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Adjunctive ondansetron for schizophrenia: A systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

The serotonin 5-hydroxytryptamine type 3 (5-HT3) receptor has been implicated in the pathogenesis of schizophrenia. This meta-analysis of randomized controlled trials (RCTs) examined the efficacy and safety of adjunctive ondansetron, a potent 5-HT3 receptor antagonist, in the treatment of schizophrenia. Only RCTs examining adjunctive ondansetron for schizophrenia were included. Standardized mean difference (SMD), risk ratio (RR) and their 95% confidence intervals (CIs) were analyzed using RevMan, Version 5.3. Study quality was evaluated with the Cochrane risk of bias and the Jadad scale. Data of 5 RCTs (n = 304) covering 149 patients on ondansetron (4-8 mg/day) and 155 patients on placebo were analyzed. Three RCTs reported "randomized allocation" with a specific description; the weighted Jadad score was 3.8. Adjunctive ondansetron outperformed placebo in the reduction of Positive and Negative Syndrome Scale (PANSS) total score [3 RCTs, n = 171; SMD: −1.06 (95%CI: −2.10, −0.02), p = 0.04, I^2 = 85%], the negative [4 RCTs, n = 209; SMD: −0.96 (95%CI: −1.71, −0.22), p = 0.01, I^2 = 80%], and general psychopathology symptom scores [3 RCTs, n = 171; SMD: −0.97 (95%CI: −1.91, −0.02), p = 0.04, I^2 = 82%], but not in the positive (p = 0.05) and depressive symptom scores (p = 0.91). The difference in PANSS total score remained significant after excluding one outlying RCT [2 RCTs, n = 141; SMD: −0.50 (95%CI: −0.84, −0.16), P = 0.004, I^2 = 0%]. Four RCTs examined the effect of ondansetron on cognition applying different instruments yielding conflicting findings. Ondansetron was superior over placebo in improving extrapyramidal symptoms, but no group differences were found in overall discontinuation rate and adverse drug reactions. In conclusion, adjunctive ondansetron appears to be efficacious and safe in improving negative symptoms and general psychopathology. The effect of ondansetron on cognitive impairment in schizophrenia needs to be further explored in large-scale RCTs.

1. Introduction

Schizophrenia is a major psychiatric disorder characterized by psychotic symptoms and cognitive dysfunction. Despite vigorous treatment with a host of antipsychotic drugs and their combinations, many schizophrenia patients still suffer from persistent psychotic symptoms, adverse drug reactions (ADRs), functional impairment, and poor quality of life (Mohammadi and Akhondzadeh, 2001). In addition, cognitive deficits occur in up to 80% of schizophrenia patients, which often appear even before the onset of the illness (Fuller et al., 2002). Domains of cognitive dysfunction encompasses verbal and working memory, attention, processing speed, and executive functioning (Bowie

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and Harvey, 2005). These deficits contribute to functional impairment and disability (Kaneko, 2018). Although both first and second generation antipsychotics (FGA and SGA, respectively) improve positive psychotic symptoms and reduce relapse risk (Samara et al., 2016), they are less effective for cognitive impairment (Matsuda et al., 2014) and may even worsen cognitive functioning (Sharma, 2002). Given that cognitive deficit, a core feature of schizophrenia (Reichenberg and Harvey, 2007), has a negative impact on patients' life, it is important to find effective treatment to improve cognitive functioning (Li et al., 2018; McGurk et al., 2007).

Although the pathophysiology of schizophrenia remains unclear, evidence is growing that central serotonin 5-hydroxytryptamine type 3 (5-HT3) receptor is implicated in the pathogenesis of schizophrenia, particularly cognitive dysfunction (Costall and Naylor, 1991, 2004). The therapeutic effect of SGAs could be partly attributed to their antagonism of the 5-HT3 receptor (Meltzer, 1995; Potvin et al., 2003). Ondansetron, a potent 5-HT3 receptor antagonist, is used to treat nausea and vomiting induced by other drugs, for instance chemotherapy (Miyata and Honda, 1994). Case reports (Briskin and Curtis, 1997; White et al., 1991) and observational studies (Hema et al., 2016; Sirota et al., 2000, 2001) found that adjunctive ondansetron was effective in treating psychotic symptoms and antipsychotic-induced tardive dyskinesia (TD), but its effect on cognitive impairment remains controversial. Randomized controlled trials (RCTs) on the efficacy and safety of adjunctive ondansetron for schizophrenia also reported inconsistent findings (Adler et al., 2005; Akhondzadeh et al., 2009; Chaudhry et al., 2014; Kulkarni et al., 2018; Levkovitz et al., 2005; Mohammadi et al., 2010; Samadi et al., 2017; Zhang et al., 2006).

