Augmentation of Antipsychotic Treatment with Memantine in Patients with Schizophrenia: A Systematic Review and Meta-Analysis

☙

Sefa VAYISOĞLU[1] ⓘ, Sevilay KARAHAN[2] ⓘ, A. Elif ANIL YAĞCIOĞLU[3] ⓘ

SUMMARY

Objective: Many patients with schizophrenia respond partially to treatment with antipsychotic medications. A wide range of pharmaceutical agents are utilized as augmentation therapy in order to increase the efficacy of antipsychotic medication treatment. Memantine, a noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist is one of these add-on agents. In this study we aimed to assess the efficacy of memantine augmentation by conducting a systematic review and meta-analysis on the psychopathology of patients with schizophrenia receving antipsychotic medication.

Method: We analyzed the double-blind, randomized, placebo-controlled trials of memantine add-on treatment given to schizophrenia patients receiving antipsychotic medications. The primary outcome measure was amelioration of negative symptoms and the secondary outcome measures were amelioration of positive, total and general psycopathology symptoms. Publication bias was evaluated by the Funnel plot and Egger test.

Results: Eleven studies on a total of 570 cases were included. Although memantine add-on treatment was superior to placebo for ameliorating negative symptoms (SMD=0.596, 95% CI=0.075-1.118, p=0.025), there were not any statistically significant differences in the amelioration of general psycopathology (SMD=0.034, 95% CI=0.419-0.488, p=0.883), the positive (SMD=-0.041, 95% CI=0.217-0.135, p=0.650) and the overall symptoms. (SMD=0.315, 95% CI=0.256-0.887, p=0.280). Publication bias was not observed between studies according to the results of the Funnel plots and Egger tests.

Conclusion: Memantine augmentation treatment is beneficial for treating particularly the negative symptoms of schizophrenia patients. Further studies on the subject with larger sample size and longer follow-up durations are needed.

Keywords: Memantine, schizophrenia, augmentation treatment

INTRODUCTION

Schizophrenia is a serious mental disorder affecting 1% of the world's population (Kirkpatrick et al. 2001) and is among the top ten medical reasons leading to disability (Bosia et al. 2005). Disease-related treatment and indirect expenses cost an annual economic burden of 50 billion US dollars (Mueser ve McGurk 2004). In patients diagnosed with schizophrenia the prominent observations consist of positive symptoms of hallucinations and delusions, negative symptoms of speech deprivation, loss of will, social withdrawal, blunting in affect and symptoms of impaired cognition as well as deterioration of social and occupational functioning (Andreasen 2000, Andreasen 1982).

Although antipsychotic drugs are the main components of the effective treatment of schizophrenia, response to treatment may be limited, and high prevalence of residual disease symptoms such as cognitive destruction and persistent positive and negative symptoms may be observed among patients (Stahl and Grady 2004). Despite the beneficial effects of antipsychotics with dopamine receptor antagonism in schizophrenia, they have less efficacy on negative symptoms and cognitive impairment (Miyamoto et al. 2012).

In schizophrenia, brain regions such as the prefontal cortex, hippocampus and thalamus are affected and the interactions of a series of chemical neurotransmitters are implicated in the pathogenesis of the disease (Sadock 2007). Although the pathophysiological mechanisms of schizophrenia are not completely known, development of the positive and negative symptoms has been attributed to altered glutamatergic signalization via the N-methyl D-aspartate (NMDA) receptors (Bosia et al. 2015, John et al. 2014), which has been supported by experimental studies showing that persistent blockage of the NMDA receptors are associated with the clinical pathological features of schizophrenia (Coyle 2012). Reduction of NMDA receptor function leads to a reduction in the stimulation of GABAergic neurons in the central nervous system (Farber 2003). This results in neuronal death due to excess secretion of glutamate in the synapse (Millan 2005). It is thought that this NMDA receptor mediated neuron death plays a role in the pathology of schizophrenia and that drugs that block excess NMDA receptor-stimulated glutamatergic activity may decrease this excitotoxic effect (Ikonomidou and Turski 2002).

According to the glutamate hypothesis in schizophrenia, impaired NMDA receptor activity may be the result of a primary defect in the NMDA receptors (Silver et al. 2005, Beneyto and Meador-Woodruff 2008). Memantine, an NMDA receptor antagonist, has been approved by the US Food and Drug Administration (FDA) for the treatment of moderate to severe Alzheimer's disease (Koch et al. 2005) and has been used off-label in various psychiatric disorders, including schizophrenia (Zdanys and Tampi 2008). Memantine demonstrates its therapeutic effect as an NMDA receptor antagonist by binding with low-to-medium affinity to non-selective voltage-dependent NMDA receptor-efficient calcium channels (Berman et al. 2012, KishiandIwata 2013). Memantine is also capable of enhancing NMDA receptor expression in the presence of a strong stimulus (Joshi et al. 2007). Based on these effects, addition of memantine to antipsychotic therapy of schizophrenia may ameliorate cognitive impairment and negative symptoms (Di Iorio et al. 2017, Sani et al. 2012).

