

REVIEW

Anti-Dementia Drugs for Psychopathology and Cognitive Impairment in Schizophrenia: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: We conducted a systematic review and meta-analysis of double-blind, randomized, placebo-controlled trials of anti-dementia drugs plus antipsychotics for schizophrenia.

Methods: Primary outcomes of efficacy and safety included improving overall symptoms (Positive and Negative Syndrome Scale and Brief Psychiatric Rating Scale scores) and all-cause discontinuation, respectively. Other outcomes included psychopathology subscales (positive, negative, general, and anxiety/depressive symptoms), cognitive function (attention/vigilance, reasoning/problem solving, social cognition, speed of processing, verbal learning, visual learning, working memory, and cognitive control/executive function), Mini-Mental State Examination scores, treatment discontinuation due to adverse events and inefficacy, and individual adverse events. We evaluated the effect size using a random effects model.

Results: We identified 37 studies (n=1574): 14 donepezil-based (n=568), 10 galantamine-based (n=371), 4 rivastigmine-based (n=146), and 9 memantine-based (n=489) studies. Pooled anti-dementia drugs plus antipsychotics treatments were superior to placebo plus antipsychotics in improving the overall symptoms (24 studies, 1069 patients: standardized mean difference = -0.34, 95% CI = -0.61 to -0.08, $P = .01$), negative symptoms (24 studies, 1077 patients: standardized mean difference = -0.62, 95% CI = -0.92 to -0.32, $P_{\text{corrected}} = .00018$), and Mini-Mental State Examination scores (7 studies, 225 patients: standardized mean difference = -0.79, 95% CI = -1.23 to -0.34, $P = .0006$). No significant differences were found between anti-dementia drugs plus antipsychotics and placebo plus antipsychotics regarding other outcomes.

Conclusions: Although the results suggest that anti-dementia drugs plus antipsychotics treatment improves negative symptoms and Mini-Mental State Examination scores in schizophrenia patients, they possibly were influenced by a small-study effect and some bias. However, it was not superior to placebo plus antipsychotics in improving composite cognitive test score, which more systematically evaluates cognitive impairment than the Mini-Mental State Examination score. Overall, the anti-dementia drugs plus antipsychotics treatment was well tolerated.

Keywords: anti-dementia drugs, cognitive impairment, psychopathology, schizophrenia, systematic review, meta-analysis

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Significance Statement

We conducted a systematic review and meta-analysis of double-blind, randomized, placebo-controlled trials of anti-dementia drugs plus antipsychotics (ADD+AP) for treating schizophrenia (37 studies, $n=1574$). The meta-analysis evaluated the effect size based on a random effects model. Pooled ADD+AP treatments were superior to placebo+AP in terms of improving overall symptoms (24 studies, 1069 patients: standardized mean difference [SMD] = -0.34 , 95% CI = -0.61 to -0.08 , $P=.01$), negative symptoms (24 studies, 1077 patients: SMD = -0.62 , 95% CI = -0.92 to -0.32 , $P_{\text{corrected}}=.00018$), and MMSE scores (7 studies, 225 patients: SMD = -0.79 , 95% CI = -1.23 to -0.34 , $P=.0006$). However, we consider that the results were influenced by a small-study effect and some bias. Notably, no significant differences were observed between ADD+AP and placebo+AP in terms of other outcomes of efficacy and safety.

Introduction

Although cognitive impairment is the major feature of schizophrenia (van Os and Kapur, 2009), antipsychotic pharmacotherapy remains the conventional treatment for schizophrenia. Antipsychotics fail to effectively treat cognitive impairments (Nielsen et al., 2015), although their efficacy in treating psychopathologies is relatively well established (Leucht et al., 2013), particularly regarding positive symptoms (Miyamoto et al., 2012). In patients with schizophrenia, cognitive impairment is commonly considered stable throughout their lifespan (Heilbronner et al., 2016). Because most patients tend to have a chronic course due to various residual schizophrenia symptoms, particularly negative and cognitive symptoms (Lang et al., 2013), antipsychotic treatments are often considered insufficient to improve the patients' quality of life.

In schizophrenia, cognitive impairment and negative symptoms share some common features with those of dementia (van Os and Kapur, 2009), although the deficits are more prominent in prefrontal functions (Kumar et al., 2017). For instance, early-onset frontotemporal dementia and schizophrenia show similar characteristics such as psychotic symptoms (Velakoulis et al., 2009). Moreover, attentional deficits in schizophrenia and dementia possibly share a common neuronal mechanism (Sarter, 1994), and cognitive impairment in schizophrenia may not be histopathologically distinguishable from that in dementia (Arnold and Trojanowski, 1996), supporting the potential of anti-dementia drugs in effectively treating schizophrenia symptoms, including cognitive impairment (Singh et al., 2012; Choi et al., 2013; Correll et al., 2017; Kishi et al., 2017).