Meta-analysis (Kishi et al., 2014) of two RCTs (Akhondzadeh et al., 2009; Zhang et al., 2006) and a review (Bennett and Vila, 2010) concluded that adjunctive ondansetron was superior to placebo for the negative symptoms of schizophrenia. However, the major limitation of the Kishi et al. meta-analysis was the very small number of included RCTs and the lack of evaluation on cognitive functions (Kishi et al., 2014). The present systematic review and meta-analysis included 3 additional RCTs (Chaudhry et al., 2014; Kulkarni et al., 2018; Samadi et al., 2017) to evaluate the efficacy and safety of adjunctive ondansetron for schizophrenia, particularlyly its effect on cognitive impairment.

2. Methods

2.1. Search strategy

This systematic review and meta-analysis were conducted following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) checklist. A comprehensive electronic literature search of articles related to topic was independently conducted by two investigators (WZ and DBC) in the PubMed, Cochrane Library, PsycINFO, EMBASE, WanFang and Chinese Journal Net databases from their inception until November 1, 2018 employing the following search terms: ("ondansetron" [Mesh] OR ondansetron) AND ("schizophrenia" [Mesh] OR schizophrenic disorder OR disorder, schizophrenic OR schizophrenic disorders OR schizophrenia OR dementia praecox). The same two investigators manually checked the bibliographies of included studies (Akhondzadeh et al., 2009; Chaudhry et al., 2014; Kulkarni et al., 2018; Samadi et al., 2017; Zhang et al., 2006) and relevant reviews (Bennett and Vila, 2010; Kishi et al., 2014) for additional publications. Retrieved studies were transferred to the EndNote, Version *X*7 software program and titles, abstracts and full texts were independently screened by the same two investigators for eligibility. Any disagreement in the literature search between the investigators was resolved by a discussion or a consultation with a senior investigator (YTX).

2.2. Inclusion criteria of the meta-analysis

The inclusion criteria of the meta-analysis followed the *PICOS* acronym: ***P***articipants: patients with schizophrenia diagnosed according to the three international diagnostic systems: CCMD, ICD and DSM. ***I***ntervention: ondansetron plus treatment as usual (TAU). ***C***omparison: TAU plus placebo or TAU alone. ***O***utcomes: primary outcome was the improvement of 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). Key secondary outcomes were negative and positive symptoms measured with the PANSS, BPRS, Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1983), or the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984), general psychopathology symptoms measured with the PANSS, cognitive function, depressive symptoms, extrapyramidal symptoms, TD, discontinuation for any reason and the rate of ADRs. Study design: RCTs on adjunctive ondansetron for schizophrenia. Following the recommendation of another meta-analysis (Kishi et al., 2014), studies with short treatment duration ($\leq$1 week) were excluded (Adler et al., 2005; Levkovitz et al., 2005).

2.3. Data extraction

Two investigators (WZ and DBC) independently extracted the following data from the studies: study characteristics (first author, year of publication and sample size), basic demographic and clinical data (illness duration, age and percentage of males), and outcomes (efficacy, safety and tolerability of ondansetron). Discrepancies in data entry between the investigators were resolved by a discussion or a consultation with a senior investigator (YTX). The first or corresponding authors of included studies were contacted by email or telephone for additional information if it was necessary.

2.4. Statistical analysis

The data were analyzed by the aid of the RevMan software, Version 5.3 (Higgins and Higgins, 2008) with a random-effects model (DerSimonian and Laird, 1986). Standardized mean difference (SMD), and risk ratio (RR) with their 95% confidence interval (CI) calculated the effect size of continuous and categorical variables, respectively. The heterogeneity between studies was examined with I^2 and Q tests (Higgins et al., 2003), with $I^2 \geq 50\%$ and $P < 0.10$ indicating significant heterogeneity. A sensitivity analysis was performed to examine the consistency of the primary outcome by excluding one outlying study (Akhondzadeh et al., 2009), which had an effect size of $>$ -2.0. Meta-regression analysis was conducted using Comprehensive Meta-Analysis software, version 2.0 to investigate the mediating effect of study quality (total Jadad score) on the primary outcome measure. Publication bias was examined with visual funnel plots and Egger's test (Egger et al., 1997). All primary and secondary outcomes were 2 tailed, with alpha set at 0.05.

