

# Systematic review and meta-analysis of the efficacy and safety of minocycline in schizophrenia

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**Objective.** Our aim was to perform an updated systematic review and meta-analysis on the efficacy and safety of adjunctive minocycline as a treatment of schizophrenia.

**Methods.** We conducted a PubMed/Scopus database search from inception to 3 February 2016 for randomized, placebo-controlled trials (RCTs), open non-randomized studies, and case reports/series evaluating minocycline in patients with schizophrenia. Random-effects meta-analysis of positive, negative, depressive, and cognitive symptom rating scales, discontinuation and adverse effects rates calculating standardized mean difference (*SMD*), and risk ratios  $\pm$  95% confidence intervals (*CI*<sub>95%</sub>) were calculated.

**Results.** Six RCTs were eligible (minocycline  $n = 215$ , placebo  $n = 198$ ) that demonstrated minocycline's superiority versus placebo for reducing endpoint Positive and Negative Syndrome Scale (PANSS) total scores (*SMD* = -0.59; *CI*<sub>95%</sub> = [1.15, -0.03];  $p = 0.04$ ), negative (*SMD* = -0.76; *CI*<sub>95%</sub> = [-1.21, -0.31];  $p = 0.001$ ); general subscale scores (*SMD* = -0.44; *CI*<sub>95%</sub> = [-0.88, -0.00];  $p = 0.05$ ), Clinical Global Impressions scores (*SMD* = -0.50; *CI*<sub>95%</sub> = [-0.78, -0.22];  $p < 0.001$ ); and executive functioning (*SMD* = 0.22; *CI*<sub>95%</sub> = [0.01, 0.44];  $p = 0.04$ ). Endpoint PANSS positive symptom scores ( $p = 0.13$ ), depression rating scale scores ( $p = 0.43$ ), attention ( $p = 0.47$ ), memory ( $p = 0.52$ ), and motor speed processing ( $p = 0.50$ ) did not significantly differ from placebo, before execution of a trim-and-fill procedure. Minocycline did not differ compared to placebo on all-cause discontinuation ( $p = 0.56$ ), discontinuation due to inefficacy ( $p = 0.99$ ), and intolerability ( $p = 0.51$ ), and due to death ( $p = 0.32$ ). Data from one open-label study ( $N = 22$ ) and three case series ( $N = 6$ ) were consistent with the metaanalytic results.

**Conclusions.** Minocycline appears to be an effective adjunctive treatment option in schizophrenia, improving multiple relevant disease dimensions. Moreover, minocycline has an acceptable safety and tolerability profile. However, more methodologically sound and larger RCTs remain necessary to confirm and extend these results.

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## Introduction

Minocycline, a second-generation tetracycline antibiotic, has pleiotropic mechanisms of action in the central nervous system that include the modulation of glutamate-*N*-methyl-D-aspartate receptors,<sup>1–6</sup> a decrease in oxidative and nitrosative stress (O&NS),<sup>2,7</sup> as well as putative anti-inflammatory effects (e.g., a decrease in the production of tumor necrosis factor- $\alpha$  and interferon- $\gamma$  by activated microglia).<sup>8,9</sup> Minocycline has demonstrated neuroprotective properties in such neurodegenerative disorders as Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis (ALS),<sup>3,4,10</sup> in addition to ischemia.<sup>11</sup>

Beyond dopaminergic signaling dysfunction, inflammatory,<sup>12,13</sup> glutamatergic,<sup>14,15</sup> and oxidative stress pathways<sup>16,17</sup> may be involved in the pathophysiology of schizophrenia, particularly in relation to negative and cognitive symptoms.<sup>18–20</sup> In addition, these pathways may interact to drive neuroprogression in this illness.<sup>12</sup> Negative<sup>21–24</sup> and cognitive<sup>25,26</sup> symptoms of schizophrenia are the main determinants of the prognosis and course of schizophrenia.<sup>22</sup>