Pioneering studies on case series (Gama et al. 2005, John et al. 2014) and an observational study (Krivoy et al. 2008) have shown that memantine may have an augmenting effect on the treatment of schizophrenia. The results shown in Table 1, of published randomized controlled trials on the efficacy and safety of adjunctive memantine therapy in schizophrenia do not show consistency with each other (Lieberman et al. 2009, de Lucena et al. 2009, Lee et al. 2012, Gu et al. 2012, Reazei et al. 2013, Omranifard et al. 2015, 2017, Fakhri et al. 2016, Veerman et al. 2016, Mazinani et al. 2017, Tavakoli-Ardakani et al. 2018). Limited number of randomized controlled trials with reduced statistical power have been included in these meta-analyses, which reported improvements in negative and general psychopathology symptoms (Singh and Singh 2011), on cognitive symptoms (Kishi and Iwata 2013), on negative and total psychopathology symptoms (Matsuda et al. 2013), only on negative symptoms (Kishi et al. 2017, Siskind et al. 2018), on negative and cognitive symptoms (Zheng et al. 2018, Kishi et al. 2018). A recent randomized controlled trial (Tavakoli-Ardakani 2018) not included in the previously published metaanalyses was included in the present study with an attempt to re-evaluate in a current context the effects of memantine augmentation therapy on the clinical psychopathological symptoms of schizophrenia. Since cognitive functions were not evaluated in this very recent study by Tavakoli-Ardakani (2018), further evaluation was not made on cognitive functions, considering that this would not contribute to the analysis of cognitive functions included in the current meta-analyses by Zheng et al. (2018) and Kishi et al. (2018).

METHOD

Research Strategy and Inclusion Criteria

Two researchers independently scanned the Pubmed, PsycINFO and Cochrane Library databases using the key words memantine, schizophrenia, and augmentation therapy without any langue constraints. The studies with schizophrenia patients receiving memantine-augmented antipsychotic treatment under double-blind, randomized, placebo-controlled conditions for at least 2 weeks were included in the analysis. The total number of patients in the studies was 570 with 288 patients being in the memantine group and 282 in the placebo group.

Data Synthesis and Result Measurements

The primary outcome criteria were based on the Negative Symptoms subscale of the Positive and Negative Syndrome Scale (PANSS), (Kay et al. 1987) and the Negative Symptoms subscale of the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham 1962), while the secondary outcome measure was based on the Positive, Total and General Psychopathology symptoms subscales of the PANSS and Positive and Total Symptoms subscales of the BPRS.

Method of Meta-Analysis

Meta-analysis was conducted by using StataCorp 14.1 for Windows. Standardized mean difference (SMD) was calculated for continuous outcomes when different rating scales were used in different studies. The difference between pre-treatment and post-treatment scores was used to indicate the mean difference. The standard deviation (SD) was used as a measure of variation for each study. When estimating the pooled pre-treatment and post-treatment scores, if the trial was of crossover type, the first evaluation was considered for the meta-analysis.

Table 1. Double Blind, Placebo Controlled, Randomized Studies on Patients with Schizophrenia Whose Antipsychotic Medication Treatment is Augmented with Memantine

