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ORIGINAL PAPER

Selective Serotonin 3 Receptor Antagonist Treatment for Schizophrenia: Meta-analysis and Systematic Review

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Abstract Double-blinded, randomized, placebo-control trials of selective serotonin 3 receptor antagonists (5-HT_3R-ANTs) for schizophrenia have differed in outcome. This meta-analysis tests the hypothesis that 5-HT_3R-ANTs are effective for the treatment for schizophrenia. We searched PubMed, the Cochrane Library database, and PsycINFO up to June 15, 2013. We conducted a systematic review and meta-analysis of individual patient data from randomized controlled trials comparing 5-HT_3R-ANTs add-on therapy with placebo. The risk ratio (RR), 95 % confidence intervals (CI), and standardized mean difference (SMD) were calculated. A random-effects model was used. Six studies (total $n = 311$) were identified. These included one granisetron plus risperidone study, one ondansetron plus risperidone study, one ondansetron plus haloperidol, and three tropisetron plus risperidone studies. The statistically significant effects of 5-HT_3R-ANTs add-on therapy on Positive and Negative Syndrome Scale (PANSS) total scores were SMD = −1.03, CI = −1.70 to −0.36, $p = 0.003$ ($I^2 = 82$ %, 5 studies, $n = 261$); on negative scores were SMD = −1.10, CI = −1.82 to −0.39, $p = 0.002$ ($I^2 = 84$ %, 5 studies, $n = 261$); and on PANSS general scores were SMD = −0.70, CI = −1.23 to −0.17, $p = 0.01$ ($I^2 = 73$ %, 5 studies, $n = 261$). However, 5-HT_3R-ANTs add-on therapy was not superior to placebo in PANSS positive scores (SMD = −0.12, $p = 0.33$). Dropout due to all cause (RR = 0.80, $p = 0.50$), inefficacy (RR = 0.76, $p = 0.65$), or adverse events (RR = 0.84, $p = 0.75$) was similar in both groups. Constipation occurred significantly more often with 5-HT_3R-ANTs than placebo (RR = 2.05, CI = 1.07–3.91, $p = 0.03$, NNH = 11, $p = 0.02$). 5-HT_3R-ANTs add-on therapy is more beneficial on the psychopathology (especially negative symptoms) than controls in patients with schizophrenia, and 5-HT_3R-ANTs seem to be well-tolerated treatments.

Keywords Schizophrenia · Serotonin 3 receptor antagonists · Meta-analysis · Granisetron · Ondansetron · Tropisetron

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Introduction

Patients with treatment-resistant schizophrenia or antipsychotic partial response schizophrenia have persistent moderate to severe symptoms for prolonged periods, and approximately 30 % (range 10–45 %) of patients with schizophrenia meet this criteria (Kane et al. 1988; Meltzer 1997). They have the following problems (Conley and Kelly 2001; Conley et al. 1999): (1) they are highly symptomatic and may require extensive periods of hospital care; (2) they have high rates of violence toward others and themselves; (3) they lack insight, information, and efficacy because of non-adherence; and (4) magnetic resonance imaging shows that they have increased cortical atrophy. It is believed that these problems aggravate the pathology of schizophrenia. Therefore, clinical trials of adjuvant therapy to antipsychotics for use against treatment-resistant schizophrenia or antipsychotic partial response schizophrenia have been conducted, and several meta-analyses combining these data have been reported. For example, serotonin $(5\text{-HT})_{1A}$ partial agonists (buspirone and tandospirone) and 5-HT_{2A} antagonist (for example: trazodone) have been demonstrated as treatments for schizophrenia.

5-HT_{1A} partial agonists (buspirone and tandospirone) were significantly superior to placebo for overall improvement in psychopathology (SMD = −0.46, $p = 0.006$) and marginally more effective in improving positive symptoms (SMD = −0.31, $p = 0.06$) (Kishi et al. 2013a). Trazodone was also superior to placebo for the improvement of negative symptoms (Singh et al. 2010). Thus, studies regarding compounds that act on serotonin receptors have been undertaken (Meltzer 2012).