2.5. Quality assessment

Two independent investigators (WZ and DBC) evaluated the quality of the included RCTs using the Jadad scale (Jadad et al., 1996) and Cochrane risk of bias (Higgins and Higgins, 2008). A Jadad total score of $\geq$3, indicated "high quality" (Linde et al., 1997). The Cochrane risk of bias has 7 domains: randomization, allocation concealment, blinding of subjects, blinding of outcome assessors, reporting incomplete outcome data, selective outcome reporting, and other potential sources of bias. The overall evidence levels of the primary and secondary outcomes of adjunctive ondansetron for schizophrenia were assessed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system (Atkins et al., 2004; Balshem et al., 2011).

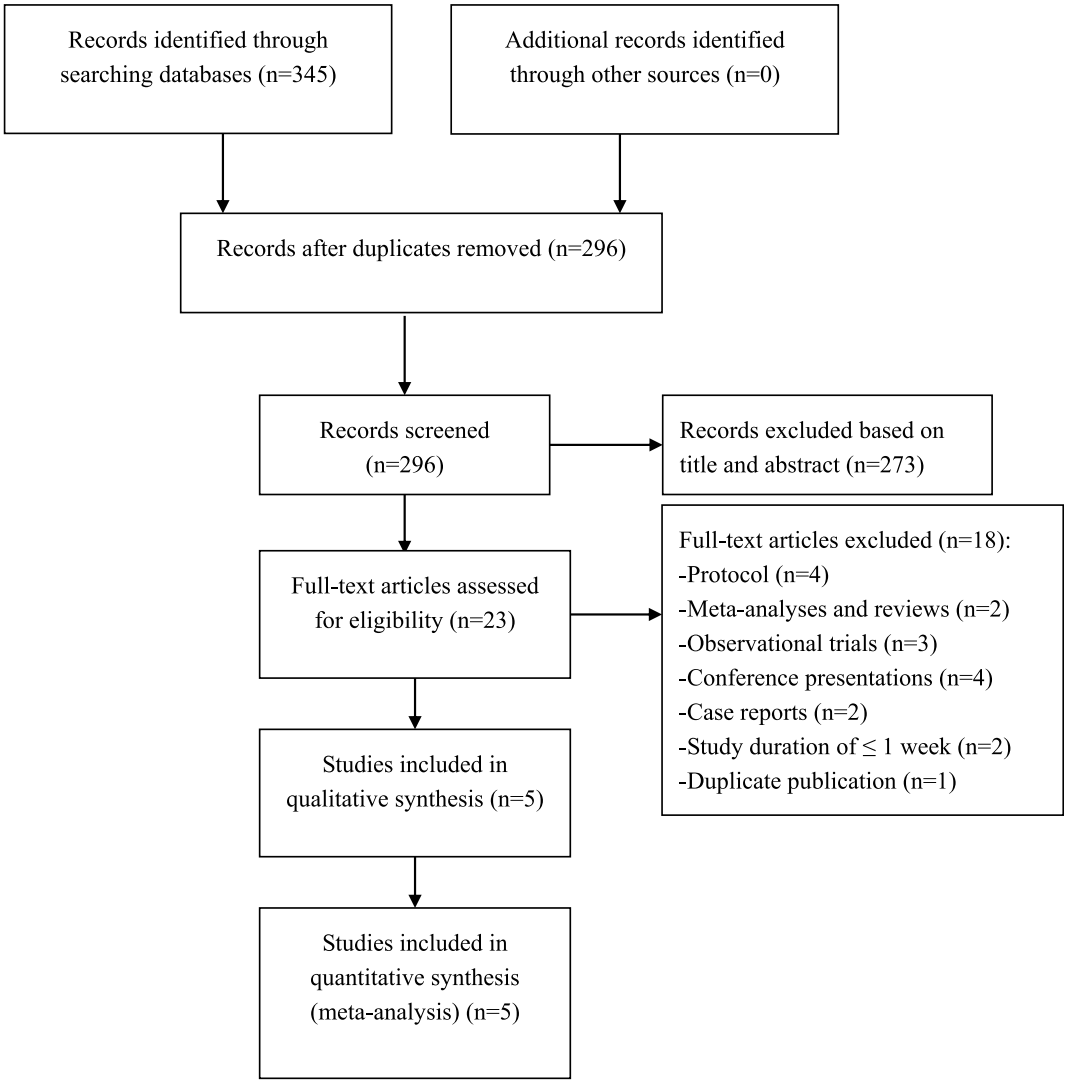

Fig. 1. PRISMA flow diagram.

3. Results

3.1. Literature search

A total of 345 records were identified from the target databases (Fig. 1). Eventually, 5 RCTs (Akhondzadeh et al., 2009; Chaudhry et al., 2014; Kulkarni et al., 2018; Samadi et al., 2017; Zhang et al., 2006) met the study criteria and were included in the meta-analysis.

3.2. Study characteristics

Five RCTs comprising 304 schizophrenia patients lasting 12 weeks compared ondansetron (n = 149) with placebo (n = 155) groups (Table 1). The weighted mean age in the 4 RCTs with available data was 39.7 years (range = 33.3–42.5 years), the weighted illness duration in 3 RCTs with available data was 13.0 years (range = 7.2–17.2 years). The dose of ondansetron ranged from 4 to 8 mg/day. Two RCTs were conducted in Iran (n = 74), and one each in China (n = 121), Pakistan (n = 24), and Australia (n = 85).