Study	Numbers of Patient			Duration (week)	Antipsychotics (%)	Result
De Lucena et al. 2009	22	Memantine	11	12	Clozapine (100%)	Memantine>Placebo BPAS total, positive, negative, CGIS and MMSE
		Placebo	11		Clozapine (100%)	
Lieberman et al. 2009	138	Memantine	70	8	Olanzapine (34.8%) Risperidone (33.3%) Aripiprazole (15.9%) Ziprasidone (8.7%) Quetiapine (7.2%)	Memantine=Placebo PANSS total, positive, negative, general, CDSandCGIS
		Placebo	68		Olanzapine (37.3%) Risperidone (31.3%) Aripiprazole (10.4%) Ziprasidone(11.9%) Quetiapine (9%)	
Lee et al. 2012	26	Memantine	15	12	First Generation Antipsychotics (100%)	Memantine=Placebo PANSS total, positive, negative, general, HDS, CGIS and MMST
		Placebo	11		First Generation Antipsychotics (100%)	
Gu et al. 2012	64	Memantine	32	12	Clozapine (100%)	Memantine>Placebo PANSS total, negative, general psychopathology
		Placebo	32		Clozapine (100%)	
Rezaei et al. 2013	40	Memantine	20	8	Risperidone (100%)	Memantine>Placebo PANSS total, negative, general psychopathology Memantine=Placebo PANSS positive, HDS
		Placebo	20		Risperidone (100%)	
Omranifard et al. 2015	64	Memantine	32	12	Olanzapine (33.3%) Risperidone (50%) Aripiprazole (3.3%) Clozapine (13.3%)	Memantine>Placebo GAF and QLS
		Placebo	32		Olanzapine (23.3%) Risperidone (53.3%) Aripiprazole (6.7%) Clozapine (16.6%)	
Fakhri et al. 2016	60	Memantine	30	6	Olanzapine (100%)	Memantine>Placebo PANSS positive and negative
		Placebo	30		Olanzapine (100%)	
Veerman et al. 2016	52	Memantine	26	26	Clozapine (100%)	Memantine>Placebo PANSS negative Memantine=Placebo PANSS total, positive, general psychopathology, CGIS
		Placebo	26		Clozapine (100%)	
Omranifard et al. 2017	64	Memantine	32	12	Risperidone (50%) Olanzapine (33.3%) Clozapine (13.3%) Aripiprazole (3.3%)	Memantine>Placebo PANSS positive, negative, total, general psychopathology and CDS
		Placebo	32		Risperidone (53.3%) Olanzapine (23.3%) Clozapine (16.6%) Aripiprazole (6.7%)	
Mazinani et al. 2017	46	Memantine	23	12	Risperidone (100%)	Memantine>Placebo PANSS negative, MMST Memantine=Placebo PANSS positive, general psychopathology
		Placebo	23		Risperidone (100%)	
Tavakoli-Ardakani et al. 2018	58	Memantine	29	12	First Generation Antipsychotic (44%) Second Generation Antipsychotic (56%)	Memantine>Placebo PANSS negative and general psychopathology
		Placebo	29		First Generation Antipsychotic (43%) Second Generation Antipsychotic (57%)	

Abbreviations: > : Greater = : Equal, BPRS: Brief Psychiatric Rating Scale, CGIS: Clinical Global Impression Scale, MSE: Mini Mental State Examination, PANSS: Positive and Negative Syndrom Scale, CDS: Calgary Depression Scale, HDS: Hamilton Depression Scale, GAF: Global Assessment of Functioning Scale, LS: Quality of Life Scale

