCZ (100)	DSM-IV	−40.3 −17.8 years	34.7 (18–65)	90.5	CLZ: Ø = 659 (NR)	CLZ: Ø = 540 (NR)	MEM: Ø = 20 (5–20)	3
Gu *et al.* (2012) (China)	T: 64 C: 32 I: 32	DB	ITT	12	Inpatients (100)	SCZ (100)	CCMD-3	−83.5 −15.7 years	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	−74.6 −13.0 years	43.9 (18–50)	61.5	AP[b]: Ø = NR (NR)	AP[b]: Ø = NR (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	−74.0 −16.5 years	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.* (2016) (Iran)	T: 46 C: 23 I: 23	DB	ITT	16	Inpatients (100)	SCZ (100)	DSM-IV	− NR −24.6 years	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	−NR −9.0 years	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	−45.3 −10.9 years	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, cross-over[e]	ITT	12	In- (12) and outpatients (88)	SCZ (100)	DSM-IV	−81.2 −22.9 years	42.4 (18–60)	75.0	CLZ[f]: Ø = NR (NR)	CLZ[f]: Ø = NR (NR)	MEM: Ø = 20 (10–20)	5

Ø = mean.

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

[b] Did not report the detailed 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 drug including non-clozapine APs, antidepressant, mood stabilizer, and benzodiazepine.

APs, antipsychotics; BPRS, Brief Psychiatric Rating Scale; C, control; CCMD-3, China's Mental Disorder Classification and Diagnosis Standard 3th edition; CLZ, clozapine; 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; FD, fixed dosage; I, intervention; ITT, intention-to-treat; MEM, memantine; NR, not reported; OC, observed cases; PANSS, Positive and Negative Syndrome Scale; RIS, risperidone; SCZ, schizophrenia; SzA, schizoaffective disorders; T, total.

