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Efficacy and tolerability of minocycline augmentation therapy in schizophrenia: a systematic review and meta-analysis of randomized controlled trials

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Objective This study aimed to perform a comprehensive meta-analysis of minocycline augmentation therapy in patients with schizophrenia receiving antipsychotic agents.
Methods Data published up to 2 June 2014 were obtained from the PubMed, PsycINFO, Google Scholar, and Cochrane Library databases. We conducted a systematic review and meta-analysis of patient data from randomized controlled trials (RCTs) comparing minocycline with placebo. Relative risk (RR), standardized mean difference (SMD), and 95% confidence intervals were calculated.
Results We included four RCTs. The total sample included 330 patients. Minocycline was superior to placebo for decreasing Positive and Negative Syndrome Scale (PANSS) total scores (SMD = −0.70), PANSS negative subscale scores (SMD = −0.86), and PANSS general subscale scores (SMD = −0.50) but was not different from placebo for PANSS positive subscale scores (SMD = −0.26) and depressive symptoms (SMD = −0.28). Minocycline was equivalent to placebo for all-cause discontinuation (RR = 1.10), discontinuation due to inefficacy (RR = 0.42), discontinuation due to adverse events (RR = 1.56), and discontinuation due to death (RR = 3.18). Minocycline was superior to placebo for extrapyramidal side-effect scores (SMD = −0.32).
Conclusions Minocycline may improve the psychopathology of schizophrenia, especially the negative symptoms, and seems to be well tolerated.

KEY WORDS—schizophrenia; minocycline; efficacy; safety; systematic review; meta-analysis

INTRODUCTION

Recent meta-analyses have revealed that some second-generation antipsychotics (e.g., amisulpride, blonanserin, clozapine, olanzapine, risperidone, and zotepine) were superior to first-generation antipsychotics for treating the negative symptoms of schizophrenia. However, their effect size has typically been small, with a standardized mean difference (SMD) of −0.13 to −0.32 (Leucht *et al*., 2009; Kishi *et al*., 2013). Thus, there seems to be a definite ceiling in the treatment of negative symptoms with antipsychotics alone. However, negative symptoms such as abulia and autism are directly related to the quality of life.

Recently, we reported that the *N*-methyl-D-aspartate (NMDA) receptor antagonist memantine has potential efficacy against negative symptoms (SMD = −1.08) and cognitive dysfunction (SMD = −0.87) in people with schizophrenia in comparison with placebo (Kishi and Iwata, 2013; Matsuda *et al*., 2013). Several investigations suggest that abnormalities in glutaminergic neural transmission are pathophysiological in schizophrenia (Kishi and Iwata, 2013). Minocycline also has a similar NMDA receptor antagonistic effect to memantine (Hashimoto, 2010; Hashimoto *et al*., 2013). Zhang and colleagues (2007) reported that minocycline improved behavioral changes (hyperlocomotion and prepulse inhibition deficits) in mice after the administration of the NMDA receptor antagonist and minocycline significantly attenuated the release of dopamine in the frontal cortex after the administration of dizocilpine. Therefore, the authors suggested that minocycline would be a potential therapeutic drug for schizophrenia. Moreover, minocycline has anti-inflammatory and neuroprotective properties, with recent studies suggesting its effectiveness for neurodegenerative disorders such as Parkinson's disease and Huntington's disease (Hashimoto, 2010; Hashimoto *et al*., 2013). The neuroprotective property of minocycline stems from its suppressive effect on 5-lipoxygenase, which is an inflammatory enzyme associated with brain aging (Hashimoto, 2010; Hashimoto *et al*., 2013).

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Therefore, minocycline augmentation may be suitable for the treatment of negative symptoms in schizophrenia (Hashimoto, 2010; Sommer *et al*., 2012; Hashimoto *et al*., 2013; Miyamoto *et al*., 2013; Fond *et al*., 2014).