The 5-HT_3 receptor constitutes a cation-permeable ligand-gated ion channel that shares structural features with γ-aminobutyric acid (GABA), glycine, and nicotinic acetylcholine (nACh) receptors (Karlin and Akabas 1995). It is expressed throughout the central and peripheral nervous systems and mediates a variety of physiological functions (Wolf 2000). The postsynaptic 5-HT_3 receptor has been shown to mediate fast excitatory synaptic transmission in neocortical interneurons, amygdala, and hippocampus, and is thought to mediate or modulate neurotransmitter release in mesolimbic and mesocortical dopamine neurons (Hagan et al. 1993). Abnormalities in dopaminergic neural transmission are considered to be one of the pathophysiologies of schizophrenia (Miyamoto et al. 2012). Although 5-HT_3 receptor antagonists (5-HT_3R-ANTs) are generally used for the treatment of patients with chemotherapy-induced or postoperative nausea and vomiting, 5-HT_3R-ANTs (ondansetron, granisetron, and tropisetron) have been demonstrated as treatments for schizophrenia. Two recent randomized placebo-controlled trials (RCTs) (Akhondzadeh et al. 2009; Zhang et al. 2006) reported that ondansetron was superior to placebo in the Positive and Negative Syndrome Scale (PANSS) (Kay et al. 1989) total score and negative subscale scores. Moreover, another study (Khodaie-Ardakani et al. 2013) reported that granisetron can improve PANSS total scores and negative score compared with placebo. However, while Shiina study showed that tropisetron was not superior to placebo by PANSS scores (Shiina et al. 2010), Noroozian study exhibited that tropisetron was significantly superior to placebo by PANSS scores (Noroozian et al. 2013). These discrepant results may be due to small sample sizes of these trials, with 15–63 participants in each treatment arm, and different outcome measures. A meta-analysis can increase the statistical power for group comparisons and can overcome the limitation of sample size in underpowered studies (Cohn and Becker 2003). Moreover, using standardized mean difference (SMD) analyses, outcomes with different metrics can be combined (DerSimonian and Laird 1986). To our knowledge, to date no meta-analysis addressing the efficacy and effectiveness of 5-HT_3R-ANTs add-on therapy in schizophrenia has been published. To bridge this gap and synthesize the available trial evidence, we carried out a systematic review and meta-analysis of RCTs of 5-HT_3R-ANTs add-on therapy for schizophrenia.

Methods

Inclusion Criteria, Search Strategy, Data Extraction, and Outcome Measures

Included in this study were RCTs of 5-HT_3R-ANTs add-on therapy for patients with schizophrenia under treatment with antipsychotics. To identify relevant studies, we searched PubMed, the Cochrane Library databases, Google Scholar, and PsycINFO citations without language restrictions published up to June 15, 2013 using the following key words: "tropisetron," "granisetron," "ondansetron," "palonosetron," "dolasetron," "metoclopramide," "ramosetron," "azasetron" or "indisetron," and "schizophrenia." Additional eligible studies were also sought by a hand search of reference lists from primary articles and relevant reviews. Moreover, we searched the clinical trials database at www.clinicaltrials.gov. The first three authors of this review (T.K., T.M., and Y.M.) scrutinized the inclusion and exclusion criteria of the studies identified. When the data required for the meta-analysis were missing, the first and/or corresponding authors were contacted for additional information (including endpoint scores). The three authors of this study independently extracted, checked, and entered the data into Review Manager.

Data Synthesis and Statistical Analysis

We included the outcome measures of at least two studies for each outcome measure. The primary outcome measure for efficacy was the psychopathology of schizophrenia, meaning the PANSS total scores, as well as positive, negative, and general subscale scores. The overall, negative and general outcome measures included PANSS endpoint scores from one study (Shiina et al. 2010) and change in total PANSS scores from baseline to endpoint from three studies (Akhondzadeh et al. 2009; Khodaie-Ardakani et al. 2013; Zhang et al. 2006). The positive outcome measures included the change in positive PANSS scores from baseline to endpoint from two studies (Khodaie-Ardakani et al. 2013; Zhang et al. 2006) and positive PANSS endpoint scores from two studies (Akhondzadeh et al. 2009; Shiina et al. 2010). The secondary outcome measures also included discontinuation for any cause, discontinuation due to adverse events, discontinuation due to inefficacy, and extrapyramidal symptoms, which were derived from Extrapyramidal Symptom Rating Scale (ESRS) (Chouinard and Margolese 2005). In addition, we pooled the data for side effects.

Meta-analysis was conducted according to the guidelines from the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) group (Moher et al. 2009). We based the analyses on intent-to-treat (ITT) or

modified ITT data (i.e., at least one dose or at least one follow-up assessment). However, the data of completer analysis were not excluded to obtain as much information as possible (Shiina's study: PANSS total, positive, negative, and general scores). The meta-analysis was performed using Review Manager version 5.1 for Windows (Review Manager version 5.0, Cochrane Collaboration, http://ims.cochrane.org/revman). To combine studies, the random-effects model by DerSimonian and Laird (1986), which is conservative, was used for all cases, because the underlying effect possibly differed across studies and populations, which are typically heterogeneous. For continuous data, the SMD was used, combining the effect-size (Hedges' g) data. For dichotomous data, the relative risk (RR) was estimated along with its 95 % confidence interval (CI).