Although anti-dementia drugs are relevant in treating schizophrenia symptoms (including cognitive symptoms), their efficacy and safety remain inconclusive, with only weak evidence available limited to only 2 subtypes of anti-dementia treatments: cholinesterase inhibitors and glutamatergic antagonists (Scheltens et al., 2016). Several randomized, placebo-controlled trials have attempted to investigate the efficacy and safety of anti-dementia drugs in treating schizophrenia (supplementary Table 1a). In schizophrenia patients treated with antipsychotics, a recent meta-analysis showed that augmentation with pooled cholinesterase inhibitors (donepezil, galantamine, and rivastigmine) was comparatively more effective than placebo in terms of improving overall and negative symptoms but not in terms of improving cognitive impairment (Choi et al., 2013). Additionally, co-treatment with memantine, a N-methyl-D-aspartate receptor antagonist, was effective in treating negative symptoms (Kishi et al., 2017). However, the meta-analysis did not include the outcomes of specific cognitive impairment domains, as insufficient data was available on these outcomes (Kishi et al., 2017). A meta-analysis can increase the statistical power for group comparisons, thus overcoming the limitation of statistically

inadequate sample size in underpowered studies (Higgins and Green, 2011). On the other hand, a low statistical power implies that small meta-analyses may not accurately estimate the efficacy of anti-dementia drugs (i.e., insufficient sample size). However, a number of randomized trials involving the use of cholinesterase inhibitors for the treatment of schizophrenia have been published since the meta-analysis was conducted (Choi et al., 2013), suggesting a potentially higher statistical power. Our previous meta-analysis regarding memantine (Kishi et al., 2017) was also updated to include the psychopathological data from a recent study (Omranifard et al., 2017), thus filling the literature gap regarding the efficacy and safety of anti-dementia drugs added onto antipsychotics (ADD+AP) for the treatment of patients with schizophrenia (supplementary Table 1a,b). This current comprehensive systematic review and meta-analysis were performed to update the available evidence regarding the efficacy (psychopathology and cognitive impairment) and safety (discontinuation rate and the incidence of individual adverse events) of ADD+AP treatment in patients with schizophrenia.

METHODS

This study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (supplementary Appendix, PRISMA Checklist) (Moher et al., 2009), and it was registered with PROSPERO (<http://www.crd.york.ac.uk/PROSPERO/>, CRD42017068991).

Search Strategy and Inclusion Criteria

We performed a systematic literature review based on the PICO (participants/population, interventions, comparator/control, outcomes) strategy as follows. Participants/population: schizophrenia or/and schizophrenia spectrum disorder patients who were receiving antipsychotics (exclusion: schizophrenia or/and schizophrenia spectrum disorder patients who were not receiving antipsychotics); interventions: anti-dementia drugs (donepezil, galantamine, rivastigmine, and memantine); comparator/control: placebo; and outcomes: efficacy and safety (detailed information is shown in the following section). In this study, only double-blind, randomized, placebo-controlled trials of >1 day-lasting ADD+AP treatment in patients with schizophrenia were exclusively included.

Accordingly, to identify relevant studies, 2 of the authors (T.K. and Y.M.) independently searched Scopus, MEDLINE, the Cochrane library, and PsycINFO without language restrictions from inception to January 6, 2018. The search terms included "schizophrenia" AND "donepezil" OR "galantamine" OR "rivastigmine" OR "memantine." Additionally, the authors searched ClinicalTrials.gov (<http://clinicaltrials.gov/>) and the International

Clinical Trials Registry Platform (<http://www.who.int/ictrp/en/>), thus ensuring a comprehensive search and minimizing publication bias. The selected studies were categorized into an inpatients or outpatients group based on whether they included >50% of inpatients or >50% of outpatients, respectively (supplementary Table 1a). Moreover, the studies that included >50% of patients who were receiving second-generation antipsychotics (SGA) were categorized into an SGA group (supplementary Table 1a). Three authors (T.K., Y.M., and S.M.) independently assessed the selected studies based on the inclusion/exclusion criteria. Additionally, the reference lists of the selected articles and reviews were searched for additional relevant published and unpublished studies, including conference abstracts.

Data Synthesis and Outcome Measures

Primary outcomes comprised the improvement of overall symptoms (efficacy) and all-cause discontinuation (safety). The overall symptoms were evaluated based on the total scores for the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1989) and the Brief Psychiatric Rating Scale (Overall and Gorham, 1962). These scores have previously been used as outcome measures in many studies on treatment efficacy and are also increasingly used in clinical practice (Fleischhacker and Kemmler, 2007). Other outcomes included psychopathology subscales (positive, negative, general, and anxiety/depressive symptoms), cognitive impairment (attention/vigilance, reasoning/problem solving, social cognition, speed of processing, verbal learning, visual learning, working memory, cognitive control/executive function, and composite cognitive test score), Mini-Mental State Examination (MMSE) scores (Folstein et al., 1975), Clinical Global Impression Severity (CGI-S) scores (Guy and Bonato, 1970), discontinuation due to adverse events or inefficacy, and individual adverse events. The assessment of cognitive impairment was based on previous studies (Choi et al., 2013; Iwata et al., 2015) that used the Measurement and Treatment Research to Improve Cognition in Schizophrenia domains (Green et al., 2004). Supplementary Tables 2a and 2b list the detailed distribution of the outcomes included in this meta-analysis.