To our knowledge, four randomized controlled trials (RCTs) of minocycline have been conducted for the treatment of schizophrenia. Of these, all four studies (Levkovitz *et al*., 2010; Chaudhry *et al*., 2012; Khodaie-Ardakani *et al*., 2014; Liu *et al*., 2014) showed that minocycline was superior to placebo when treating negative symptoms. However, the study of Levkovitz *et al*. (2010) showed that minocycline was superior to placebo in the improvement of Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1982) scores but not of Positive and Negative Syndrome Scale (PANSS) (Kay *et al*., 1987) negative subscale scores. To date, only one meta-analysis has considered the role of minocycline for the treatment of schizophrenia (Sommer *et al*., 2012). Although this meta-analysis included three RCTs (Levkovitz *et al*., 2010; Chaudhry *et al*., 2012; Weiser *et al*., 2012), one was an unpublished study (Weiser *et al*., 2012); moreover, it only considered one outcome: PANSS total scores. However, their meta-analysis did indicate that minocycline was not superior to placebo when managing overall symptoms (SMD = 0.22, $p = 0.48$).

A meta-analysis can increase the statistical power for group comparisons and can overcome the limitation of sample size when larger trials are lacking. Using random effects models and SMD analysis, outcomes with different metrics can be combined (Green, 2005; Cochrane Collaboration, http://www.cochrane.org/). Moreover, the safety outcomes of minocycline are important. Considering this, we performed an updated meta-analysis of minocycline for the treatment of schizophrenia. This meta-analysis used only four published RCTs (Levkovitz *et al*., 2010; Chaudhry *et al*., 2012; Khodaie-Ardakani *et al*., 2014; Liu *et al*., 2014). It comprehensively evaluates the efficacy and safety of minocycline in the management of schizophrenia (including the discontinuation rate and individual side effects).

METHODS

Inclusion criteria and search strategy, data extraction, and outcomes

This meta-analysis was performed according to the preferred reporting items for systematic reviews and meta-analyses guidelines (Moher *et al*., 2009). We performed a systematic literature review according to the Patient, Intervention, Comparison, and Outcome strategy: patients, schizophrenia; intervention, minocycline; comparator, placebo; and outcome, efficacy and safety. We included only double-blind RCTs comparing minocycline with placebo for patients with schizophrenia. Relevant studies were identified through searches in PubMed, the Cochrane Library databases, Google Scholar, and PsycINFO citations. There were no language restrictions, and we accepted data published up to 2 June 2014 using the keywords "minocycline" and "schizophrenia." Additional eligible studies were also sought by scrutiny of the reference lists from primary articles and relevant reviews. Two authors (K. O. and T. K.) checked the inclusion and exclusion criteria for each of the identified studies and resolved discrepancies in coding by discussion. The same authors independently extracted, checked, and entered data into the Review Manager (RevMan) version 5.2 for Windows (Review Manager version 5.2, Cochrane Collaboration, http://www.cc-ims.net/RevMan). When data required for the meta-analysis were missing, the first/corresponding authors were contacted for additional information (including endpoint scores). We also assessed the methodological quality of the trials using the Cochrane risk-of-bias criteria (Cochrane Collaboration, http://www.cochrane.org/).

Data synthesis

The primary efficacy measures were the PANSS total score (endpoint PANSS total scores from all studies) and the PANSS subscale scores (positive, negative, and general subscale scores from all studies). Secondary outcomes were as follows: SANS (Andreasen, 1982), Clinical Global Impression—Severity (Guy

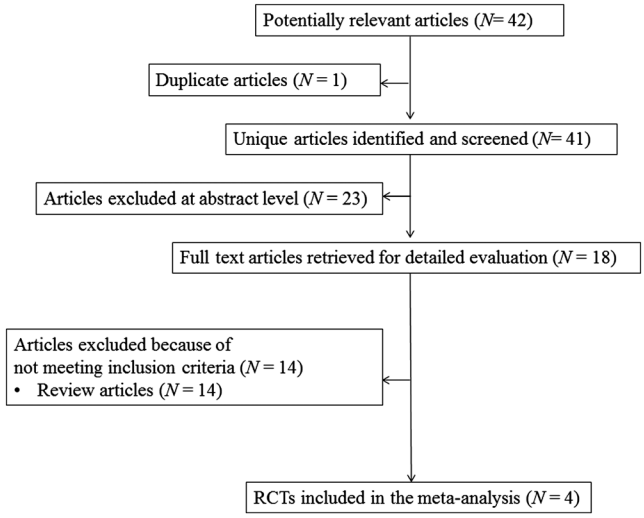

Figure 1. Preferred reporting items for systematic reviews and meta-analyses flow diagram