3.3. Assessment of study quality

Supplemental Fig. 1 shows the risk of bias assessment. Three RCTs reported "randomized allocation" with specific description and all RCTs were rated as low risk with regards to attrition and reporting bias. The weighted Jadad score was 3.8 (range = 3 to 4), and all RCTs were rated as 'high quality' (Table 1). The overall evidence level of meta-analyzable outcome measures were rated"low" (14.3%, 1/7) or "moderate" (85.7%, 6/7) by the GRADE approach (Table 2).

3.4. Psychotic symptoms

Supplemental Table 1 presents clinical outcomes, finding one RCT without available data (Kulkarni et al., 2018). Meta-analyses of PANSS total [3 RCTs, n = 171; SMD: −1.06 (95%CI: −2.10, −0.02), p = 0.04, I^2 = 85%, Fig. 2], negative symptom [4 RCTs, n = 209; SMD: −0.96 (95%CI: −1.71, −0.22), p = 0.01, I^2 = 80%, Fig. 2], and general psychopathology [3 RCTs, n = 171; SMD: −0.97 (95%CI: −1.91, −0.02), p = 0.04, I^2 = 82%, Fig. 2] scores found that adjunctive ondansetron was superior to placebo in these outcomes. Superiority of PANSS total score remained significant after removing the one outlying RCT (Akhondzadeh et al., 2009) [2 RCTs, n = 141; SMD: −0.50 (95%CI: −0.84, −0.16), p = 0.004, I^2 = 0%]. In meta-regression analysis, lower study quality was associated with greater efficacy of ondansetron in improving PANSS total score (p = 0.019). In contrast, meta-analyses of PANSS positive (p = 0.05, Fig. 2) and depressive symptoms measured by Hamilton Rating Scale for Depression (p = 0.91, Fig. 2) did not show significant group differences.

Table 1
Patient and study characteristics.