We explored study heterogeneity using the χ^2 test of homogeneity ($p < 0.05$), together with the I^2 statistic, considering values of 50 % or higher to reflect considerable heterogeneity (Higgins et al. 2003). In cases of I^2 values >50 % for the primary outcome measures, we planned to conduct sensitivity analyses to determine the reasons for the heterogeneity. A sensitivity analysis can be performed to look for confounding factors on the effects in the individual studies included in the meta-analysis. We tried to reduce heterogeneity by limiting our meta-analysis to studies with specific characteristics. Since more than ten studies are usually considered a minimum for funnel plots to be useful, the number of studies included in the meta-analysis (six studies) was too small to allow any reasonable interpretation of funnel plots. However, since we found significant heterogeneities in the PANSS total, negative, and general scores with the exception of positive scores between the treatment groups, funnel plots were inspected visually to explore the possibility of publication bias. We also assessed the methodological qualities of the articles included in the meta-analysis based on Cochrane risk-of-bias criteria (Cochrane Collaboration, http://www.cochrane.org/).

Results

Study Characteristics

The search using the key words given above yielded 84 references. Six RCTs of 5-HT_3R-ANTs could be included in the current meta-analysis, and 61 references were excluded based on the title and review of the abstract. Ten references were also excluded based on full text, because two were short duration studies (≤1 week), three were no placebo-controlled trials, three were review articles, and two were case reports (Fig. 1). In total, we identified six RCTs, including 311 patients with schizophrenia, that met our inclusion criteria. All six studies included one granisetron plus risperidone study (Khodaie-Ardakani et al. 2013), one ondansetron plus risperidone study (Akhondzadeh et al. 2009), one ondansetron plus haloperidol (Zhang et al. 2006), and three tropisetron plus risperidone studies (Noroozian et al. 2013; Shiina et al. 2010; Zhang et al. 2012) (Table 1). The mean study duration was 8.25 weeks, with one trial lasting 10 days, three trials lasting 8 weeks, and two trials lasting 12 weeks. Sample sizes ranged from 30 to 121 patients. The mean age of the study population was 37.1 years. The studies were not sponsored by the pharmaceutical industry and were published in English. Three of the six studies were conducted in Iran, two were conducted in China, and the remaining study was conducted in Japan. The characteristics of the trials included in our study are shown in Table 1. All studies were of high methodological quality based on Cochrane risk-of-bias criteria, as all studies were double-blind, placebo-controlled, and mentioned the required details of the study design. We based the analyses on ITT or modified ITT data. However, the data of completer analysis were not excluded to obtain as much information as possible (only Shiina's study: PANSS total, positive, negative, and general scores).

Meta-analysis Results

There were significant effects of 5-HT_3R-ANTs add-on therapy on PANSS total scores (SMD = −1.03, CI = −1.70 to −0.36, $p = 0.003$, $I^2 = 82$ %; 5 studies, $n = 261$) (Fig. 2), negative scores (SMD = −1.10, CI = −1.82 to −0.39, $p = 0.002$, $I^2 = 84$ %; 5 studies, $n = 261$) (Fig. 3), and PANSS general scores (SMD = −0.70, CI = −1.23 to −0.17, $p = 0.01$, $I^2 = 73$ %; 5 studies, $n = 261$). However, 5-HT_3R-ANTs add-on therapy was not superior to placebo in PANSS positive scores (SMD = −0.12,

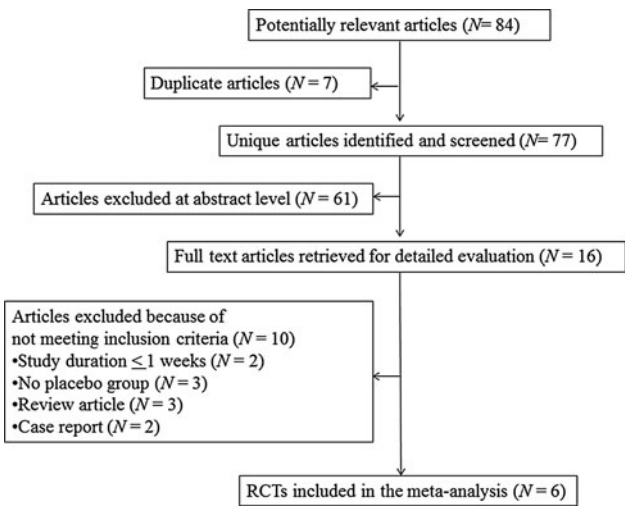

Fig. 1 PRISMA flow diagram

Table 1 Study, patient, and treatment characteristics of included double-blind randomized placebo-controlled trials