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Table 1. Study, patient, and treatment characteristics of the included double-blind, randomized placebo-controlled trials of patients with schizophrenia

Study	Total *n*	Patients	Diagnosis	Duration	Age (mean ± SD)	Male, %	Race (%)	Drug (%)	*n*	Dose (dose mg/day)	Outcomes
Chaudhry *et al.*, 2012 (Brazil and Pakistan); non-industry	Brazil: 30, Pakistan: 114	(i) Age: 18–65 years; (ii) DSM-IV diagnosis of SZ, schizoaffective disorder, psychosis not otherwise specified or schizophreniform disorder; (iii) within first 5 years of diagnosis; (iv) stable on medication 4 weeks prior to baseline; (v) able to take oral medication	DSM-IV	12 months	MINO: 25.87 ± 7.07, PBO: 26.59 ± 8.26	MINO: 57.75, PBO: 64.64	NR	MINO + AP PBO + AP	Brazil: 15, Pakistan: 56 Brazil: 15, Pakistan: 58	MINO: 50–200 [flexible], AP: NR AP: NR	PANSS total: MINO = PBO. PANSS positive: MINO = PBO, PANSS negative: MINO > PBO, PANSS general: MINO = PBO
Khodaie-Ardakani *et al.*, 2014 (Iran); non-industry	40	(i) Outpatients; (ii) age: 18–50 years; (iii) DSM-IV-TR diagnosis (SCID) of SZ; (iv) a minimum disease duration of 2 years; (v) a stable dose of RIS for a minimum of 8 weeks; (vi) clinically stable for at least 4 weeks before the study; (vii) clinical stability was defined as ≦20% total score change on PANSS	DSM-IV-TR	8 weeks	MINO: 41.05 ± 7.47, PBO: 38.95 ± 7.78	MINO: 70, PBO: 75	Iran (100)	MINO + RIS PBO + RIS	20 20	MINO: 100 for 1 week, 200 for 7 weeks [fixed], RIS: 4.40 ± 0.52 [fixed] RIS: 4.30 ± 0.62 [fixed]	PANSS total: MINO > PBO, PANSS positive: MINO = PBO, PANSS negative: MINO > PBO, PANSS general: MINO > PBO
Levkovitz *et al.*, 2010 (Israel); non-industry	54	(i) Age: 18–35 years; (ii) DSM-IV diagnosis (SCID) of SZ; (iii) early phase of the disorder; (iv) did not receive antipsychotic treatment for 6 months preceding current symptom exacerbation; (v) PANSS total scores at baseline >60; (vi) initiated on treatment with AAP medication (OLA: 21 patients, QUE: 3 patients, RIS: 20 patients, CLO: 9 patients) ≦14 days prior to study entry	DSM-IV	24 weeks	MINO: 25.14 ± 4.77, PBO: 24.67 ± 4.24	MINO: 69.44, PBO: 83.33	NR	MINO + AAP (OLA: 45.7, QUE: 5.7, RIS: 25.7, CLO: 22.9) PBO + AAP (OLA: 27.8, QUE: 5.6, RIS: 61.1, CLO: 5.6)	36 18	MINO: 200 [fixed], APP: 200–600 mg/day CP equivalent dose [fixed] APP: 200–600 mg/day CP equivalent dose [fixed]	PANSS total: MINO = PBO, PANSS positive: MINO = PBO, PANSS negative: MINO = PBO, PANSS general: MINO = PBO, SANS: MINO > PBO

(Continues)

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Table 1. (Continued)

Study	Total *n*	Patients	Diagnosis	Duration	Age (mean ± SD)	Male, %	Race (%)	Drug (%)	*n*	Dose (dose mg/day)	Outcomes
Liu *et al.*, 2014 (China) Non-industry	92	(i) Age: 18 and 40 years; (ii) course of disease ≤5 years; (iii) previous treatment with RIS, without dose change within 4 weeks prior to screening; (iv) a stable living arrangement	DSM-IV	16 weeks	MINO: 27.05 ± 5.68, PBO: 27.70 ± 7.27	MINO: 64.1, PBO: 60.00	Chinese (100)	MINO + RIS	46	MINO: 200 [fixed], RIS: 3.77 ± 0.85 [fixed]	PANSS total: MINO > PBO,
								PBO + RIS	46	RIS: 3.85 ± 0.94 [fixed]	PANSS positive: MINO = PBO, PANSS negative: MINO > PBO, PANSS general: MINO = PBO, SANS: MINO > PBO