Data Extraction

Three authors (T.K., S.M., and K.O.) independently extracted the data from the selected studies. Where possible, intention-to-treat (ITT) or modified ITT (mITT) analyses were used. In the absence of such data, the results from observed case analysis were extracted from each study (supplementary Table 1a). For crossover studies, period 1 data (before crossover) were used for the meta-analysis, if available (supplementary Table 1a). Missing data essential for the meta-analysis were obtained by contacting the authors (or industries) of that particular study or by requesting for unpublished data.

Meta-Analysis Methods

To obtain a higher statistical power than that obtained by previous meta-analyses (Choi et al., 2013; Kishi et al., 2017), we pooled the studies that used cholinesterase inhibitors and memantine as anti-dementia drugs. The current meta-analysis was conducted using the Review Manager software (Collaboration, 2014), and a random effects model was used to account for potential heterogeneity across studies. Dichotomous outcomes are presented as risk ratios with a 95% CI. Further, continuous outcomes were analyzed using standardized mean difference

(SMD), allowing the combination of the data generated by the use of the different scales. In cases of unavailability of the SD values, the SD values from similar studies (using the same drug) were used (Higgins and Green, 2011). SMD corresponded to the difference between the 2 means, divided by the pooled SD, with a correction for small sample bias. Because lower scores (e.g., MMSE) indicate a higher impairment or symptom severity, we reversed the algebraic sign of the numerical scores for these scales. Regarding cognitive impairment, the meta-analysis method was followed as that described in previous studies (Choi et al., 2013; Iwata et al., 2015). Briefly, the overall cognitive function outcome was derived from the composite scores of cognitive batteries or from the average SMD of the cognitive domains on condition that ≥ 6 of the 8 cognitive domains were measured. When one cognitive domain had ≥ 2 cognitive tests, the average SMD values were used (supplementary Table 2a).

For a 3-arm study (donepezil, 5 mg/d; donepezil, 10 mg/d; and placebo) (Friedman et al., 2002), we combined the data of 2 donepezil arms. The methodological quality of the included trials was assessed based on the Cochrane risk-of-bias criteria (Higgins and Green, 2011). Further, heterogeneity was tested using the I^2 statistic, where $I^2 \geq 50\%$ indicated considerable heterogeneity (Higgins and Green, 2011). The following subgroup/sensitivity analyses were performed to detect the confounding factors for the primary and other efficacy outcomes (negative symptoms and MMSE scores), showing the superiority of ADD+AP to placebo+AP: anti-dementia drug class (cholinesterase inhibitor vs memantine), individual anti-dementia drug (donepezil, galantamine, rivastigmine, and memantine), antipsychotic class (SGA vs first-generation antipsychotic [FGA]), clozapine (clozapine vs other antipsychotic), sponsorship (industry vs non-industry), patient status (inpatient vs outpatient), the scale of psychiatric symptoms (Brief Psychiatric Rating Scale and PANSS vs Scale for the Assessment of Negative Symptoms [SANS, for negative symptoms] (Andreasen, 1982), we did not include this subgroup/sensitivity analysis of MMSE scores), geographical region (Asia vs other regions), and population analysis (ITT/mITT vs non-ITT/mITT). The other subgroup/sensitivity analyses of the negative symptoms were performed in terms of the PANSS negative subscale (original vs other versions) and the negative symptoms of patients (studies that included only patients with defined negative symptoms vs other studies) (supplementary Table 2b). Subgroup/sensitivity analysis was performed even if there was only one study included in a subgroup. However, we did not discuss results for subgroup that included only one study.

A meta-regression analysis was performed to evaluate the association between the meta-analysis results for overall symptoms, negative symptoms, MMSE scores, and certain modulators (PANSS total scores at baseline, CGI-S scores at baseline, the age of a patient, the duration of illness, the total number of patients, the percentage of males, the percentage of smokers, and study duration) using the Comprehensive Meta-Analysis software version 2 (Biostat Inc.). Further, a second meta-regression analysis was performed to examine whether the effect size of the anti-dementia drugs, in terms of negative symptoms, was associated with baseline PANSS negative subscale scores using the data from studies that exclusively used the original version of the PANSS negative subscale (supplementary Table 2b). In cases of multiple comparisons, Bonferroni corrections were performed. Cognitive impairment is considered a symptom of schizophrenia; however, since the scales differ from psychopathology scales, cognitive impairment and psychopathology were set as independent outcomes. Lastly, funnel plots were used to explore

potential publication bias, and Egger's regression was used to detect publication bias in the meta-analyses. The methodological quality of the included articles was assessed according to the Cochrane Risk of Bias criteria (Cochrane Collaboration, <http://www.cochrane.org>).

RESULTS

Study Characteristics

Our literature search identified a total of 1649 studies; of these, we excluded 895 duplicate studies, 647 after reviewing their title/abstract, and 72 after full-text review (60 review articles, 1 single-arm study, 1 case study, and 10 duplicated studies; [supplementary Figure 1](#)). Additionally, 2 studies were retrieved by searching review articles (Ribeiz et al., 2010; Singh et al., 2012) ([supplementary Figure 1](#)).