The mechanism of action of minocycline in schizophrenia has been reviewed elsewhere.<sup>27</sup> This second-generation tetracycline antibiotic has anti-inflammatory properties, inhibits microglial activation, decreases O&NS, inhibits apoptosis, and modulates glutamate-mediated excitotoxicity. Minocycline may have beneficial effects in patients with schizophrenia in whom antipsychotic agents are insufficiently effective on neuroinflammation involving microglia,<sup>28</sup> apoptotic mechanisms,<sup>29</sup> oxidative stress,<sup>30</sup> and glutamate dysfunction,<sup>31</sup> which appear to interact with dopamine- and serotonin-related signaling, thus promoting neuroprogression of this severe mental illness.<sup>12</sup> While second-generation antipsychotics (SGAs) mainly act on positive symptoms modulating dopamine and serotonin pathways with mostly questionable or minor effects on glutamate signaling,<sup>32–34</sup> the minocycline pharmacodynamic profile may be used in a multimodal treatment approach in schizophrenia. In this context, add-on minocycline may mechanistically address the areas that are mainly not improved by available antipsychotics (namely, improve negative and cognitive symptoms) and which remain a clear unmet need in the therapeutic management of schizophrenia.<sup>35,36</sup>

Thus, minocycline has been investigated as a novel therapeutic target for schizophrenia. Two previous meta-analyses have investigated the effects of minocycline on the symptom domains of schizophrenia.<sup>37,38</sup> Overall, these studies have concluded that minocycline is superior to placebo in improving total, negative, and general symptom scores on the Positive and Negative Syndrome Scale (PANSS),<sup>39</sup> the Scale for the Assessment of Negative Symptoms (SANS),<sup>40</sup> and the Clinical Global Impressions–Severity scale (CGI-S),<sup>41</sup> whereas

no significant differences relative to placebo were found for positive and depressive symptoms and global cognitive symptoms, but minocycline did appear to be safe and tolerable.<sup>38</sup> Those conclusions deserve reassessment, as both meta-analyses were preliminary and based on four and two studies, with 330 and 100 patients,<sup>37,38</sup> and as additional studies have become available.<sup>42,43</sup> Therefore, a larger sample size will increase the power and confidence in the findings, potentially enabling meaningful subgroup or meta-regression analyses to identify potential sources of heterogeneity.

We aimed at providing a wide overview of the extant literature on minocycline's role in the treatment of schizophrenia, consisting of a descriptive plus a systematic review not limited to randomized controlled trials (RCTs). We further aimed to reassess minocycline's efficacy and safety in a formal meta-analysis, with a larger sample size, focusing on psychopathology and cognition as well as tolerability and safety.

## Methods

This systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Statement,<sup>44</sup> following a predetermined, but unpublished, protocol.

### Search strategy

An electronic literature search was conducted in PubMed and Scopus from database inception until 3 February 2016 by two independent reviewers (M.S, N.V.), using the search terms (minocycline) AND (“schizophrenia” OR “psychosis” OR “psychotic disorder” OR “schizoaffective”) to identify RCTs, open-label trials, and case series or reports that investigated the efficacy and safety of minocycline in patients diagnosed with schizophrenia or schizoaffective disorder.

### Inclusion and exclusion criteria

Studies eligible for the meta-analysis were RCTs that (1) compared minocycline with placebo; (2) included patients diagnosed with schizophrenia or schizoaffective disorder according to structured clinical assessments; and (3) reported efficacy data using a standardized rating scale, such as the Scale for Assessment of Negative Symptoms (SANS),<sup>40</sup> the Positive and Negative Syndrome Scale (PANSS),<sup>39</sup> the Brief Psychiatric Rating Scale (BPRS),<sup>45</sup> the Clinical Global Impressions Scale (CGI),<sup>41</sup> the Calgary Depression Scale for Schizophrenia (CDSS),<sup>46</sup> the Hamilton Depression Rating Scale (HDRS),<sup>47</sup> the Beck Depression Inventory (BDI),<sup>48</sup> the MATRICS Consensus Cognitive Battery (MCCB),<sup>49,50</sup> the Cambridge Neuropsychological Test Automated Battery,<sup>51</sup> discontinuation rates, frequencies of side