AP, antipsychotics; APP, atypical antipsychotics; CLO, clozapine; CP, chlorpromazine; DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders Fourth Edition, Text Revision; MINO, minocycline; NR, not reported; OLA, olanzapine; PANSS, Positive and Negative Syndrome Scale; PBO, placebo; QUE, quetiapine; RIS, risperidone; SANS, Scale for the Assessment of Negative Symptoms; SCID, Structured Clinical Interview for DSM; SZ, schizophrenia.

and Bonato, 1970), depressive symptoms (the Calgary Depression Scale for Schizophrenia (Addington *et al.*, 1990) or the Hamilton Depression Rating Scale (Hamilton, 1960)), Global Assessment of Functioning Scale, extrapyramidal symptom (the Extrapyramidal Symptom Rating Scale (Chouinard and Margolese, 2005) or the Abnormal Involuntary Movement Scale (Simpson *et al.*, 1979)), and discontinuation (all-cause, inefficacy, and adverse events). In addition, we pooled the data for individual side effects.

Statistical analysis

We based our analyses on intention-to-treat (ITT) or modified ITT data (i.e., at least one dose or at least one follow-up assessment); no observed case data were included. The meta-analysis was performed using RevMan version 5.2 (Review Manager version 5.2, Cochrane Collaboration, http://ims.cochrane.org/revman). To combine studies, we used the random effects model described by DerSimonian and Laird (1986). We used this conservative model to address the possibility that the underlying effects that differ across the studies and populations would be heterogeneous. For continuous data, we used SMD, combining effect size (Hedges' g) data, and 95% confidence intervals (CI). For dichotomous data, the relative risk (RR) was estimated along with the 95% CI. Study heterogeneity was measured using the chi-squared and I^2 statistics, with values of $p < 0.05$ and $\geq 50\%$, respectively, indicating heterogeneity (Higgins *et al.*, 2003). In cases when I^2 values were $\geq 50\%$, sensitivity analyses were performed to determine the reasons for the heterogeneity. Finally, funnel plots were visually inspected to explore the possibility of publication bias.

RESULTS

Study characteristics

The searches in the PubMed, Cochrane Library, and PsycINFO databases yielded 42 hits; we then excluded one duplicate study, 23 studies based on title or abstract review, and 14 review papers. Therefore, four eligible studies were included (Figure 1). Across the four RCTs (mean duration 25 weeks (range 8–52)), 330 adult patients with schizophrenia were randomized to either minocycline ($n = 173$) or placebo ($n = 157$). The study of Chaudhry *et al.* (2012) was one RCT, but a multicenter trial (one conducted in Brazil and another in Pakistan). Sample sizes showed ranges of 30–114 participants. All studies were published in English. No studies were sponsored by the pharmaceutical industry. All studies were of high methodological

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quality on the basis of the Cochrane risk-of-bias criteria: They were double-blind RCTs, with the required study design detail. The characteristics of the studies are summarized in Table 1.

Results of the meta-analysis

Efficacy. Minocycline was superior to placebo in the reduction of PANSS total scores (SMD = −0.70, 95% CI = −1.31 to −0.08, $p = 0.03$, $I^2 = 81$; five comparisons, $n = 267$) (Figure 2(a)), PANSS negative subscale scores (SMD = −0.86, 95% CI = −1.32 to −0.41, $p = 0.0002$, $I^2 = 66$; five comparisons, $n = 267$) (Figure 2(c)), PANSS general subscale scores (SMD = −0.50, 95% CI = −0.99 to −0.01, $p = 0.05$, $I^2 = 72$; five comparisons, $n = 267$) (Figure 2(d)), SANS (SMD = −0.74, 95% CI = −1.23 to −0.25, $p = 0.003$, $I^2 = 44$; two comparisons, $n = 133$), and Clinical Global Impression—Severity (SMD = −0.47, 95% CI = −0.82 to −0.13, $p = 0.007$, $I^2 = 34$; four comparisons, $n = 227$). Minocycline was not different from placebo for PANSS positive (SMD = −0.26, 95% CI = −0.55 to 0.02, $p = 0.07$, $I^2 = 22$; five comparisons, $n = 267$) (Figure 2(b)) and depressive symptoms (SMD = −0.28, 95% CI = −0.70 to 0.14, $p = 0.20$, $I^2 = 0$; two comparisons, $n = 94$).