Following exclusions, 37 studies were selected for inclusion, comprising a total of 1574 patients. Among the 37 studies, there were 14 donepezil-based ($n=568$), 10 galantamine-based ($n=371$), 4 rivastigmine-based ($n=146$), and 9 memantine-based ($n=489$) studies. A summary of the included studies is presented in [supplementary Table 1a](#).

All included studies were double-blind, placebo-controlled trials published in English ([supplementary Table 1a](#)). However, most of the included studies were small ([supplementary Table 1a](#)) and had inconsistent results ([supplementary Table 1b](#)). Thirteen studies were sponsored by pharmaceutical companies ([supplementary Table 1a](#)). The mean study duration, mean duration of illness, and mean patient age were 13.5 weeks, 17.2 years, and 40.1 years, respectively, and 68.3% of the patients were males. Out of the 37 studies, 15 were conducted in Asia. The data from 31 studies were used for the meta-analysis, as the remaining 6 studies (Allen et al., 2003; Hussain and Chaudhry, 2003; Erickson et al., 2005; Mazeh et al., 2006; Sacco et al., 2008; Swerdlow et al., 2016) did not report the data required to perform a meta-analysis. Notably, although 10 of the 31 studies included in the meta-analysis did not use ITT/mITT populations in their analyses ([supplementary Table 1a](#)), they were included to maximize the sample size. Additionally, most included studies did not provide sufficient information about selection, performance, and detection biases. The results of the evaluation of the methodological quality based on the Cochrane risk-of-bias criteria is shown in [supplementary Figure 2](#).

Efficacy Outcomes

Compared with the placebo+AP treatment, the pooled treatments with ADD+AP (24 studies, 1069 patients) significantly improved the overall symptoms (SMD = -0.34, 95% CI = -0.61 to -0.08, $P=.01$, $I^2=74\%$; [Figure 1](#); [Table 1](#)). Notably, no publication bias was detected within each treatment group (Funnel plot: [supplementary Figure 3a](#), Egger's test $P=.100$).

The pooled ADD+AP treatments were also superior to placebo+AP in terms of improving the negative symptoms (24 studies, 1077 patients: SMD = -0.62, 95% CI = -0.92 to -0.32, corrected $P=.00018$, $I^2=80\%$; [Figure 2](#); [Table 1](#)) and MMSE scores (7 studies, 225 patients: SMD = -0.79, 95% CI = -1.23 to -0.34, $P=.0006$, $I^2=60\%$; [Figure 3](#); [Table 1](#)). However, publication bias was detected for the negative symptoms (Egger's test $P=.00588$; Funnel plot: [supplementary Figure 3b](#)) but not for the MMSE scores (Egger's test $P=.139$; Funnel plot: [supplementary Figure 3c](#)).

No significant differences were found between the ADD+AP and placebo+AP treatments in terms of other efficacy outcomes.

Sensitivity/Subgroup Analysis

Overall Symptoms

Regarding the overall symptoms, a considerable heterogeneity was found ($I^2=74\%$; [Table 1](#)), which disappeared in the sensitivity analyses using the data from the rivastigmine-based, industry-sponsored, and non-ITT/mITT studies ([supplementary Table 3a](#)). Following Bonferroni corrections, there were remarkably no subgroups wherein ADD+AP treatment was superior to placebo+AP in terms of improving the overall symptoms ([supplementary Table 3a](#)).

Negative Symptoms

Regarding the negative symptoms score, considerable heterogeneity was found ($I^2=80\%$; [Table 1](#)), which disappeared in the sensitivity analyses using the data from the galantamine-based, rivastigmine-based, FGA, SANS, and non-ITT/mITT studies ([supplementary Table 3b](#)). Following Bonferroni corrections, the subgroups with superior ADD+AP outcomes than placebo+AP in terms of the negative symptom improvements included the SGA studies, the studies using antipsychotics other than clozapine, non-industry-sponsored studies, the studies other than those including only patients with defined negative symptoms, Asia-based studies, and non-ITT/mITT studies ([supplementary Table 3b](#)).

MMSE Score

Regarding the MMSE scores, there was considerable heterogeneity ($I^2=60\%$; [Table 1](#)), which disappeared in the sensitivity analyses using the data from the memantine-based, galantamine-based, FGA, non-industry-sponsored, inpatient, Asia-based, and ITT/mITT studies ([supplementary Table 3c](#)). Following Bonferroni corrections, the subgroups wherein the ADD+AP treatment was superior to placebo+AP in terms of improving the MMSE scores included the memantine-based, FGA, non-industry-sponsored, inpatient, Asia-based, and ITT/mITT studies ([supplementary Table 3c](#)).

Meta-Regression Analysis

Overall Symptoms

In terms of the overall symptoms, the effect size of the ADD+AP treatment was associated with the CGI-S scores at baseline ([supplementary Table S4a](#); [supplementary Figure 4a](#)).

Negative Symptoms

In terms of the negative symptoms, the effect size of the ADD+AP treatment was associated with the CGI-S scores at baseline and with the total number of patients ([supplementary Table 4b](#); [supplementary Figure 4b,c](#)).

MMSE Score

In terms of MMSE score, the effect size of the ADD+AP treatment was associated with the age of a patient ([supplementary Table 4c](#); [supplementary Figure 4d](#)).