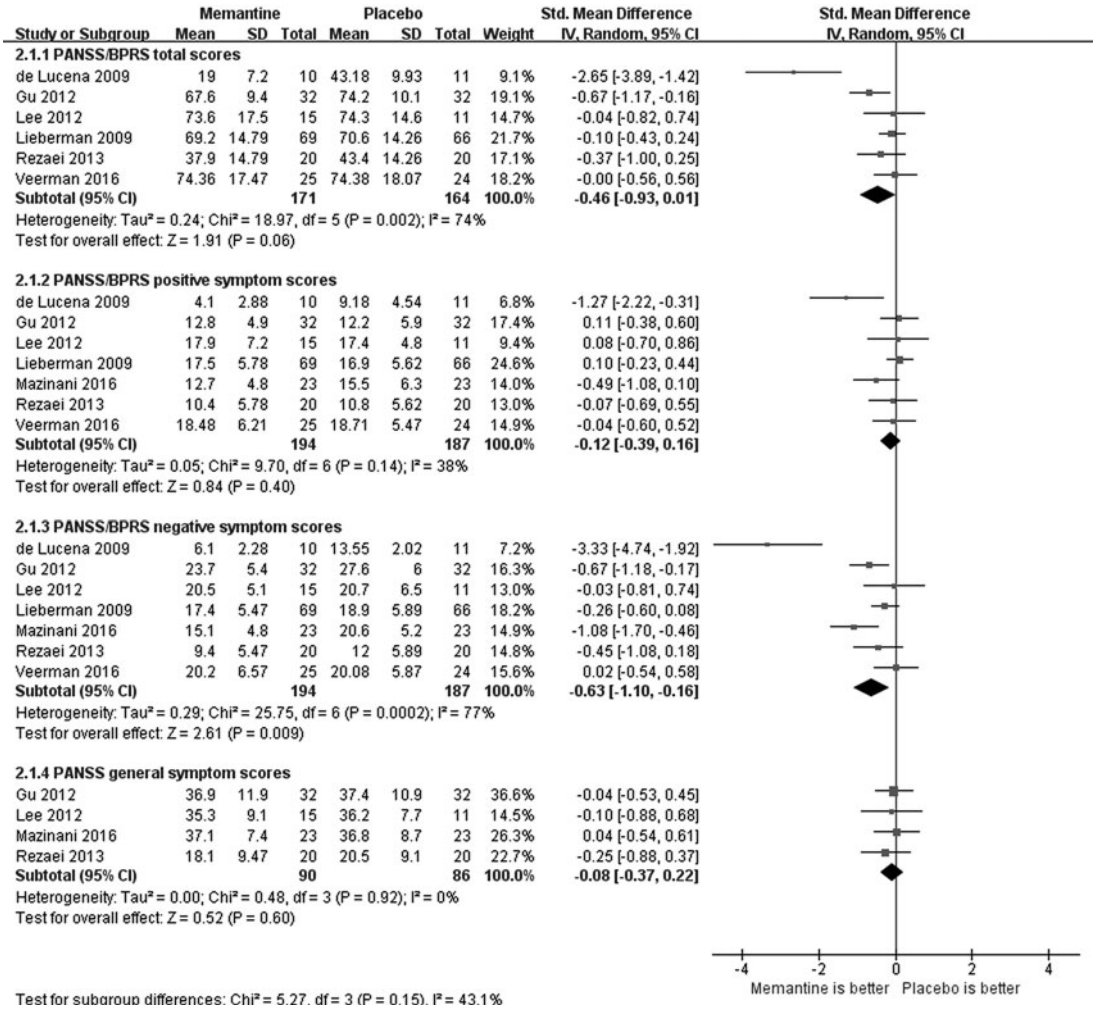

Fig. 2. Adjunctive memantine for schizophrenia: forest plot for the endpoint Positive and Negative Syndrome Scale (PANSS)/Brief Psychiatric Rating Scale (BPRS) total scores, PANSS/BPRS positive symptom scores, PANSS/BPRS negative symptom scores, and PANSS general symptom scores.

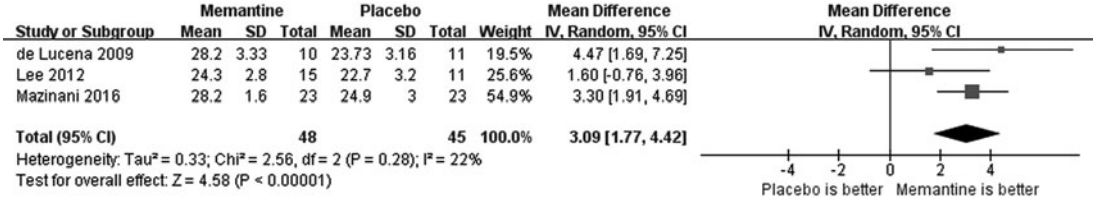

Fig. 3. Adjunctive memantine for schizophrenia: forest plot for neurocognitive function as assessed by the Mini-Mental State Examination (MMSE) at endpoint.

Fig. S5] was similar between adjunctive memantine and placebo groups.

Meta-analyses of ADRs, including fatigue, dizziness, constipation, anxiety, headache, diarrhea, and nausea [RR: 1.07–1.97 (95% CI 0.40–4.91), $p = 0.14$–0.88, $I^2 = 0\%$; online Supplementary Fig. S6] did not show significant group difference. Only one RCT (Omranifard *et al.* 2015) assessed global function and quality of life, showing an advantage with adjunctive memantine. Furthermore, one study (de Lucena *et al.* 2009) found memantine was associated with weight loss.

Discussion

This comprehensive meta-analysis of eight randomized, double-blinded, placebo-controlled studies of

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Table 2. *Subgroup analysis of the effect of mediator variables on the 'negative symptoms outcome'*

Variables	*N* (subjects)	SMDs (95% CI)	I^2 (%)	*p*
1. Chinese	1 (64)	−0.67 (−1.18 to −0.17)	N/A	**0.009**
Non-Chinese	6 (317)	−0.64 (−1.21 to −0.07)	80	**0.03**
2. Antipsychotic class: clozapine	3 (134)	−1.12 (−2.39 to 0.14)	90	0.08
Other than clozapine	4 (247)	−0.45 (−0.85 to −0.05)	51	**0.03**
3. Trial duration (weeks): 8	2 (175)	−0.30 (−0.60 to −0.01)	0	0.05
12	4 (160)	−0.80 (−1.74 to 0.14)	85	0.09
16	1 (46)	−1.08 (−1.70 to −0.46)	N/A	**0.0007**
4. Male predominance (⩾60%)	5 (277)	−0.72 (−1.42 to −0.02)	84	**0.04**
No sex predominance	2 (104)	−0.59 (−0.98 to −0.19)	0	**0.004**
5. Age (years)[a]: ⩾39.5	5 (320)	−0.41 (−0.77 to −0.44)	57	**0.03**
<39.5	2 (61)	−1.82 (−4.64 to 1.00)	93	0.21
6. Jadad score[a] ⩾4	4 (161)	−0.39 (−0.90 to 0.12)	61	0.13
Jadad score <4	3 (220)	−1.13 (−2.16 to −0.10)	89	**0.03**

[a] Analyzed using a mean split.

N/A, not applicable; SMDs, standard mean differences. Bolded values: $p < 0.05$.

adjunctive memantine for schizophrenia found that 8–16 weeks adjunctive memantine outperformed placebo in terms of negative and neurocognitive symptoms.