A fixed effect model or a random effects model was used for meta-analysis, depending on the heterogeneity of trials which was evaluated using the Chi-square heterogeneity test and also on the I^2-statistics. A result of $I^2 > 50\%$, was interpreted as the indication of significant heterogeneity. The overall efficacy of outcomes was estimated by dividing the effect size estimate by the standard error of the effect size estimate. Publication bias was determined by using the Funnel plot and the Egger test. The Z values have two-tailed statistical significance and p values less than 0.05 were accepted as statistically significant.
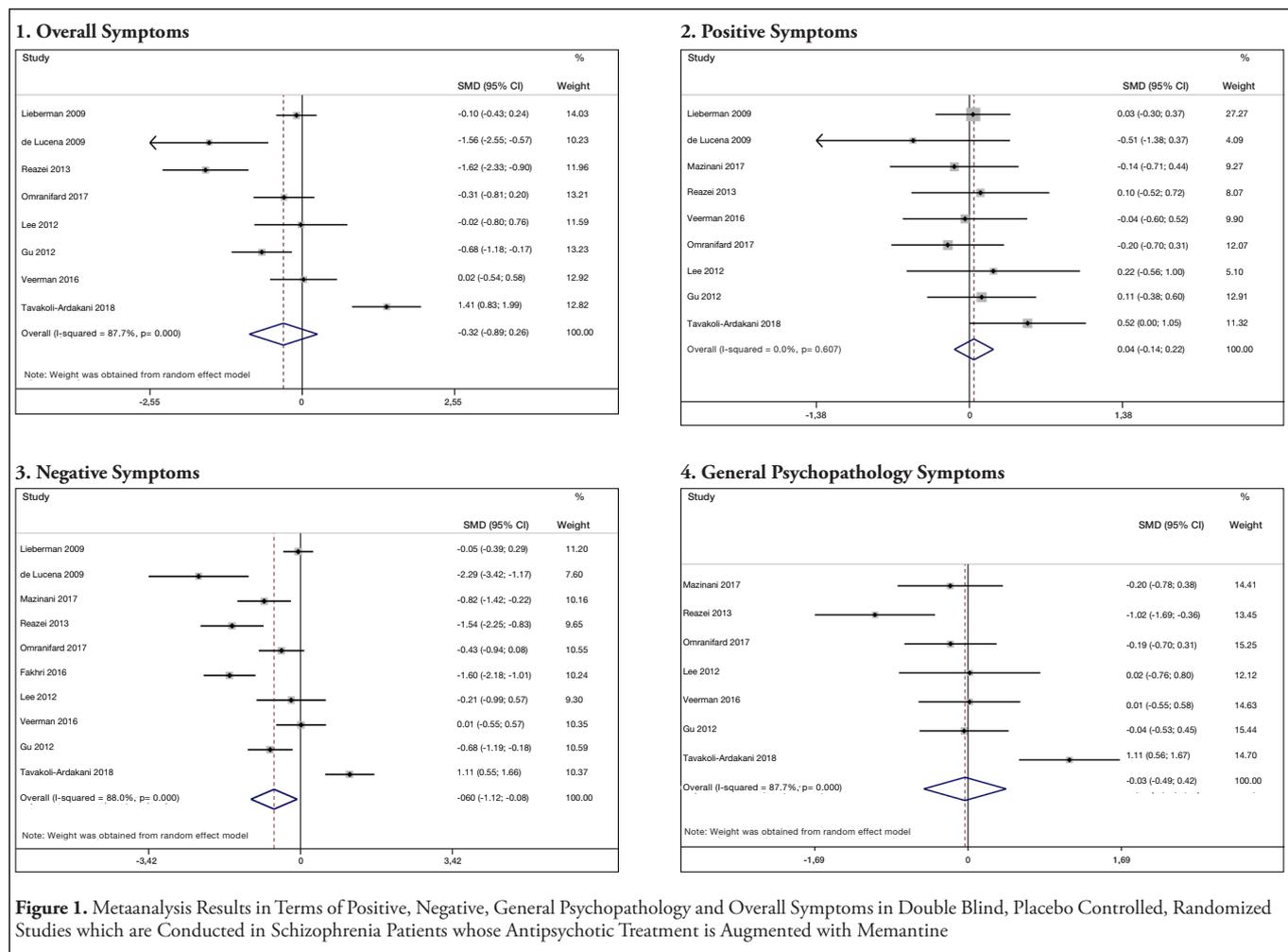
RESULTS

The titles and summaries of the 202 studies obtained from the literature scan were examined and 38 studies were determined to be suitable for the purposes of the study. After identifying and deleting 26 repeated studies, full texts of the remaining studies were obtained and 11 of these found to meet the inclusion criteria, were selected. Two of these studies were by the same authors evaluating different parameters of the same study two years apart (Omranifard 2015, 2017). Only clozapine was used for antipsychotic therapy in
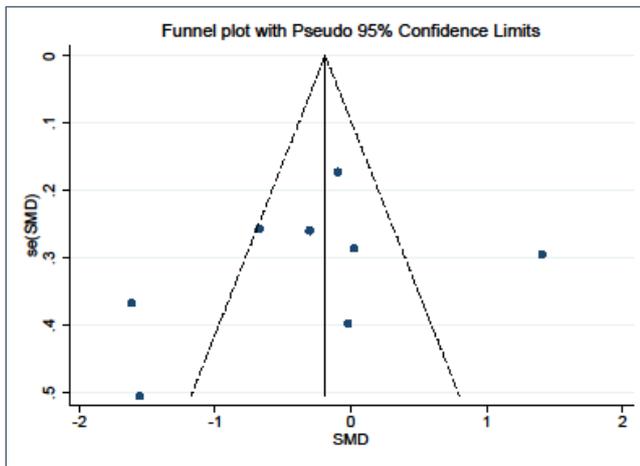
three of the eleven studies only (Lucena et al. 2009, Gu et al. 2012, Veerman et al. 2016), only risperidone was used in two studies (Rezaei et al. 2013, Mazinani et al. 2017), only olanzapine was used one study (Fakhri et al. 2016), different first generation antipsychotics were used in one study (Lee et al. 2012) and different second generation antipsychotics were used in two studies (Omranifard 2015, 2017). In another study first generation and non-clozapine second generation antipsychotics were used in a 50:50 ratio on a group of schizophrenia patients (Tavakoli-Ardakani 2018). In all studies, the daily dose of memantine was 20 mg / day. One of the studies (Lieberman et al. 2009) was sponsored by a pharmaceutical company.
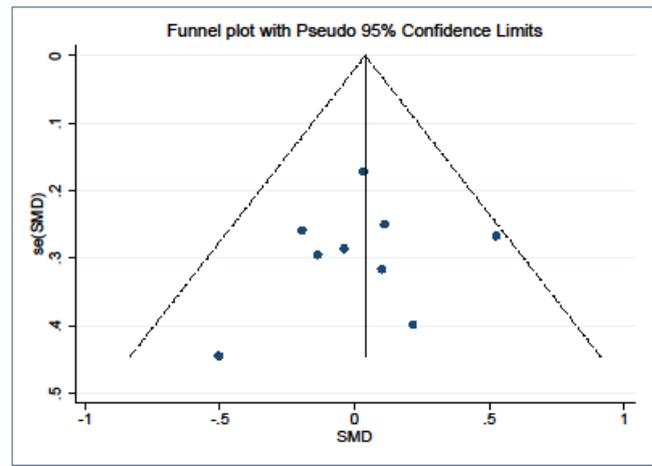
Meta-Analysis Results