Safety Outcomes

Notably, no significant difference was found between the ADD+AP and placebo+AP treatment groups in terms of all-cause discontinuation (28 studies, 1328 patients: risk ratio = 1.16, 95% CI = 0.90–1.49, $P=.26$, $I^2=0\%$; [supplementary Table 5](#); [supplementary Figure 5](#)). No publication bias was found within each

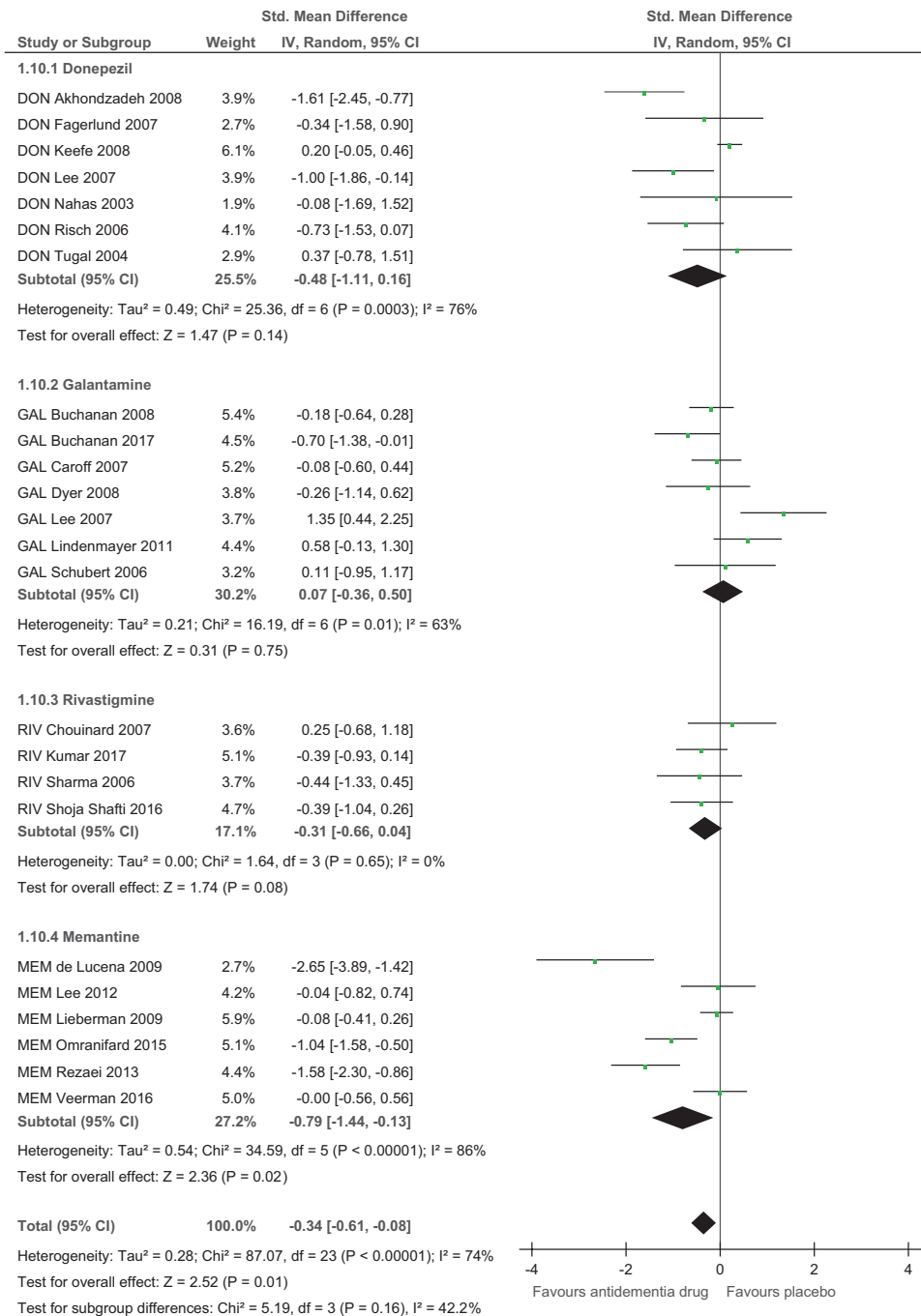


Figure 1. Forest plot for overall symptoms. 95% CI, 95% confidence interval; DON, donepezil; GAL, galantamine; IV, inverse variance; MEM, memantine; RIV, rivastigmine; Std. Mean Difference, standardized mean difference.

treatment group in terms of all-cause discontinuation (Funnel plot: [supplementary Figure 3d](#), Egger's test $P = .155$). Additionally, there were no significant differences between the treatment groups in terms of the occurrence of other adverse events ([supplementary Table 5](#)).

Discussion

This updated and comprehensive systematic review and meta-analysis investigated the use of anti-dementia drugs (donepezil, galantamine, rivastigmine, and memantine) in schizophrenia patients, and it was observed that the pooled ADD+AP treatment

group experienced superior efficacy than the placebo+AP treatment group in terms of safety, without significant differences. In particular, anti-dementia drugs effectively treated overall and negative symptoms.