effects, results on extrapyramidal symptom scales (such as the Extrapyramidal Symptom Rating Scale<sup>2</sup> and the Abnormal Involuntary Movement Scale<sup>41</sup>), as well as weight change and metabolic abnormalities. For the systematic review, we also included case reports, case series, and open-label studies, reporting the effects of the use of minocycline in patients affected by schizophrenia or schizoaffective disorder. Studies were excluded if they reported on minocycline for patients with a different disease or were on a different drug.

### Outcomes

The primary outcome was the PANSS total endpoint score. Secondary outcomes included PANSS positive, negative, and general endpoint subscores; SANS and CGI scores; depressive rating scales endpoint scores; cognitive endpoint scores; and all-cause and specific cause discontinuation rates. Safety outcomes included extrapyramidal symptom scales and individual side-effect frequencies. When studies reported cognitive outcomes, we grouped the individual tests into broad domains to enable pooled analyses across different tests (for details, see Supplementary Table 1).

### Data extraction

Three reviewers (M.S., N.V., S.F.) independently extracted data from the included studies into a standardized Microsoft Excel spreadsheet. Any disagreement was resolved by consensus. The following information was extracted: author, year, country, study design, sponsor/funding, inclusion and exclusion criteria, trial duration, setting, sample size, population demographics, minocycline and other medication doses, outcome measures, baseline, follow-up, and change in all rating scales, discontinuation rates, side effects, and quality indicators. Whenever data were not reported or we needed clarification, we contacted authors up to three times requesting additional information.

### Quality assessment

Evaluation of methodological study quality was conducted by two independent reviewers (M.S., N.V.) using the Cochrane Collaboration's tool for assessing risk of bias.<sup>53</sup> This tool includes six domains that can indicate low, unclear, or high risk of bias. Considering the six domains, a study is defined as having low risk of bias when all domains indicate low risk of bias, unclear risk of bias when one or more domains indicate unclear risk of bias, and high risk of bias when high risk of bias is present for one or more key domains.

### Data analysis

The meta-analysis was performed using Review Manager<sup>54</sup> (v. 5.1 for Windows) (<http://tech.cochrane.org/revman>).

All outcomes were meta-analyzed when at least two studies provided data for a given outcome. When combining studies, the random effects model<sup>55,56</sup> was used to account for study heterogeneity. For continuous data, we calculated the standardized mean difference (SMD) with its 95% confidence interval as the effect size; for dichotomous data, we used risk ratio (RR) with its 95% confidence interval. The SMD as effect size allowed us to group together different scales measuring the same dimensions (e.g., depression). Study heterogeneity was measured using  $\chi^2$  and  $I^2$  statistics, with  $p < 0.05$  for  $\chi^2$  and  $\geq 50\%$  for  $I^2$  indicating significant heterogeneity.<sup>57</sup> We compared endpoint rating scale values, all-cause and specific-cause discontinuation, and side-effect rates. When heterogeneity was high, as defined by  $I^2 \geq 50\%$ , when at least four studies were available, meta-regression analyses were performed with Comprehensive Meta-Analysis (v. 3),<sup>58</sup> investigating the following potential moderator variables: age, sex, study duration, and illness duration.

Finally, funnel plots were visually inspected, and Egger's test<sup>59</sup> and Begg-Mazumdar Kendall's tau<sup>60</sup> were utilized to determine if a publication bias was likely, and if it was part of the trim-and-fill procedure,<sup>61</sup> it was run in order to evaluate if the results changed after imputing potentially missing studies.