Since significant heterogeneity was observed, random effects meta-analysis model was used for total, negative and general psycopathology scores. Fixed effect model was used for negative scores. Memantine was found superior to placebo for negative scores (SMD=0.596, 95% CI=0.075-1.118, p=0.025). Memantine did not have significant effects on general psycopathology (SMD= 0.034), the positive

Figure 1. Metaanalysis Results in Terms of Positive, Negative, General Psychopathology and Overall Symptoms in Double Blind, Placebo Controlled, Randomized Studies which are Conducted in Schizophrenia Patients whose Antipsychotic Treatment is Augmented with Memantine
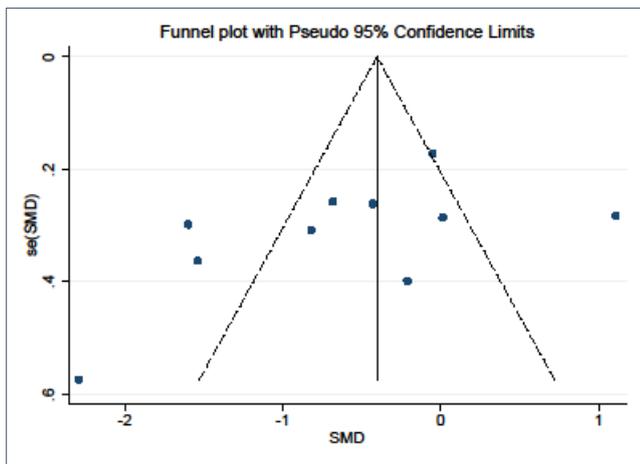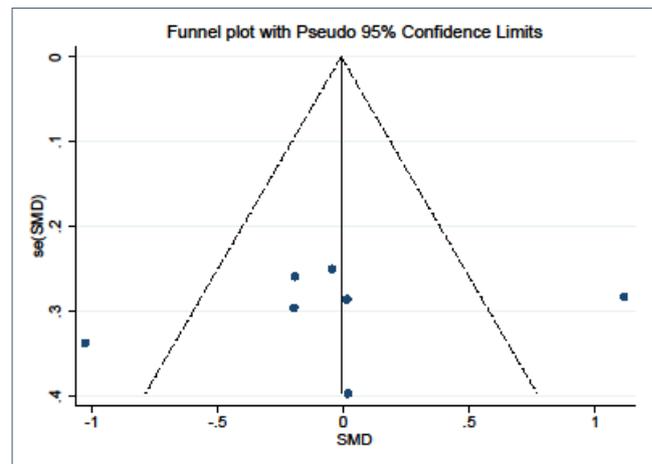
1. Overall Symptoms

2. Positive Symptoms

3. Negative Symptoms

4. General Psychopathology Symptoms

Figure 2. Funnel Plot Test Results in Terms of Positive, Negative, General Psychopathology and Overall Symptoms in Randomised, Double Blind, Placebo Controlled Studies which are Conducted in Schizophrenia Patients whose Antipsychotic Treatment is Augmented with Memantine

symptom scores (SMD= -0.041) and total scores (SMD =0.315). According to the funnel plot (Figure 2) and the Egger test results (p values for the positive, negative, general psychopathology and total scores were, respectively, 0.643, 0.163, 0.635 and 0.485), and study bias was not observed.