Although there was considerable heterogeneity, the drugs improved the overall symptoms, negative symptoms, and MMSE scores in schizophrenia patients. To date, a meta-regression and several sensitivity/subgroup analyses have been performed to study these outcomes, particularly to identify the causes of heterogeneity. For the overall symptoms, the subgroups that did not present considerable heterogeneity included the rivastigmine-based, industry-sponsored, and non-ITT/mITT studies.

Table 1. Results of Efficacy Outcomes

	N	n	SMD	95% CI	P	Corrected P	I ²
Overall symptoms ^a	24	1069	-0.34	-0.61, -0.08	.01		74%
Positive symptoms	21	805	-0.21	-0.45, 0.04	.10		60%
Negative symptoms	24	1077	-0.62	-0.92, -0.32	.000045	.00018 ^b	80%
Anxiety/depressive symptoms	12	483	-0.20	-0.39, -0.02	.03	.12 ^b	4%
PANSS general subscale scores	12	367	-0.23	-0.62, 0.16	.24		68%
CGI-S score	8	356	-0.03	-0.38, 0.32	.87		53%
Composite cognitive test scores	6	532	-0.02	-0.22, 0.18	.83		37%
Working memory scores	15	501	0.08	-0.18, 0.34	.53		65%
Verbal learning scores	14	487	-0.23	-0.44, -0.01	.04	.32 ^c	57%
Speed of processing scores	12	417	0.16	-0.08, 0.40	.19		33%
Attention/vigilance scores	9	330	-0.13	-0.38, 0.13	.34		28%
Reasoning/problem solving scores	4	130	-0.10	-0.45, 0.24	.56		0%
Cognitive control/executive function scores	10	279	0.02	-0.27, 0.31	.90		45%
Social cognition scores	2	64	0.06	-0.43, 0.55	.82		0%
Visual learning scores	5	181	-0.03	-0.26, 0.21	.82		0%
MMSE scores	7	225	-0.79	-1.23, -0.34	.0006		60%

95% CI, 95% confidence interval; CGI-S, Clinical Global Impression Severity; MMSE, Mini-Mental Status Examination; N, number of comparisons; n, number of patients; PANSS, Positive and Negative Syndrome Scale; SMD, standardized mean difference.

^a Primary outcome for efficacy.

^b Bonferroni correction was performed for multiple comparisons: 4 tests (4 psychopathology subscales).

^c Bonferroni correction was performed for multiple comparisons: 8 tests (8 cognitive domains).

Markedly, the anti-dementia drugs were not superior to placebo in any of these subgroups. Therefore, although we could not identify an apparent cause for heterogeneity, sponsor and attrition biases (non-ITT/mITT studies) possibly influenced the meta-analytic results of the overall symptoms. The association found in the meta-regression analysis between the effect size of the anti-dementia drugs for the overall symptoms and CGI-S scores at baseline suggests that the baseline illness severity influences this positive result. Moreover, the small effect size of the anti-dementia drugs in terms of the overall symptoms was remarkably small.

In terms of the negative symptoms, considerable heterogeneity and a publication bias were detected. The subgroups lacking considerable heterogeneity included the galantamine-based, rivastigmine-based, FGA, SANS, and non-ITT/mITT studies; among these, we detected that the anti-dementia drugs were superior to placebo only in the non-ITT/mITT study subgroup. The meta-regression analysis also showed an association between the effect sizes of anti-dementia drugs in terms of the negative symptoms and the studies with small sample size. The studies included in the meta-analysis comprised small sample size (the median number of patients=34). In fact, the studies with a high-quality study design and large sample size (>100 patients) reported that anti-dementia drugs were not superior to placebo (Keefe et al., 2008; Lieberman et al., 2009), possibly attributable to the lack of power and type 1 errors in the included studies. A previously published article concluded that 35% of the published meta-analyses failed to accurately predict the outcomes of subsequently conducted large RCTs regarding the same topics (LeLorier et al., 1997). Therefore, the possibility that the result of meta-analysis in terms of negative symptoms is influenced by an attrition bias and a small-study effect cannot be denied (Sterne et al., 2000). Furthermore, this result possibly was a type I error owing to its small sample size. The meta-regression analysis demonstrated that the effect sizes of anti-dementia drugs for negative symptoms might be associated with disease severity (the CGI-S scores at baseline). However, the second meta-regression analysis showed

no association between the effect size of anti-dementia drugs and the original version of the PANSS negative subscale score at baseline. Although only 2 studies included only patients with defined negative symptoms (de Lucena et al., 2009; Buchanan et al., 2017), the subgroup analysis did not show the superiority of anti-dementia drugs over placebo. Therefore, further studies involving a large number of patients with defined negative schizophrenia symptoms are warranted to examine whether anti-dementia drugs actually improve the negative symptoms of schizophrenia.

We found that the pooled ADD+AP treatment was superior to the placebo+AP treatment based on the MMSE score. The subgroups with the anti-dementia drugs superior to placebo in terms of the MMSE score without considerable heterogeneity included the memantine-based, FGA, non-industry-sponsored, inpatient, Asia-based, and ITT/mITT studies. All 3 memantine studies were non-industry-sponsored studies. Among these, the memantine studies have the largest effect size for anti-dementia drugs.