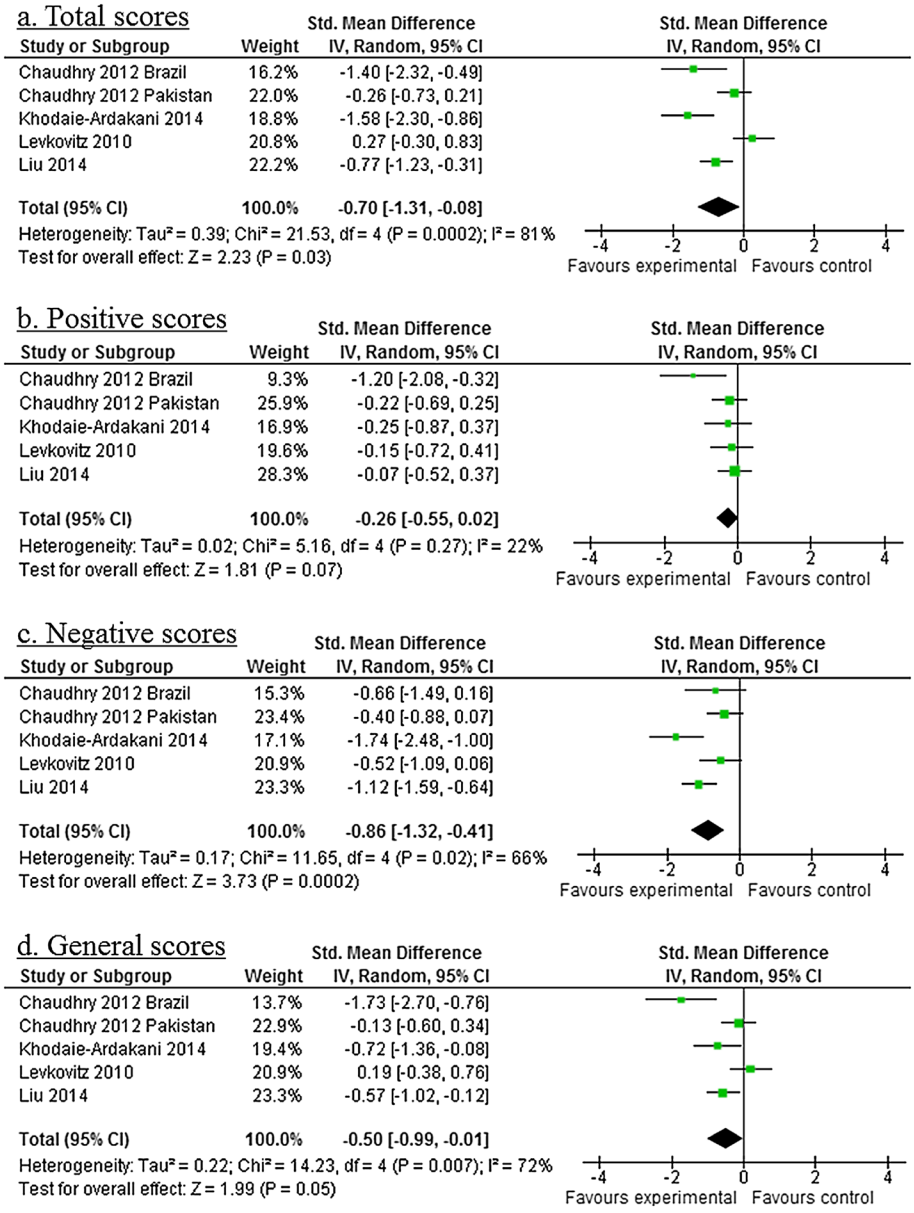

Figure 2. Forest plot of Positive and Negative Syndrome Scale scores: (a) total scores, (b) positive scores, (c) negative scores, and (d) general scores