Study	Total *n*	Patients	Diagnosis	Duration	Age (mean ± SD)	Male, %	Race (%)	Drug	*n*	Dose (mg/day)	Outcomes
Granisetron											
Khodaie-Ardakani et al. (2013) (Iran) Non-industry	40	SZ. Outpatients (100 %). All patients had demonstrated clinical stability (no more than 20 % on PANSS) change for a minimum of 4 weeks despite an adequate trial of RIS	DSM-IV-TR	8 weeks	GRA: 36.7 ± 11.3, PLA: 37.9 ± 9.3	GRA: 60.0, PLA: 55.5	Iranian (100)	GRA + RIS	20	GRA: 2 (fixed), RIS: 4.35 ± 0.67 (NR)	PANSS total: GRA > PLA. PANSS positive: GRA = PLA, PANSS negative: GRA > PLA, PANSS general: GRA = PLA
								PLA + RIS	20	RIS: 4.30 ± 0.68 (NR)	
Ondansetron											
Akhondzadeh et al. (2009) (Iran) Non-industry	30	SZ. Outpatients (93.3 %). All patients had demonstrated clinical stability (no more than 20 % on PANSS) change for a minimum of 4 weeks despite an adequate trial of RIS	DSM-IV-TR	12 weeks	GRA: 33.0 ± 5.88, PLA: 33.5 ± 5.95	GRA: 66.7, PLA: 60.0	Iranian (100)	OND + RIS	15	OND: 8 (fixed), RIS: 4–6 (NR)	PANSS total: OND > PLA. PANSS positive: OND = PLA, PANSS negative: OND > PLA, PANSS general: OND > PLA
								PLA + RIS	15	RIS: 4–6 (NR)	
Zhang et al. (2006) (China) Non-industry	121	SZ. Inpatients (100 %). All patients had a documented treatment-resistant status (the absence of clinically significant improvement after treatment with at least two neuroleptics for 6 weeks or longer at a full dose equivalent to 800 mg/day of CHL), had persistent negative symptoms or significant cognitive dysfunction (a score of at least 20 on PANSS negative score or at least 15 on PANSS cognition score, and had at least 70 on the total PANSS scores and at least 4 on CGI-S score	DSM-IV	12 weeks	GRA: 39.6 ± 10.1, PLA: 40.0 ± 9.9	GRA: 77.6, PLA: 68.3	Chinese (100)	OND + HAL	58	OND: 8 (fixed) (7.8 ± 0.5), HAL = 11.4 ± 4.4 (flexible)	PANSS total: OND > PLA. PANSS positive: OND = PLA, PANSS negative: OND > PLA, PANSS general: OND > PLA
								PLA + HAL	63	HAL = 11.4 ± 4.6 (flexible)	
Tropisetron											
Shiina et al. (2010) (Japan) Non-industry	40	SZ. Outpatients (100 %). All patients received RIS (2–6 mg/day) for at least 8 weeks	DSM-IV-TR	8 weeks	TRO: 35.0 ± 6.82, PLA: 35.2 ± 8.54	TRO: 45.0, PLA: 50.0	Japanese (100)	TRO + RIS	20	TRO: 10 (fixed), RIS: 4.03 ± 1.59 (fixed)	PANSS total: TRO = PLA. PANSS positive: TRO = PLA, PANSS negative: TRO = PLA, PANSS general: TRO = PLA
								PLA + RIS	20	RIS: 3.8 ± 1.58 (fixed)	
Noroozian et al. (2013) (Iran) Non-industry	40	SZ. Outpatients (100 %). All patients had demonstrated clinical stability (no more than 20 % on PANSS) change for a minimum of 4 weeks despite an adequate trial of RIS	DSM-IV-TR	8 weeks	TRO: 33.8 ± 7.0 PLA: 33.7 ± 5.9	TRO: 80, PLA: 75	Iranian (100)	TRO + RIS	20	TRO: 10 (fixed), RIS: 4 (fixed) (2 patients received RIS 6 mg/day throughout the study period)	PANSS total: TRO > PLA. PANSS positive: TRO = PLA, PANSS negative: TRO > PLA, PANSS general: TRO > PLA
								PLA + RIS	20	RIS: 3.8 ± 1.58 (fixed) (1 patient received RIS 6 mg/day throughout the study period)	
Zhang et al. (2012) (China) Non-industry	40	SZ. Nonsmoking inpatients (100 %). All patients received a stable dosage of RIS (3–6 mg/day) for at least 1 month prior to entry into the study, without any other antipsychotic drugs, and all had deficits in sensory gating, with P50 ratios > 0.5	DSM-IV	10 days	20–55 years	NR	Chinese (100)	TRO + RIS	30	TRO: 5, 10 and 20 (fixed), RIS: 3–6 (fixed)	NR
								PLA + RIS	10	RIS: 3–6 (fixed)	

CHL chlorpromazine, *CGI-S* clinical global impression-severity scale, *DSM* (*TR*) diagnostic and statistical manual of mental disorders (text revision), *GRA* granisetron, *HAL* haloperidol, *n* number of patient, *OND* ondansetron, *PANSS* positive and negative syndrome scale, *PLA* placebo, *RIS* risperidone, *SZ* schizophrenia, *TRO* tropisetron