Study (Country)	No. of patients	Blindness	Analyses	Trial Duration (wks)	Setting (%)	Diagnosis (%)	Diagnostic criteria	Illness duration[b]	Age[b]: yrs (range)	Sex[b]: Male (%)	Control-Group: Dose (mg/d): mean (range)	Intervention-Group: Dose (mg/d): mean (range)		Jadad score
Akhondzadeh et al. (2009) (Iran)	T: 30 C: 15 I: 15	DB	ITT	12	Inpatients (6.7) and Outpatients (93.3)	SCZ (100)	DSM-IV	−7.2 yrs[c]	33.3 (22–44)	63.3	RIS: Ø = NR (4–6)	RIS: Ø = NR (4–6)	OND: Ø = 8 (FD)	3
Chaudhry et al. (2014) (Pakistan)	T: 24 C: 12 I: 12	DB[a]	ITT	12	Two psychiatric units (100)	SCZ (NR)	DSM-IV	-NR	NR (18–65)	NR	APs[d]: Ø = NR (NR)	APs[d]: Ø = NR (NR)	OND: Ø = 8 (FD)	3
Kulkarni et al. (2018) (Australia)	T: 85 C: 43 I: 42	DB	OC	12	In (NR)-outpatients (NR)	SCZ (65.9), SzA (30.6)	DSM-IV-TR	−17.2 yrs	42.5 (18–65)	NR	APs[d]: Ø = NR (NR)	APs[d]: Ø = NR (NR)	OND: Ø = 8 (FD)	4
Samadi et al. (2017) (Iran)	T: 44 C: 22 I: 22	DB	OC	12	In (NR)-outpatients (NR)	SCZ (NR)	DSM-IV-TR	-NR	38.6 (20–60)	92.1	RIS: Ø = 8 (FD)	RIS: Ø = 8 (FD)	OND: Ø = NR (4–8)	4
Zhang et al. (2006) (China)	T: 121 C: 63 I: 58	DB	ITT	12	Inpatients (100)	SCZ (100)	DSM-IV	−16.2 yrs	39.8 (18–65)	72.7	HAL: Ø = 11.4 (4–30)	HAL: Ø = 11.4 (4–30)	OND: Ø = 7.8 (NR)	4

Abbreviations: APs = antipsychotics; C = control; 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; HAL = haloperidol; I = intervention; ITT = intent to treat; NR = not report; OC = observed cases; OND = ondansetron; RIS = risperidone; SCZ = schizophrenia; SzA = schizoaffective disorders; T = total; wks = weeks; yrs = years.

[a] This study was rated as double blind study based on the description "rater-blind placebo-controlled study" in the paper.

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

[c] Time since diagnosis.

[d] Did not report the details of AP use.

Publication bias could not be examined due to the small number ($n < 10$) of included RCTs (Sterne et al., 2011).

3.5. Cognitive functions

Although 80% RCTs examined the effects of ondansetron on cognitive functions, different measures were applied rendering the data unsuitable for meta-analysis (Supplemental Table 2). Two RCTs found ondansetron superior over placebo in the cognitive items of the PANSS (Kulkarni et al., 2018; Zhang et al., 2006). Ondansetron could significantly improve visual memory measured with the Wechsler Memory Scale-Revised (WMS-R) (Akhondzadeh et al., 2009) and object assembly and comprehension measured with the Wechsler's Adult Intelligence Scale-Revised (WAIS-R) (Samadi et al., 2017).

3.6. ADRs and discontinuation rate

All RCTs examined the ADRs related to ondansetron, but their specific data were not reported (Supplemental Table 3). No group differences regarding ADRs were reported in two RCTs (Akhondzadeh et al., 2009; Kulkarni et al., 2018). Superiority of ondansetron in improving extrapyramidal symptoms measured with the Extrapyramidal Symptom Rating Scale (ESRS) was observed in one RCT (Akhondzadeh et al., 2009).

Meta-analyses of TD measured with the Abnormal Involuntary Movements Scale (AIMS) ($P = 0.38$, Supplemental Fig. 2) and all-cause discontinuation rate did not show group difference ($P = 0.55$, Supplemental Fig. 3).

Table 2
GRADE analyses: adjunctive ondansetron for schizophrenia.

Primary and *secondary* outcomes	No. of study and (subjects)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Large effect	Overall quality of evidence[a]
PANSS total psychopathology	3 (171)	No	Serious[b]	No	No	Serious[c]	Large[e]	+/+/+/−/; Moderate
PANSS positive symptoms	4 (209)	No	No	No	No	Serious[c]	No	+/+/+/−/; Moderate
PANSS negative symptoms	4 (209)	No	Serious[b]	No	No	Serious[c]	Large[e]	+/+/+/−/; Moderate
PANSS general psychopathology	3 (171)	No	Serious[b]	No	No	Serious[c]	Large[e]	+/+/+/−/; Moderate
Depressive symptoms	2 (68)	No	No	No	No	Serious[c]	No	+/+/+/−/; Moderate
TD	2 (104)	No	Serious[b]	No	No	Serious[c]	No	+/+/−/-/; Low
Discontinuation for any reason	4 (274)	No	No	No	No	Serious[d]	No	+/+/+/−/; Moderate

Abbreviations: GRADE = Gading of Recommendations Assessment, Development, and Evaluation; PANSS = Positive and Negative Syndrome Scale; TD = tardive dyskinesia.