Although memantine is marketed to treat moderate to severe Alzheimer's disease (i.e., mostly older adult patients) (Scheltens et al., 2016), it was noteworthy that the effect size of anti-dementia drugs for improving the MMSE score increased in younger adult patients with schizophrenia. Considering the fact that anti-dementia drugs possess a neuroprotective effect (Villarroya et al., 2007; Parsons et al., 2013), they may recover the scores in younger adult schizophrenia patients without severe neuron impairment further than in older adult patients. However, the number of studies and patients in the MMSE score meta-analysis was statistically small. Moreover, the pooled ADD+AP treatment was not superior to placebo+AP in terms of the composite cognitive test score, which evaluates cognitive impairment more comprehensively than the MMSE score. In addition, it was unclear whether the negative symptoms were actually corrected for the MMSE scores.

There were several limitations to this study that need to be addressed. First, the sample size of the included studies was small. Although our study had a larger sample size than

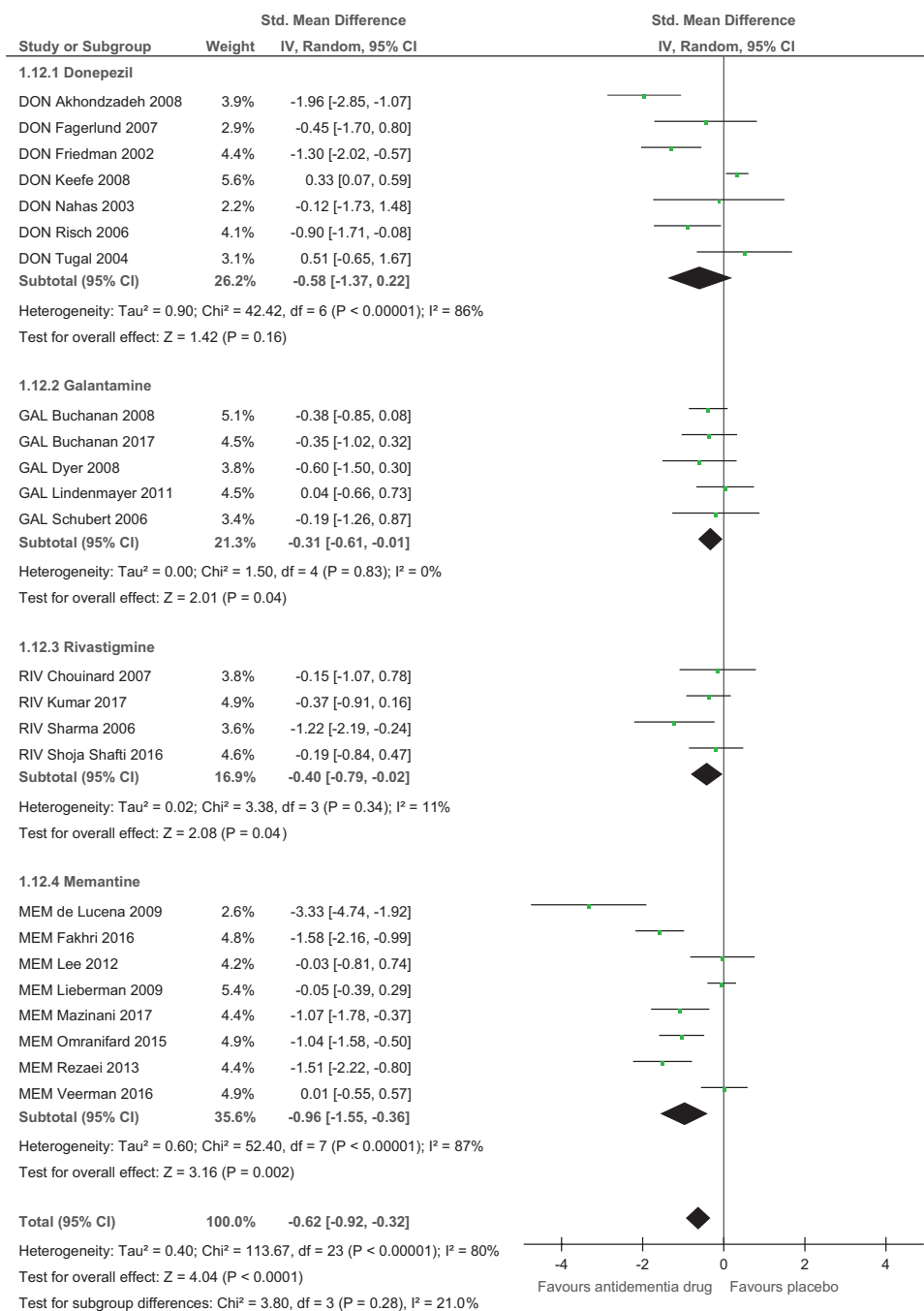


Figure 2. Forest plot for negative symptoms. Although the overall P value in this figure was <.0001, the more detailed overall P value was .000045. 95% CI, 95% confidence interval; DON, donepezil; GAL, galantamine; IV, inverse variance; MEM, memantine; RIV, rivastigmine; Std. Mean Difference, standardized mean difference.