Memantine was associated with significant improvement of negative symptoms ($n = 381$, SMD = −0.63) in schizophrenia, which is in line with several other adjunctive therapies for schizophrenia, such as Tai Chi ($n = 451$, SMD = −0.87) (Zheng *et al.* 2016*a*), topiramate ($n = 436$, SMD = −0.58) (Zheng *et al.* 2016*b*), minocycline ($n = 476$, SMD = −0.69) (Xiang *et al.* 2017), aripiprazole ($n = 2294$, SMD = −0.61) (Zheng *et al.* 2016*c*), and amantadine ($n = 83$, SMD = −0.56) (Zheng *et al.* 2017). The mechanism of the effect on negative symptoms may be related to the role memantine in reducing activation of the NMDAR subtype (Tsai & Coyle, 2002), improving glutamatergic tonus in certain brain areas (de Lucena *et al.* 2009) and enhancing neuroprotective effects (Lipton, 2004; Koch *et al.* 2005).

The improvement of neurocognitive function associated with memantine is consistent with the findings of previous studies (Koch *et al.* 2005; Pieta Dias *et al.* 2007) and meta-analyses (Kishi & Iwata, 2013; Matsuda *et al.* 2013). This effect could be attributed to the inhibition of NMDAR overactivity (de Lucena *et al.* 2009). Furthermore, memantine may have a role in reducing neuronal oxidative stress by increasing brain-derived neurotrophic factor levels and preventing dopamine deficit in treating schizophrenia (Gama *et al.* 2005, 2007).

This is the largest meta-analysis of adjunctive memantine for schizophrenia ($n = 452$), surpassing the previous meta-analysis (Matsuda *et al.* 2013), which had only four RCTs ($n = 226$) (de Lucena *et al.* 2009; Lieberman *et al.* 2009; Lee *et al.* 2012; Rezaei *et al.* 2013). Larger samples can improve the power in detecting significant results and decrease the type I error for meta-analytic results (Lelorier *et al.* 1997). Furthermore, unlike the previous meta-analyses, quality assessment using the Cochrane risk of bias and Jadad scale, and GRADE analyses were conducted in this study.

There are several limitations of this study. First, there was significant heterogeneity in the result of the meta-analysis of negative symptoms, and even in nine out of the 13 subgroups. However, the heterogeneity as assessed by I^2 decreased from 77% to 47% when one outlying study (de Lucena *et al.* 2009) was removed. Second, only one RCT (Mazinani *et al.* 2016) with 16 weeks follow-up found an advantage of adjunctive memantine *v.* placebo with regard to negative symptoms, but not the other RCTs (7/8, 88%) with shorter duration (8–12 weeks). A robust memantine treatment effect is probably attributed to a longer treatment duration (>12 weeks). For instance, a meta-analysis of six RCTs ($n = 2311$) of adjunctive memantine ($n = 1242$) *v.* placebo ($n = 1069$) for AD showed superiority in the improvement of delusional symptoms after 24–28 weeks treatment compared with 12 weeks (Puangthong & Hsiung, 2009). Third, clozapine is usually prescribed for treatment-resistant schizophrenia (Leucht *et al.* 2013). Thus, the lack of efficacy of adjunctive memantine in patients receiving clozapine compared with those receving other APs could have been due to treatment resistance. Fourth, the MMSE is not a suitable instrument to measure cognitive functions in schizophrenia. Specific cognitive batteries, such as the MATRICS (Measurement and

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Treatment Research to Improve Cognition in Schizophrenia) (Marder & Fenton, 2004), should be used in future studies. Similarly, scales specifically designed to assess negative symptoms, such as the SANS (Scale for the Assessment of Negative Symptoms), would have been more appropriate to confirm the therapeutic effect of memantine for negative symptoms in schizophrenia. Finally, ADRs were not routinely assessed or reported in some studies. In particular, data regarding weight loss were only provided in one study (de Lucena *et al.* 2009).

Conclusion

This meta-analysis showed that adjunctive memantine appears to be a useful adjunctive treatment for schizophrenia in improving negative and neurocognitive symptoms. However, these findings need to be replicated in higher quality and larger RCTs with longer follow-up duration.

Supplementary material

The supplementary material for this article can be found at https://doi.org/10.1017/S0033291717001271.

Acknowledgements

The study was supported by the University of Macau (SRG2014-00019-FHS; MYRG2015-00230-FHS; MYR G2016-00005-FHS). The University of Macau had no role in the study design, generating, or interpreting the results and publication of the study.

Declaration of Interest

None.

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