[a] GRADE Working Group grades of evidence: High quality = further research is very unlikely to change our confidence in the estimate of effect. Moderate quality = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality = we are very uncertain about the estimate.

[b] Meta-analytic results presented a serious inconsistency when I^2 values were greater than 50% or $P < 0.1$ in the Q statistics.

[c] For continuous outcomes, $N < 400$.

[d] For dichotomous outcomes, $N < 300$.

[e] Studies with large effects provided increased quality of evidence. Large effects = effect size ≥ 0.8.

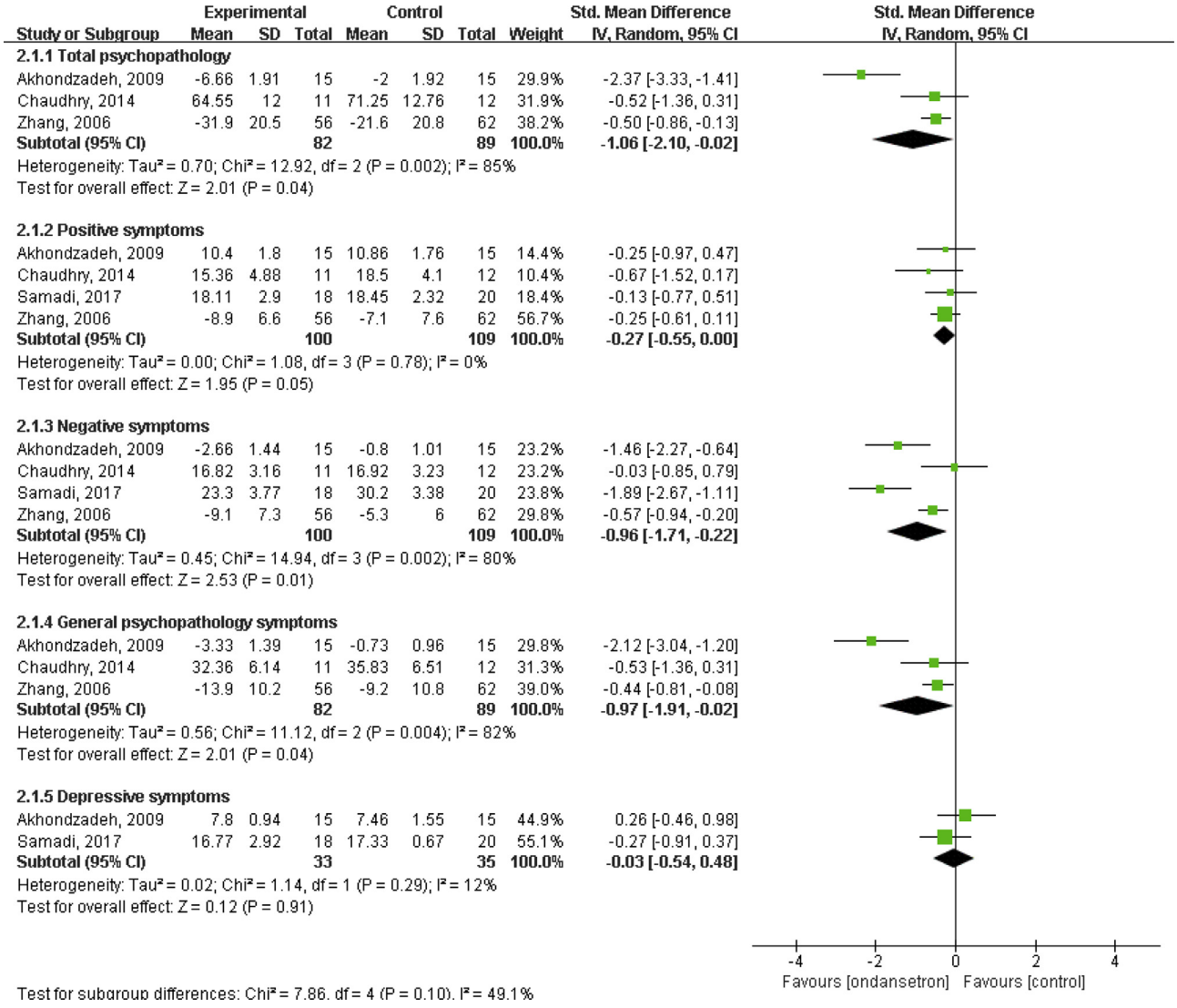

Fig. 2. Adjunctive ondansetron for schizophrenia: forest plot for total, positive, negative, and general symptoms of the Positive and Negative Syndrome Scale (PANSS) as well as depressive symptoms.

4. Discussion

The main finding of the systematic review and meta-analysis is that 12 weeks of adjunctive ondansetron could significantly improve negative symptoms and general psychopathology in schizophrenia. This confirms the conclusion of a previous meta-analysis of RCTs that examined the impact of adjunctive selective 5-HT3 receptor antagonists for schizophrenia (Kishi et al., 2014). In addition, there are preliminary data to suggest that adjunctive ondansetron may be beneficial for certain aspects of cognitive functions. Further studies are warranted in this area of research.

Consistent with several other adjunctive medications for schizophrenia, among others raloxifene (n = 240, SMD = −0.43) (Zhu et al., 2018), topiramate (n = 436, SMD = −0.58) (Zheng et al., 2016), amantidine (n = 83, SMD = −0.56) (Zheng et al., 2017), and minocycline (n = 476, SMD = −0.69) (Xiang et al., 2017), adjunctive ondansetron proved to be efficacious for negative symptoms (n = 209, SMD = −0.96), However, the mechanism of ondansetron therapeutic effect on negative symptoms remains unclear. Given that negative symptoms could overlap with, or being secondary to extrapyramidal and depressive symptoms (Kishi et al., 2014; Miyamoto et al., 2012), the effect of ondansetron on extrapyramidal symptoms could, in turn improve negative symptoms to some extent.