## Results

### Search results

The study selection flow is depicted in Figure 1. Out of 322 initial hits, 307 were excluded through title/abstract reading. A total of 15 full texts were reviewed, and 1 study was excluded since it reported neuroimaging data on a previously reported sample,<sup>62</sup> 2 because they were meta-analyses,<sup>37,38</sup> and 2 were trial protocols.<sup>63,64</sup> Among the remaining 10 studies, 6 RCTs were included in the quantitative meta-analysis.<sup>42,43,65-68</sup> Out of the four studies included in the systematic review, one was an open-label study<sup>69</sup> and three were case series.<sup>70-72</sup>

### Included studies, treatments, and participants (Table 1)

We meta-analyzed 6 placebo controlled RCTs,<sup>42,43,65-68</sup> including 215 patients taking minocycline and 198 patients taking placebo. In the minocycline group, the patients were on average  $29.91 \pm 10.2$  years old, their age of illness onset was  $20.24 \pm 5.28$  years, illness duration was  $17.79 \pm 12.98$  years, duration of education was  $10.39 \pm 3.6$  years, and 67.92 % were male. In the placebo group, patients were  $29.88 \pm 9.9$  years of age, their age of illness onset was  $20.3 \pm 5.04$  years, illness duration was  $20.18 \pm 14.69$  years, duration of education was  $10.21 \pm 3.79$  years, and 73.4% were male. The mean