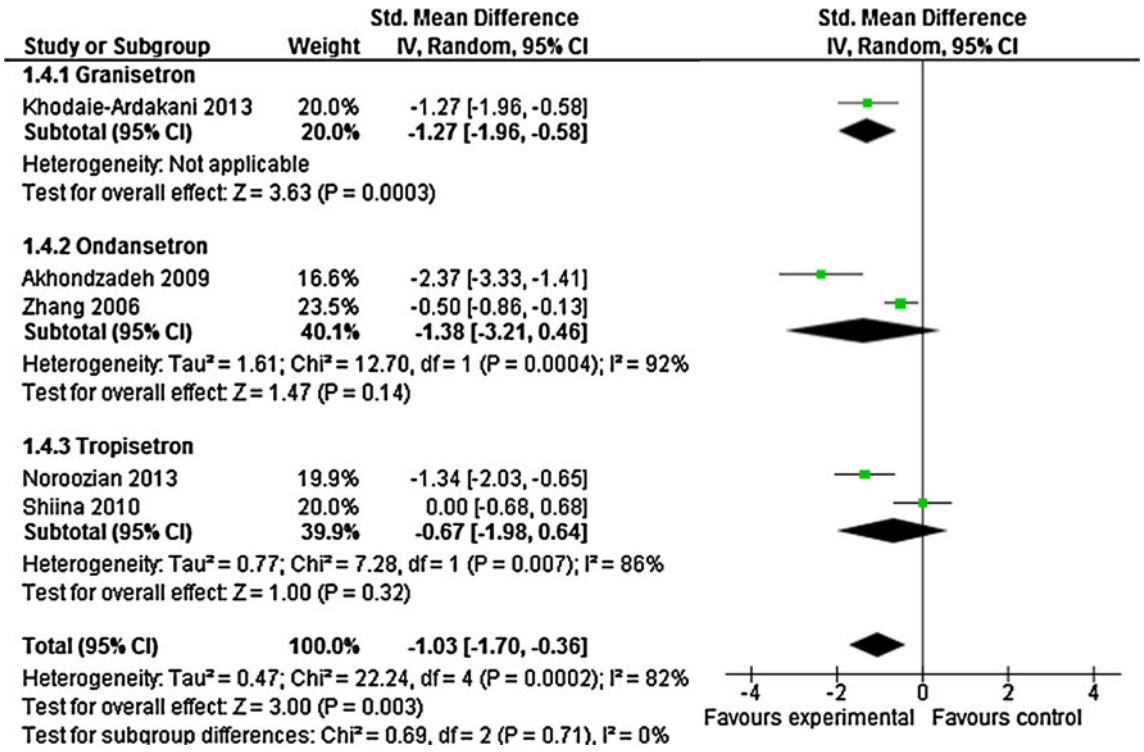

Fig. 2 Forest Plot of Efficacy for the Overall Symptoms

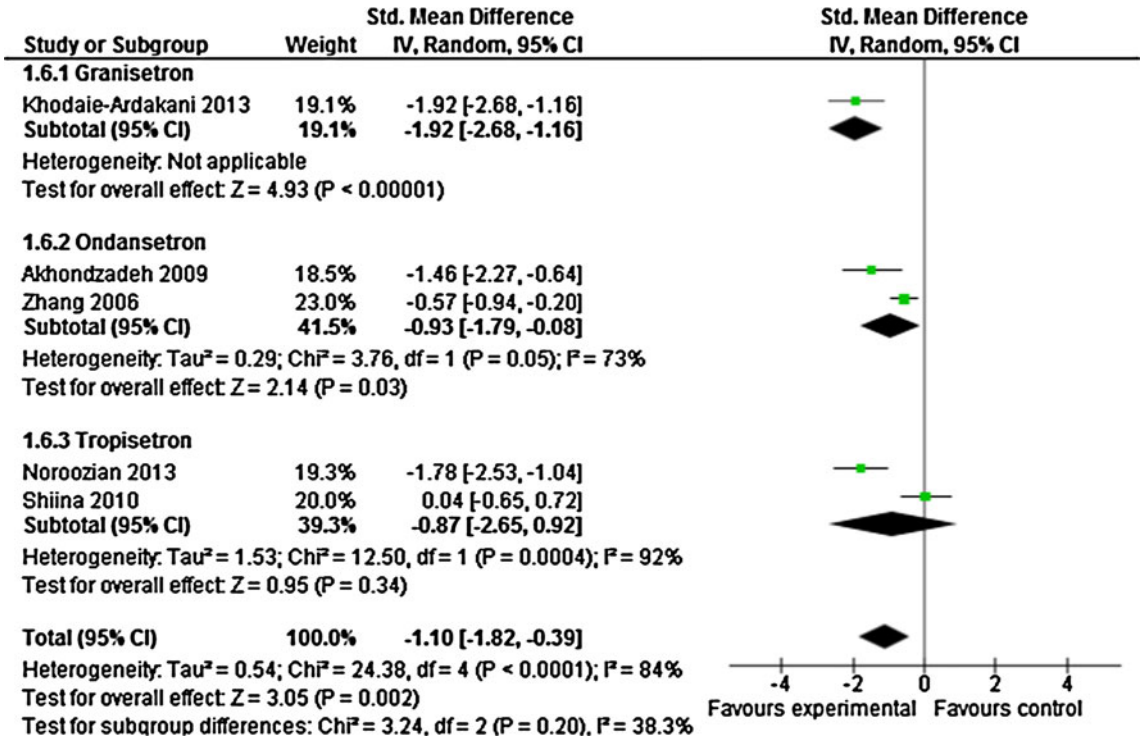

Fig. 3 Forest Plot of Efficacy for the Negative Symptoms

CI = −0.36 to 0.12, $p = 0.33$, $I^2 = 0$ %; 5 studies, $n = 261$). Individually, granisetron was superior to placebo in PANSS total scores (SMD = −1.27, $p = 0.0003$) and negative scores (SMD = −1.92, $p < 0.00001$). Ondansetron was superior to placebo in PANSS negative scores (SMD = −0.93, $p = 0.03$). The data in each treatment

Table 2 Sensitivity analysis of efficacy of selective serotonin 3 receptor antagonists add-on therapy

Outcome	Variable	Subgroup	*N*	*n*	I^2 (%)	SMD	95 % CI	*p* value*
Total scores	Antipsychotic class	Second-generation antipsychotic	4	143	83	−1.21	−2.10 to −0.31	**0.008**
		First-generation antipsychotic	1	118	na	−0.50	−0.86 to −0.13	**0.008**
	Intent-to-treat analysis	Intent-to-treat analysis	4	228	82	−1.29	−2.03 to −0.54	**0.0007**
		Completer analysis	1	33	na	0.00	−0.68 to 0.68	1.00
	Country	Japan + China	2	151	36	−0.33	−0.79 to 0.12	0.15
		Iran	3	110	47	−1.58	−2.18 to −0.97	**<0.00001**
Positive scores	Antipsychotic class	Second-generation antipsychotic	4	143	0	−0.01	−0.34 to 0.31	0.94
		First-generation antipsychotic	1	118	na	−0.25	−0.61 to 0.11	0.18
	Intent-to-treat analysis	Intent-to-treat analysis	4	228	0	−0.14	−0.40 to 0.12	0.29
		Completer analysis	1	33	na	0.03	−0.65 to 0.71	0.93
	Country	Japan + China	2	151	0	−0.19	−0.51 to 0.13	0.25
		Iran	3	110	0	−0.03	−0.40 to 0.35	0.89
Negative scores	Antipsychotic class	Second-generation antipsychotic	4	143	84	−1.27	−2.21 to −0.33	**0.008**
		First-generation antipsychotic	1	118	na	−0.57	−0.94 to −0.20	**0.0003**