Adjuvant ondansetron affects certain facets of cognitive functions, for instance visual memory, in schizophrenia (Akhondzadeh et al., 2009). Cognition functioning in studies of the systematic review was measured with different instruments, hence the data were not pooled together. Only one RCT evaluated cognition administering the MATRICS Consensus Cognitive Battery (MCCB), which was recommended as the gold standard on exploring cognitive functions in schizophrenia (Nuechterlein et al., 2008). Thus the effect of ondansetron on cognitive function in schizophrenia needs to be examined in future studies.

The current meta-analysis included three more RCTs (Chaudhry et al., 2014; Kulkarni et al., 2018; Samadi et al., 2017) compared to an earlier meta-analysis (Kishi et al., 2014) that had only two RCTs (Akhondzadeh et al., 2009; Zhang et al., 2006) allowing more comprehensive analyses (such as meta-regression analysis) and yielding more robust evidence. In addition, the effects of ondansetron on cognitive functioning were summarized in the current meta-analysis, although the data measured with different instruments were not suitable for meta-analysis.

There are several limitations to this study. First, there were still relatively few RCTs with sample sizes varying from 24 to 121 patients. Important data, for example on cognitive functions, were not uniformly available, precluding further analyses. Second, the meta-analytic results for PANSS total (I^2 = 85%) and negative symptoms scores (I^2 = 80%)

showed considerable heterogeneity, therefore the findings should be interpreted with caution. The overall quality level of the studies was rated as "moderate" with the GRADE approach, which characterizes the validity of the findings. Finally, neither of 5 RCTs examined the long-term efficacy (> 12 weeks) and safety of adjunctive ondansetron.

In conclusion, adjunctive ondansetron appears to be efficacious and safe in the short-term treatment of schizophrenia with respect to negative symptoms and general psychopathology. It should be noted, however, that due to the small number of RCTs, the findings of the meta-analysis are preliminary. The effectiveness of ondansetron on cognitive deficits and long-term effectiveness in schizophrenia needs to be further tested in large-scale RCTs.

Review registration

PROSPERO: CRD42018115539.

Conflicts of interest

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

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None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2019.02.024.

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