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Sensitivity analysis. Significant heterogeneity existed between the studies in PANSS total ($I^2 = 81\%$, $p = 0.0002$), PANSS negative ($I^2 = 66\%$, $p = 0.02$), and general ($I^2 = 72\%$, $p = 0.007$) subscale scores. Visual inspection of the funnel plot for primary outcomes did not suggest publication bias (data not shown). Therefore, we performed two sensitivity analyses of primary outcomes (antipsychotic class and study duration) (Table 2). We did not find any cause for the heterogeneity despite performing two sensitivity analyses of PANSS total scores. With regard to PANSS negative subscale scores, the heterogeneity disappeared following two sensitivity analyses. For PANSS general subscale scores, when only including studies with risperidone and of short duration (<6 months), the heterogeneity disappeared, and the significant effect of minocycline for PANSS general subscale scores was maintained.

Safety. Minocycline and placebo did not differ regarding all-cause discontinuation (RR = 1.10, 95% CI = 0.82–1.46, $p = 0.53$, $I^2 = 0\%$; five comparisons, $n = 330$) (Figure 3(a)), discontinuation due to inefficacy (RR = 0.42, 95% CI = 0.05–3.32, $p = 0.41$, $I^2 = 0\%$; five comparisons, $n = 330$) (Figure 3(b)), discontinuation due to adverse events (RR = 1.56, 95% CI = 0.54–4.49, $p = 0.41$, $I^2 = 0\%$; five comparisons, $n = 330$) (Figure 3(c)), and discontinuation due to death (RR = 3.18, 95% CI = 0.32–31.28, $p = 0.32$, I^2 = not applicable; five comparisons, $n = 330$) (Figure 3(d)).

Although we performed meta-analyses for side effects (e.g., pigmentation, suicide attempt, anorexia/loss of appetite, dizziness, nausea, extrapyramidal symptoms, constipation, urinary retention, and dry mouth), there was no significant difference in any side effects between minocycline and placebo. Minocycline was superior to placebo in Extrapyramidal Symptom Rating Scale/Abnormal Involuntary Movement Scale scores (SMD = −0.32, 95% CI = −0.64 to −0.01, $p = 0.04$, $I^2 = 0$; four comparisons, $n = 189$) (Figure 4).

DISCUSSION

To our knowledge, this is the first comprehensive meta-analysis of minocycline augmentation therapy for schizophrenia. Although minocycline was no more efficacious than placebo in positive and depressive symptoms, it was superior to placebo in the reduction of overall and negative symptoms. However, there was significant heterogeneity of the meta-analyses for primary outcomes, with the exception of positive symptoms. Although we found no confounding factors for the meta-analysis of overall symptoms, the significant heterogeneities of the meta-analyses for negative symptoms disappeared in two sensitivity analyses. Moreover, studies with risperidone as the primary antipsychotic had larger effect sizes than other studies (SMD: risperidone studies −1.36; other studies −0.49). However, longer-duration studies (≥6 months) had smaller effect sizes than shorter-duration studies (SMD: longer-duration studies −0.49; shorter-duration studies −1.36). We did identify an RCT of minocycline augmentation therapy for schizophrenia that lasted 16 weeks and included large samples (minocycline, $n = 100$; placebo, $n = 100$), but this study was only reported as a meeting abstract and was unpublished (Weiser *et al.*, 2012). This study reported that minocycline was not superior to placebo for overall

Table 2. Sensitivity analysis for the efficacy of minocycline augmentation therapy