	Intent-to-treat analysis	Intent-to-treat analysis	4	228	82	−1.38	−2.14 to −0.63	**0.0003**
		Completer analysis	1	33	na	0.04	−0.65 to 0.72	0.92
	Country	Japan + China	2	151	57	−0.34	−0.91 to 0.24	0.25
		Iran	3	110	0	−1.73	−2.18 to −1.29	**<0.00001**
General scores	Antipsychotic class	Second-generation antipsychotic	4	143	78	−0.81	−1.57 to −0.05	**0.04**
		First-generation antipsychotic	1	118	na	−0.44	−0.81 to −0.08	**0.02**
	Intent-to-treat analysis	Intent-to-treat analysis	4	228	75	−0.86	−1.47 to −0.26	**0.005**
		Completer analysis	1	33	na	−0.04	−0.72 to 0.65	0.92
	Country	Japan + China	2	151	6	−0.35	−0.69 to −0.01	0.05
		Iran	3	110	78	−1.07	−1.96 to −0.18	**0.02**

N number of study, *n* number of patient, *SMD* standardized mean difference, *95 % CI* 95 % confidence interval

* *p* values < 0.05 are bold

group were simulated with no publication bias (data not shown).

We also conducted a sensitivity analysis (Table 2). There were significant heterogeneities in the PANSS total, negative, and general scores with the exception of positive scores between the treatment groups. Although 5-HT_3R-ANTs add-on therapy in patients primarily treated with SGAs was significantly superior to placebo for PANSS total scores, negative scores, and general scores, the significant heterogeneities remained in these sensitivity analyses (Table 2). The effect sizes of SGAs subgroups in these outcomes were larger than that of FGA subgroup (Table 2). When dividing by ethnicity (Iranian or Japanese plus Chinese), studies of 5-HT_3R-ANTs therapy for Iranian patients demonstrated significant benefits on both PANSS total scores, negative scores, and general scores compared with control groups. However, the significant heterogeneities remained in these sensitivity analyses.