some previous studies (Singh et al., 2012; Choi et al., 2013; Kishi et al., 2017), there might be a small-study effect in the results for the overall and negative symptoms (Sterne et al., 2000). Accordingly, a future study using a larger sample size should be conducted to obtain more robust results. Second, the patient characteristics among the examined studies differed in terms of the symptom severity, inclusion criteria, the scales for evaluating the schizophrenia symptoms, geographical region, race, ethnicity, drug dose, and study duration; these differences may have generated heterogeneity while combining the data for the systematic review and meta-analysis. Additionally, there were considerable heterogeneities

in terms of the overall symptoms, negative symptoms, and MMSE scores. We also detected some bias (sponsor, publication, and attrition biases) associated with the effect size of the anti-dementia drugs in the treatment of these outcomes. Of the 37 studies, 15 were conducted in Asia. However, we failed to find the reason for the results of Asia-based studies influencing those of our meta-analysis. Because there was no standard calculation method with respect to equivalent doses of anti-dementia drugs, we did not examine whether anti-dementia drug doses had an impact on the meta-analytic results. Lastly, most included studies were industry-sponsored studies. Therefore, the impact of sponsorship bias

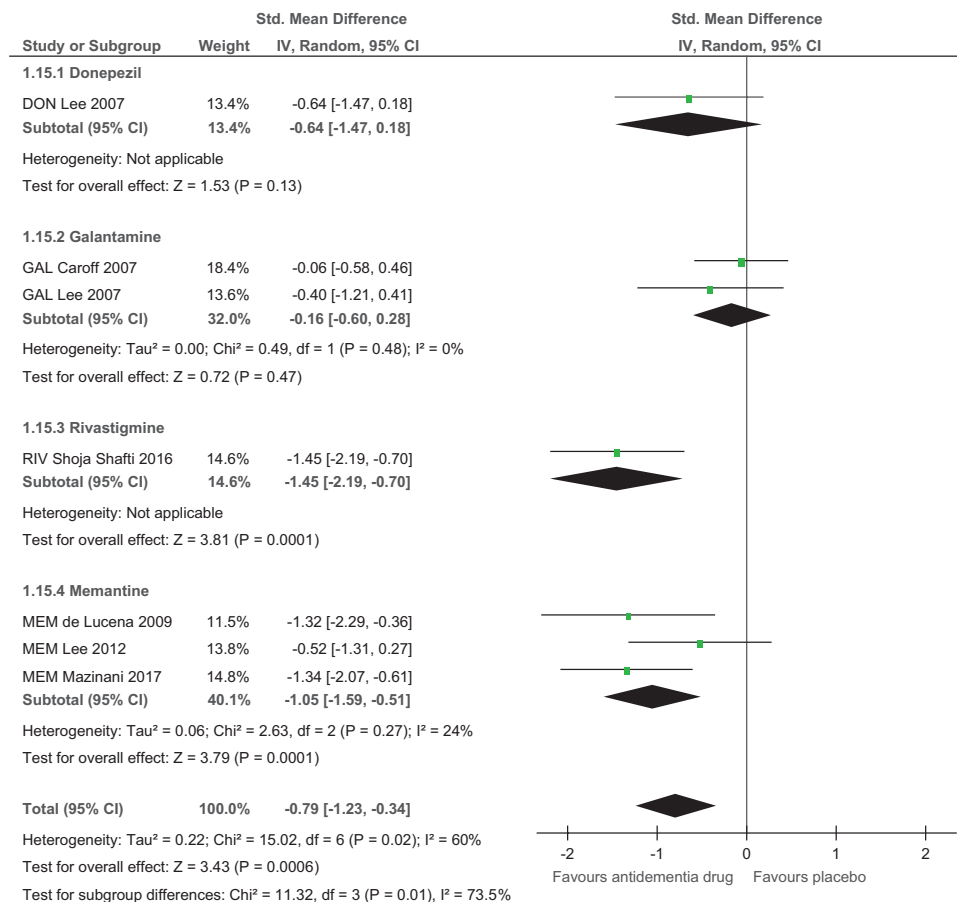


Figure 3. Forest plot for Mini-Mental State Examination (MMSE) scores. 95% CI, 95% confidence interval; DON, donepezil; GAL, galantamine; IV, inverse variance; MEM, memantine; RIV, rivastigmine; Std. Mean Difference, standardized mean difference.

(Naci et al., 2014) needs to be considered while interpreting our results.

In conclusion, the current meta-analysis suggests that the ADD+AP treatment influences psychopathology, particularly the negative symptoms of schizophrenia. However, the effect size of ADD+AP treatment for the overall and negative symptoms was small to medium. Moreover, since we cannot discard the possibility that a small-study effect and some bias (attrition, publication, and sponsorship biases) influenced the results, further studies using larger sample sizes with defined negative symptoms should be conducted to investigate whether the ADD+AP treatment improves the schizophrenia symptoms (particularly the negative symptoms) in patients with schizophrenia.

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