DISCUSSION

This work is an updated systematic review and meta-analysis of the effects of adjunctive memantine therapy on psychopathology in patients with schizophrenia who are on antipsychotic medication and includes 11 reported studies. In comparison, the meta-analyses by Kishi et al. (2017) and Zheng et al. (2018), among the other most recently published meta-studies, include 8 studies and differ in context. The meta-analysis by Kishi et al. (2017) includes the results of Fakhri et al. (2016) and that by Zheng et al. (2018) includes the results

of Gu et al. (2012). Results of studies on the effects of not only add-on memantine but also of add-on donepezil, galantamine and rivastigmine on psychopathology, dementia and cognitive impairment in schizophrenia were included in a very recent systematic review and meta-analysis (Kishi et al. 2018), which also updated the efficacy analysis of adjunctive memantine therapy by adding the results of the psychopathology data of Omranifard et al. (2017). There are only 3 studies evaluating adjunctive memantine therapy in another recent systematic review and metaanalysis on treatment-augmenting strategies in patients with schizophrenia resistant to clozapine therapy (Siskind et al. 2018). Large-sample meta-analyses increase the power to detect significant results, while reducing the incidence of type 1 errors (Lelorier et al. 1997). This study constitutes the largest and current comprehensive meta-analysis on the efficacy of adjunctive memantine therapy in patients with schizophrenia and schizoaffective disorder by including the recent double-blind, placebo-controlled,

5

randomized study by Tavakoli-Ardakani et al. (2018) in comparison to the recently reported meta-analyses cited above (Kishi et al. 2017, 2018, Zheng et al. 2018, Siskind et al. 2018). In this meta-analysis, the effect of memantine on cognitive functions was not re-examined since the study by Tavakoli-Ardakani et al. (2018), did not include assessments on cognitive functions, and, therefore, further contribution to the results of the previous recently published meta-analyses on the subject was seen not to be necessary. While Kishi et al. (2017) and Zheng et al. (2017) reported in their meta-analyses a positive effect of adjunctive memantine therapy on cognitive symptoms, the Mini Mental State Examination (MMSE) relied upon in these analyses is not the appropriate method for evaluating cognitive impairment in schizophrenia (Andrade 2017).

The beneficial effect of adjunctive memantine therapy shown in this study on negative symptoms in schizophrenia patients is consistent with previously published meta-analysis results (Kishi et al. 2017, 2018, Zheng et al. 2018, Siskind et al. 2018). This effect of memantine on negative symptoms may be related to hypofunction of a subpopulation of cortico-limbic NMDA receptors (Tsai and Coyle 2002), improvement of the glutamatergic tone in certain brain regions (de Lucena et al. 2009), increased neuron protective activity (Lipton 2004, Koch et al. 2005) and, given the memantine agonist action at dopamine D2 high receptors (Seeman et al. 2008). The amelioration of the hypodopaminergic condition in the prefrontal cortex and mesocortical pathways thought to be associated with negative symptoms (Juckel 2016, Kambeitz et al. 2014),

Another strength of this study when compared to the previous meta-analyses is in meeting the criteria of including 10 or more studies for evaluation of the data on the funnel plot test to assess publication bias, which was not detected in this analysis.

When we examine the limitations of the study, the sample size is insufficient although the total patient population of studies included in this study is larger than those in the previously published meta-analyses on the adjunctive memantine therapy. Therefore, the 'small study effect', the tendency of small sample studies to show greater treatment efficiency, cannot be excluded (Moreno et al. 2009). Also, durations of the studies included in this meta-analysis were generally between 8-12 weeks and did not allow determination of the long-term effects of adjunctive memantine therapy on schizophrenia symptoms.

CONCLUSION

This systematic review and meta-analysis suggest that adjunctive memantine therapy with antipsychotic treatment in schizophrenia has positive effects on negative symptoms. Further studies with longer term and large patient sample sizes are required on adjunctive memantine therapy in schizophrenia.

REFERENCES

Andreasen NC (2000) Schizophrenia: the fundamental questions. Brain Res. Rev. 31: 106-12.

Andrade C (2017) Memantine as an Augmentation Treatment for Schizophrenia: Limitations of Meta-analysis for evidence-based evaluation of research. J Clin Psychiatry 78: e1307-e9.

Andreasen NC (1982) Negative symptoms in schizophrenia. Definition and reliability. Arch Gen Psychiatry 39:784-8.

Beneyto M, Meador-Woodruff JH (2008) Lamina-specific abnormalities of NMDA receptor-associated postsynaptic protein transcripts in the prefrontal cortex in schizophrenia and bipolar disorder. Neuropsychopharmacology 33: 2175-86.

Berman K, Brodaty H, Withall A et al (2012) Pharmacologic treatment of apathy in dementia. Am J GeriatrPsychiatr: Off J Am Assoc Geriatr Psychiatr 20: 104-22.

Bosia M, Pigoni A, Cavallaro R (2015) Genomics and epigenomics in novel schizophrenia drug discovery: Translating animal models to clinical research and back. Expert Opin Drug Discov 10: 125-39.