While dropout due to all cause (RR = 0.80, CI = 0.41–1.54, $p = 0.50$; 6 studies, $n = 311$), inefficacy (RR = 0.76, CI = 0.24–2.46, $p = 0.65$; 5 studies, $n = 271$), or adverse events (RR = 0.84, CI = 0.30–2.39, $p = 0.75$; 6 studies, $n = 311$) was similar in both groups, constipation occurred significantly more often with 5-HT_3R-ANTs than placebo (RR = 2.05, CI = 1.07–3.91, $I^2 = 0$ %, $p = 0.03$, NNH = 11, $p = 0.02$; 4 studies, $n = 241$) (Fig. 4). Conversely, there were no significant differences in nausea/vomiting (RR = 0.45, $p = 0.35$) and ESRS scores (SMD = −0.90, $p = 0.25$) between both treatment groups. However, ondansetron had less ESRS scores than control (SMD = −1.70, $p < 0.0001$; 1 study, $n = 30$), and nausea/vomiting was significantly less frequent in patients treated with ondansetron compared with placebo (RR = 0.14, $p = 0.008$, NNH = 5, $p = 0.0005$; 1 study, $n = 121$).

Discussion

To our knowledge, this is the first comprehensive meta-analysis on the effectiveness and tolerability of 5-HT_3R-ANTs add-on therapy used as an adjunct to antipsychotic medications in the treatment for schizophrenia. For this meta-analysis, 6 RCTs involving 311 patients were examined. Our study suggested significant clinical benefits of 5-HT_3R-ANTs add-on therapy