Outcome	Variable	Subgroup	*N*	*n*	I^2	SMD	95% CI	*p*-value*
Total scores	Antipsychotic class	Risperidone	2	119	71	−1.13	−1.91 to −0.34	**0.005**
		Other than risperidone	3	148	78	−0.38	−1.16 to 0.39	0.33
	Study duration	≥6 months	3	148	78	−0.38	−1.16 to 0.39	0.33
		<6 months	2	119	71	−1.13	−1.91 to −0.34	**0.005**
Positive subscores	Antipsychotic class	Risperidone	2	119	0	−0.13	−0.49 to 0.23	0.47
		Other than risperidone	3	148	53	−0.42	−0.94 to 0.1	0.12
	Study duration	≥6 months	3	148	53	−0.42	−0.94 to 0.1	0.12
		<6 months	2	119	0	−0.13	−0.49 to 0.23	0.47
Negative subscores	Antipsychotic class	Risperidone	2	119	49	−1.36	−1.96 to −0.77	**<0.00001**
		Other than risperidone	3	148	0	−0.49	−0.82 to −0.15	**0.004**
	Study duration	≥6 months	3	148	0	−0.49	−0.82 to −0.15	**0.004**
		<6 months	2	119	49	−1.36	−1.96 to −0.77	**<0.00001**
General subscores	Antipsychotic class	Risperidone	2	119	0	−0.62	−0.99 to −0.25	**0.001**
		Other than risperidone	3	148	83	−0.46	−1.34 to 0.42	0.31
	Study duration	≥6 months	3	148	83	−0.46	−1.34 to 0.42	0.31
		<6 months	2	119	0	−0.62	−0.99 to −0.25	**0.001**

N, number of study; *n*, number of patient; SMD, standardized mean difference; CI, confidence interval.
*p-values < 0.05 are in bold.

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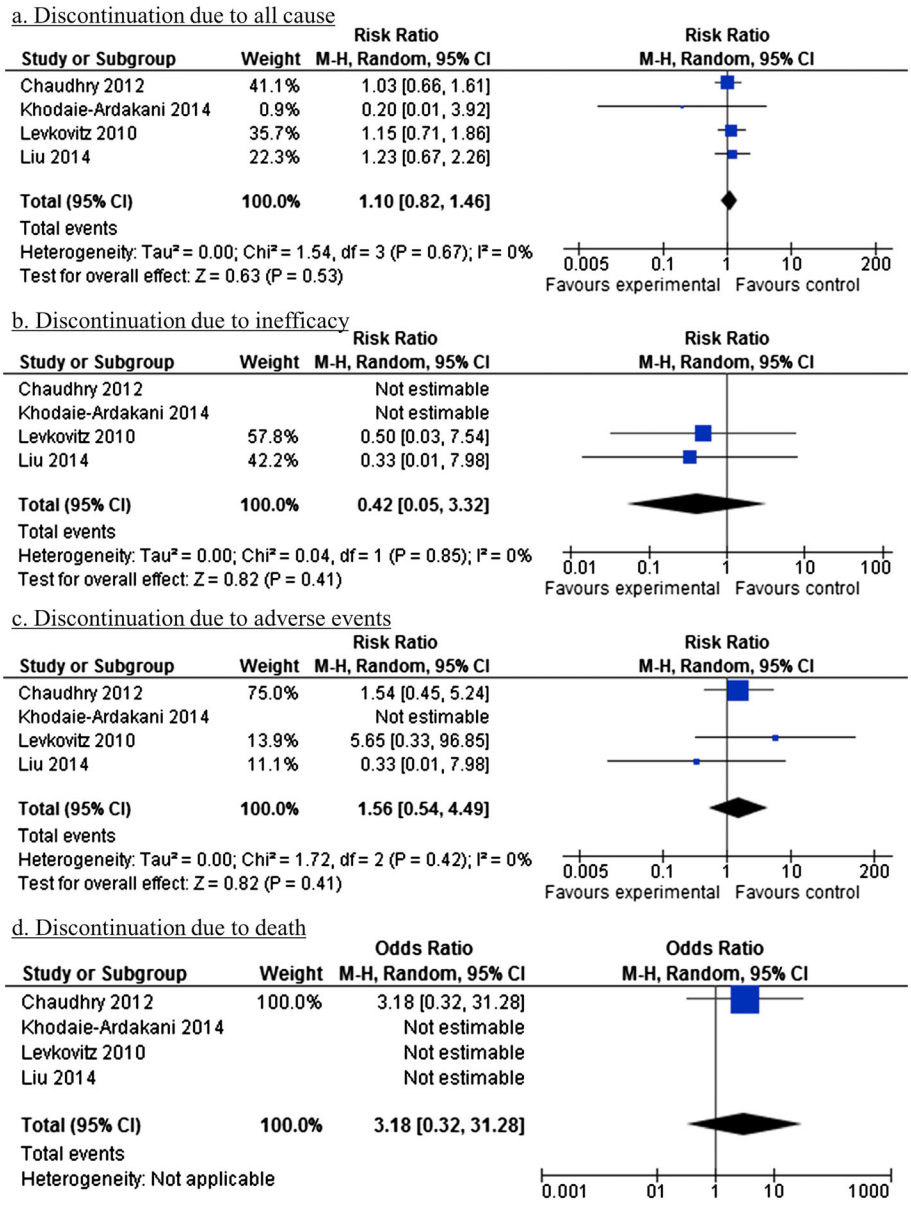