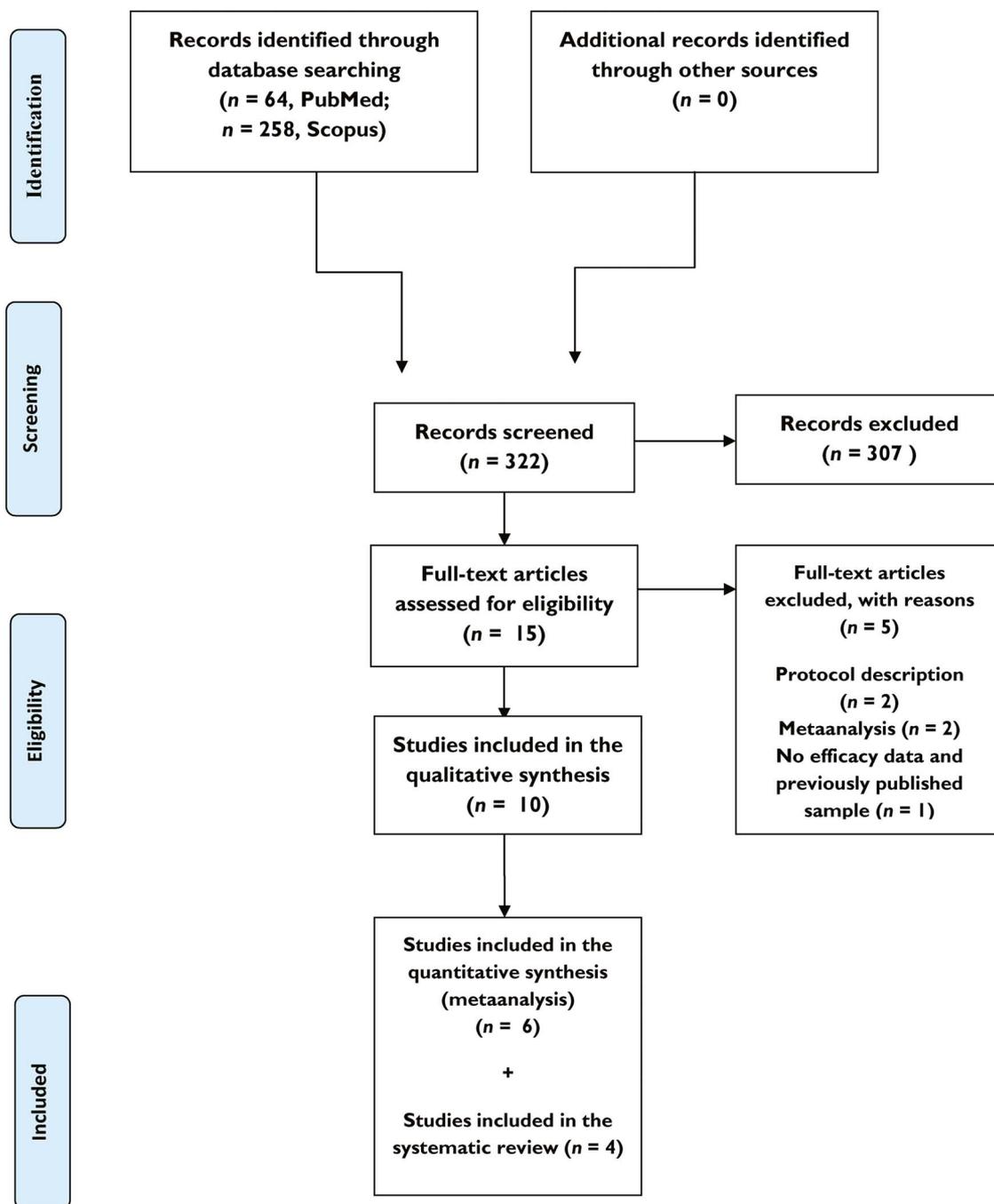


FIGURE 1. PRISMA flowchart.

study duration was 19.7 (range = 8–24) weeks, and all 6 studies used minocycline (target dose = 200 mg/day) as an augmentation strategy. Baseline antipsychotics included risperidone in three studies,<sup>42,66,67</sup> clozapine in one study,<sup>43</sup> and mixed antipsychotics in two studies.<sup>65,68</sup> Two studies were conducted in Iran,<sup>42,66</sup> and one each in the United States,<sup>43</sup> China,<sup>67</sup> Brazil and Pakistan,<sup>65</sup> and Israel.<sup>68</sup> Two studies allowed inclusion of patients with schizoaffective disorder.<sup>43,65</sup> All studies except one<sup>43</sup> used the PANSS, four studies used the CGI,<sup>43,65,67,68</sup> four

studies used the SANS,<sup>42,43,67,68</sup> four used rating scales for depression,<sup>42,43,66,68</sup> and three studies assessed cognitive functioning.<sup>43,67,68</sup>

The open-label study conducted in Japan<sup>69</sup> lasted 4 weeks and included 22 patients with schizophrenia, with a mean age of  $31.2 \pm 5.5$  years, mean age of illness onset of  $22.8 \pm 9.73$  years, and illness duration of  $3.4 \pm 2.3$  years, with 63.6% being male.

Three case series—one from the United Kingdom,<sup>72</sup> one from India,<sup>71</sup> and one from the United States<sup>70</sup>—with