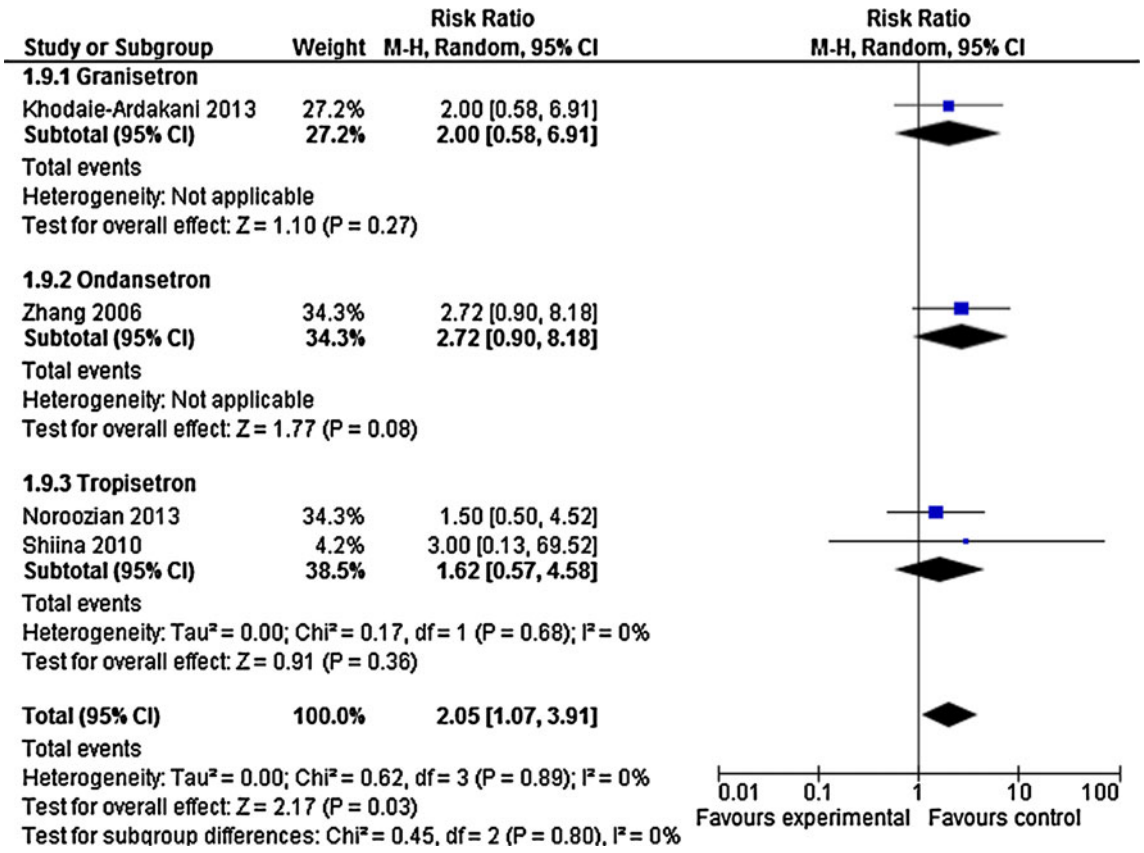

Fig. 4 Forest Plot of Constipation

for the PANSS total scores and negative and general subscale scores of schizophrenia. Effect sizes of improvement of PANSS total scores and PANSS negative subscale scores were large. A previous meta-analysis comparing the use of SGAs and FGAs for negative symptoms showed that none of the FGAs were superior to the SGAs (Leucht et al. 2009), although in two recent meta-analyses, amisulpride, clozapine, olanzapine, blonanserin, and risperidone demonstrated greater efficacy than FGAs for the treatment for negative symptoms (Kishi et al. 2013b; Leucht et al. 2009). Aripiprazole, quetiapine, sertindole, ziprasidone, and zotepine were not efficacious for negative symptoms than FGAs (Leucht et al. 2009). While most antipsychotics have shown benefits for negative symptoms in recent meta-analyses, they have potential risks, including weight gain and subsequent cardio-metabolic events. Recently, it has been recommended that the antipsychotics that have less risk of side effects, such as aripiprazole, should be used for the treatment for schizophrenia (Buchanan et al. 2010). However, aripiprazole does not treat negative symptoms compared with FGAs (Leucht et al. 2009). The results of our meta-analysis suggest that 5-HT_3R-ANTs compensate for aripiprazole efficacy for negative symptoms.

The fact that 5-HT_3R-ANTs appear to have efficacy for the treatment for negative symptoms in schizophrenia is tantalizing. However, the mechanism of action of 5-HT_3R-ANTs for the treatment for negative symptoms is still unclear. Miyamoto et al. suggested that negative symptoms are divided into three subtypes: (1) primary enduring (or deficit); (2) primary non-enduring; and (3) negative symptoms that are secondary to other causes such as depression, positive symptoms, extrapyramidal symptoms, substance abuse, or iatrogenic effects such as under-stimulation during long-term hospitalization (Miyamoto et al. 2012). From the meta-analysis result (ondansetron had less ESRS scores than control), it appears that 5-HT_3R-ANTs improve extrapyramidal symptoms. Thus, 5-HT_3R-ANTs may be effective for the treatment for secondary negative symptoms. Conversely, antiparkinsonian drugs, which are used for the treatment for extrapyramidal symptoms, have the risk of worsening negative symptoms and cognitive function, and causing constipation (Meltzer 2013). Although 5-HT_3R-ANTs also have a risk of causing constipation, as do antiparkinsonian drugs, 5-HT_3R-ANTs do enhance cognitive function (for example, improved visual memory and rapid visual information processing) (Akhondzadeh et al. 2009; Shiina et al. 2010). However, 5-HT_3R-ANTs have not been approved by the Food and Drug Administration (FDA) for the treatment for schizophrenia. It also remains unclear which antipsychotic should be used in association with 5-HT_3R-ANT. Therefore, if a future study using larger samples establishes that 5-HT_3R-ANTs can be

beneficial for the treatment for extrapyramidal symptoms, 5-HT_3R-ANTs may be used as an adjunct to antipsychotic medications for the treatment for schizophrenia.

Tropisetron is both a potent 5-HT_3R-ANTs and a high-affinity partial agonist of the nACh receptor, including α7 nicotinic receptor (Zhang et al. 2012). Recently, a α7 nACh receptor partial agonist was shown to be beneficial for improvement of cognitive dysfunction (especially executive function) and negative symptoms in schizophrenia (Lieberman et al. 2013). Zhang et al. reported that tropisetron significantly improved overall cognitive deficits (especially memory disturbance) (Zhang et al. 2012). Additionally, the P50 deficits, which are considered to reflect a sensory gating deficit that has been demonstrated as an endophenotype of schizophrenia, were also improved (Zhang et al. 2012). Taken together, tropisetron may be a highly effective drug for the treatment for schizophrenia. Because there are only three studies included in the meta-analysis, it is necessary to confirm these findings by performing a double-blind, randomized, placebo-controlled, large-sample trial of tropisetron add-on therapy for the treatment for schizophrenia.

The main limitation of this study is the small number of studies included. In addition, there were only two base antipsychotics (risperidone and haloperidol). Since each antipsychotic has a different pharmacological receptor profile (Kishi et al. 2013b), further study will be required to examine the effect of combining antipsychotics with 5-HT_3R-ANTs. Another limitation is potential poor adherence with medications, which led patients to receive limited benefits from pharmacological interventions. Finally, all trials included in this meta-analysis were of a short duration (10 days–12 weeks). Future research should investigate the long-term effectiveness of 5-HT_3R-ANTs add-on therapy and provide more safety data using larger samples.

Conclusions

The results of this meta-analysis demonstrated that 5-HT_3R-ANTs add-on therapy is effective for the treatment for schizophrenia, especially regarding negative symptoms. 5-HT_3R-ANTs add-on therapy appears to be well tolerated. It is necessary to confirm these findings by performing a double-blind, randomized, placebo-controlled, large-sample trial of 5-HT_3R-ANTs add-on therapy for the treatment for schizophrenia.

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