Coyle JT (2012) NMDA receptor and schizophrenia: A brief history. Schizophr Bull 38: 920-6.

de Lucena D, Fernandes BS, Berk M et al (2009) Improvement of negative and positive symptoms in treatment-refractory schizophrenia: a double blind, randomized, placebo-controlled trial with memantine as add-on therapy to clozapine. Journal of Clinical Psychiatry 70: 1416-23.

Di Iorio G, Baroni G, Lorusso M et al (2017) Efficacy of memantine in schizophrenic patients: a systematic review. J Amino Acids 2017: 7021071.

Fakhri A, Pakseresht S, Haghdoost MR et al (2016) Memantine enhances the effect of olanzapine in patients with schizophrenia: a randomized, placebo-controlled study. Acta Med Iran 54: 696-703.

Farber NB (2003) The NMDA receptor hypofunction model of psychosis. Ann NY Acad Sci 1003: 119-30.

Gama CS, Antunes P, Moser C et al (2005) Memantine as an adjunctive therapy for schizophrenia negative symptoms. RevistaBrasileiria de Psiquiatria 27: 257-8.

Gu J, Wu Y, Tang L (2012) A controlled study of clozapine plus memantine in schizophrenia negative symptoms. Journal of Clinical Psychiatry 22: 261-3.

Ikonomidou C, Turski L (2002) Why did NMDA receptor antagonists fail clinical trials for stroke and traumatic brain injury? Lancet Neurol 1: 383-6.

John JP, Lukose A, Manjunath S (2014) Off-label use of memantine as adjunctive treatment in schizophrenia: A retrospective case series study. Pharmacopsychiatry 47: 202-9.

Joshi I, Yang Y-M, Wang L-Y (2007) Cellular/molecular coincident activation of metabotropic glutamate receptors and NMDA receptors (NMDARs) down regulates perisynaptic/extrasynaptic NMDARs and enhances high-fidelity neurotransmission at the developing calyx of the heldsynapse. Journal of Neuroscience 27: 9989-99

Juckel G (2016) Inhibition of the reward system by antipsychotic treatment. Dialogues Clin Neurosci 18: 109-14.

Kambeitz J, Abi-Dargham A, Kapur S et al (2014) Alterations in cortical and extrastriatal subcortical dopamine function in schizophrenia: systematic review and meta-analysis of imaging studies. Br J Psychiatry 204: 420-9.

Kay SR, Fiszbein A, Opler LA (1987) The positive and negative syndrom scale (PANSS) for schizophrenia. Schizophr Bull 13: 261-75.

Kirkpatrick B, Buchanan RW, Ross DE et al (2001) A separate disease within the syndrome of schizophrenia. Arch Gen Psychiatry 58: 165-71.

Kishi T, Iwata N (2013) NMDA receptor antagonists interventions in

schizophrenia: meta-analysis of randomized, placebo-controlled trials. J PsychiatrRes 47: 1143-9.

Kishi T, Matsuda Y, Iwata N (2017) Memantine add-on to antipsychotic treatment for residual negative and cognitive symptoms of schizophrenia: a meta-analysis. Psychopharmacology 234: 2113-25.

Kishi T, Ikuta T, Oya K et al (2018) Anti-dementia drugs for psychopathology and cognitive impairment in schizophrenia: a systematic review and meta-analysis. International Journal of Neuropsychopharmacology 21: 748-57.

Koch HJ, Uyanik G, Fischer-Barnicol D (2005) Memantine: a therapeutic approach in treating Alzheimer's and vascular dementia. Current drug targets CNS and neurological disorders 4: 499-506.

Krivoy A, Weizman A, Laor L et al (2008) Addition of memantine to antipsychotic treatment in schizophrenia in patients with residual symptoms: a preliminary study. European Neuropsychopharmacology 18: 117-21.

Lee JG, Lee SW, Lee BJ et al (2012) Adjunctive memantine therapy for cognitive impairment in chronic schizophrenia: a placebo-controlled pilot study. PsychiatryInvestigation 9: 166-73.

Lelorier J, Gregoire G, Benhaddad A et al (1997) Discrepancies between meta-analyses and subsequent large randomized, controlled trials. New England Journal of Medicine 337: 536-42.

Lieberman JA, Papadakis K, Csernansky J et al (2009) A randomized, placebo-controlled study of memantine as adjunctive treatment in patients with schizophrenia. Neuropsychopharmacology 34: 1322-9.

Lipton SA (2004) Paradigm shift in NMDA receptor antagonist drug development: molecular mechanism of uncompetitive inhibition by memantine in the treatment of Alzheimer's disease and other neurologic disorders. Journal of Alzheimers Disease 6: S61-S74.