Figure 3. Forest plot of discontinuation rates: (a) all-cause discontinuation rate, (b) discontinuation rate due to inefficacy, (c) discontinuation rate due to adverse events, and (d) discontinuation rate due to death

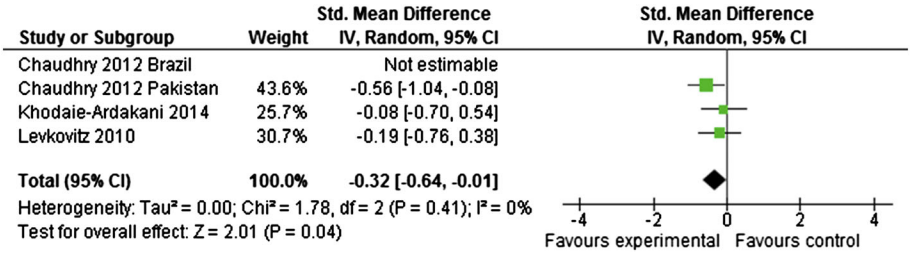

Figure 4. Forest plot of extrapyramidal symptoms

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and positive symptoms but that minocycline showed trends for significance for negative symptoms in comparison with placebo (effect size = −0.93, $p = 0.095$). Given that, although the effect of minocycline for negative symptoms may reduce with longer durations, we considered that minocycline has the potential to improve the negative symptoms of schizophrenia.

Although we did not perform a meta-analysis of minocycline augmentation therapy regarding cognitive functions in patients with schizophrenia, several studies reported that minocycline might have potential therapeutic effect on their cognitive dysfunctions. Fujita and colleagues (2008) reported that phencyclidine-induced cognitive deficits in mice were significantly improved by administration of minocycline. Liu and colleagues (2014) reported that there was the significant difference between the minocycline and placebo groups in attention domains scores of MATRICS Consensus Cognitive Battery (Green *et al*., 2004). Levkovitz and colleagues (2010) reported that minocycline augmentation therapy might improve working memory, cognitive shifting, and cognitive planning.

The main limitation of this study is the paucity of studies. In particular, future research should investigate the long-term efficacy and generate more safety data using larger samples. The second limitation is the shortness of the follow-up period, which was 6 months in one study and 8–24 weeks in the others. The third limitation is that we have not investigated the optimal therapeutic dose of minocycline for augmentation therapy.

In conclusion, our results suggest that minocycline was a well-tolerated treatment and that minocycline augmentation therapy may improve the psychopathology (especially the negative symptoms) of schizophrenia. Future research should investigate the long-term efficacy and should generate more safety data for patients with schizophrenia receiving minocycline augmentation of antipsychotics.

CONFLICTS OF INTEREST

We have the following interests. Dr. Kishi has received speaker's honoraria from AbbVie, Astellas, Daiichi Sankyo, Dainippon Sumitomo, Eisai, Eli Lilly, GlaxoSmithKline, Janssen, Yoshitomi, Otsuka, Meiji, Shionogi, Tanabe-Mitsubishi, Tsumura, Novartis, and Pfizer. Dr. Iwata has received speaker's honoraria from Astellas, Dainippon Sumitomo, Eli Lilly, GlaxoSmithKline, Janssen, Yoshitomi, Otsuka, Meiji, Shionogi, Novartis, and Pfizer.

AUTHOR CONTRIBUTIONS

Drs. Oya and Kishi had full access to all of the data in the study and bear responsibility for the integrity of the data and the accuracy of the data analysis. Kishi is responsible for the study concept and design. Oya and Kishi carried out the analysis and interpretation of data and statistical analysis. Data were acquired by Oya and Kishi. Drafting of the manuscript was carried out by Oya, Kishi, and Iwata. The study was supervised by Iwata. Drs. Kishi and Oya contributed equally to this work.

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