Matsuda Y, Kishi T, Iwata N (2013) Efficacy and safety of NMDA receptor antagonists augmentation therapy for schizophrenia: an updated meta-analysis of randomized placebo-controlled trials. Journal of Psychiatric Research 47: 2018-20.

Mazinani R, Nejati S, Khodaei M (2017) Effects of memantine added to risperidone on the symptoms of schizophrenia: a randomized double-blind, placebo-controlled clinical trial. Psychiatry Res 247: 291-5.

Millan MJ (2005) N-Methyl-D-aspartatereceptors as a target for improved antipsychotic agents: novel insights and clinical perspectives. Psychopharmacology (Berl) 179: 30-53.

Miyamoto S, Miyake N, Jarskog LF et al (2012) Pharmacological treatment of schizophrenia: a critical review of the pharmacology and clinical effects of current and future therapeutic agents. Mol Psychiatry 17: 1206-27.

Moreno SG, Sutton AJ, Ades AE et al (2009) Assessment of regression-based methods to adjust for publication bias through a comprehensive simulation study. BMC Med Res Methodol 9:2

Mueser KT, McGurk SR (2004) Schizophrenia. Lancet 363: 2063-72.

Sadock B (2007) Kaplan&Sadock's Comprehensive Textbook of Psychiatry 8 th ed. (Transl. by: H Aydın, A Bozkurt) Ankara, Güneş Kitabevi Yayınları, 2007 s. 1408-12.

Omraniford V, Rajabi F, Mohammadian-Sichani M et al (2015) The effect of add-on memantine on global function and quality of life in schizophrenia: a randomized, double-blind, controlled clinical trial. Adv Biomed Res 4: 211

Omranifard V, Rajabi F, Mohammadian-Sichani M et al (2017) The effect of add-on memantine on positive, negative and depressive symptoms of schizophrenia: a double blind, randomized, controlled trial. Actas Esp Psiquiatr 45: 108-15.

Overall JE, Gorham D (1962) The Brief Psychiatric Rating Scale. Psychol Rep 10: 779-812.

Rezaei F, Mohammad-Karimi M, Seddighi S et al (2013) Memantine add-on to risperidone for treatment of negative symptoms in patients with stable schizophrenia: randomized, double blind, placebo-controlled study. Journal of Clinical Psychopharmacology 33: 336-42.

Sani G, Serra G, Kotzalidis GD et al (2012) The role of memantine in the treatment of psychiatric disorders other than the dementias: a review of currentpreclinicalandclinicalevidence. CNS drugs 26: 663-90.

Seeman P, Caruso C, Lasaga M (2008) Memantine agonist action at dopamine D2 high receptors. Synapse 62: 149-53.

Silver H, Goodman C, Isakov V et al (2005) A double-blind, cross-over comparison of the effects of amantadine or placebo on visuomotor and cognitive function in medicated schizophrenia patients. Int Clin Psychopharmacol 20: 319-26.

Singh SP, Singh V (2011) Meta-analysis of the efficacy of adjunctive NMDA receptor modulators in chronic schizophrenia. CNS Drugs 25: 859-85.

Siskind DJ, Lee M, Ravindran A et al (2018) Augmentation strategies for clozapine refractory schizophrenia: A systematic review and meta-analysis. Australian & New Zealand Journal of Psychiatry 52: 751-67.

Stahl SM, Grady MM (2004) A critical review of atypical antipsychotic utilization: comparing monotherapy with polypharmacy and augmentation. Curr Med Chem 11: 313-27.

Tavakoli-Ardakani M, Abbaspour H, Nasab AF et al (2018) Study of the effect of memantine on negative sign in patients with schizophrenia and schizoaffective disorders. IranianJournal of Pharmaceutical Research 17: 122-9.

Tsai G, Coyle JT (2002) Glutamatergic mechanisms in schizophrenia. Annu Rev Pharmacol 42: 165-79.

Veerman SR, Schulte PF, Smith JD et al (2016) Memantine augmentation in clozapine-refractory schizophrenia: a randomized, double-blind, placebo-controlled crossover study. Psychol Med 46: 1909-21.

Zdanys K, Tampi RR (2008) A systematic review of off-label uses of memantine for psychiatric disorders. Prog Neuro-Psychopharmacol Biol Psychiatry 32: 1362-74.

Zheng W, Li X-H, Yang X-H et al (2018) Adjunctive memantine for schizophrenia: a meta-analysis of randomized, double-blind, placebo-controlled trials. Psychol Med 48: 72-81.