**TABLE 1. Study, patient, illness and treatment characteristics on the meta-analyzed studies**

Study	Design	In/ outpatients	Inclusion criteria	Duration (weeks)	Minocycline dose	Other drug dose	<i>n</i> mcy	<i>n</i> control	Funding
<b>Randomized controlled trials</b>									
Kelly <i>et al.</i> (2015), <sup>53</sup> NCT01433055, USA	R, DB, PC, augmentation to clozapine	In + outpatients	DSM-IV schizophrenia or schizoaffective, 18–65 yo, taking clozapine > 6 months, >200 mg/day, >350 ng/ml.	10	50 mg twice daily 1st week, 100 mg twice daily weeks 2 to 10	clozapine > 6months, > 200 mg/day, >350 ng/ml; mcy 423,1 (189,5) mg/day; PLC 433,7 (140,1) mg/day.	27	23	National Institute of Mental Health R21MH091184-01A1
Ghanizadeh <i>et al.</i> (2014), <sup>42</sup> IRCT201108223930-N12, Iran	R, DB, PC, augmentation to risperidone	Inpatients	DSM-IV schizophrenia, 18–65 yo, no therapeutic dose of AP the week before.	8	200 mg/day	Risperidone, started 2 mg/day, increased by 2 mg/day, until target dose reached. Mcy 6,9 (1,3) mg/day; PLC 6,7 (1,4) mg/day	15	18	Shiraz University of Medical Sciences
Liu <i>et al.</i> (2014), <sup>67</sup> China	R, DB, PC, augmentation to risperidone	–	DSM-IV schizophrenia, 18–40 yo, risperidone.	16	200 mg/day	Risperidone mcy 3,77 (0.85) mg/day; PLC 3,85 (0.94) mg/day.	46	46	National R&D Special Fund for Health Profession, National Natural Science Foundation of China, National Science and Technology Major Projects for Major New Drugs Innovation and Development
Khodaie-Ardakani <i>et al.</i> (2014), <sup>66</sup> IRCT2012022415566-N34, Iran	R, DB, PC augmentation to risperidone	Outpatients	DSM-IV-TR schizophrenia, 18–50 yo, risperidone.	8	100 mg/day first week, then 200 mg/day	Risperidone 4–6 mg/day	20	20	Tehran University of Medical Sciences
Chaudhry <i>et al.</i> (2012), <sup>65</sup> Brazil and Pakistan	R, DB, PC, augmentation to standard treatment	In + outpatients.	DSM-IV schizophrenia, schizoaffective disorder, psychosis NOS or schizophreniform disorder, 18–65 yo.	52	Starting with 50 mg/day, increased by 50 mg, up to 200 mg/day in single dose.	–	71	73	Stanley Medical Research Institute Research Grant 04T-583.
Levkovitz <i>et al.</i> (2010), <sup>68</sup> Israel	R, DB, PC, augmentation to recently started SGA	–	DSM-IV schizophrenia, 18–65 yo, SGA (olanzapine, risperidone, quetiapine, clozapine at 200–600 chlorpromazine equivalent doses.	24	200 mg/day.	Olanzapine mcy 45, 71%, PLC 27, 77%; risperidone mcy 25,71%, PLC 61,11%; quetiapine mcy 5, 71%, PLC5, 55%; clozapine mcy 22, 85%, PLC 5, 55% at 200–600 chlorpromazine equivalent doses.	36	18	Stanley Medical Research Institute Research Grant 02T-244.
<b>Total</b>	<b>3 augmenting risperidone, 1 augmenting clozapine, 2 augmenting standard treatment.</b>	<b>2 in- + outpatients, 1 inpatient, 1 outpatient, 2 not declared.</b>	<b>2 schizophrenia or schizoaffective, 4 schizophrenia</b>	<b>19,67</b>	<b>200 mg/day</b>	<b>3 risperidone, 1 clozapine, 2 other antipsychotics</b>	<b>215</b>	<b>198</b>	<b>No drug sponsorship</b>
<b>Open-label studies</b>									
Miyaoka <i>et al.</i> (2008), <sup>69</sup> Japan	OL	In + outpatients	DSM-IV schizophrenia, treatment resistant, 1 stable antipsychotic.	4	100 mg/day first week, 150 mg/day weeks 2 to 4.	1039,3 (896,1) chlorpromazine equivalents / die.	22		
<b>Case reports</b>									

**TABLE 1. Continued**

Study	Design	In/ outpatients	Inclusion criteria	Duration (weeks)	Minocycline dose	Other drug dose	<i>n</i> mcy	<i>n</i> control	Funding
Qurashi <i>et al.</i> (2014), <sup>72</sup> UK	2 case reports	Case 1	Age 20s, male, paranoid schizophrenia, failed to respond to risperidone, olanzapine, and actual treatment clozapine 400 mg/day (>0.4 mg/L): started on minocycline 100 mg twice daily; after 3 months, improvement in BPRS positive and negative scores, and subjective improvement in mental health. After minocycline discontinuation, symptoms reemerged.			Case 2			Age 40s, male, paranoid schizophrenic, failed to respond to several typical and atypical antipsychotics, now on clozapine > 0,8 mg/L, started minocycline 100 mg twice daily. After 6 weeks, improvement in BPRS scores, mostly in positive symptoms
Jhamnani <i>et al.</i> (2013), <sup>71</sup> India	2 case reports	Case 1	25-yo male, undifferentiated schizophrenia, failed to respond to clozapine 300 mg/day, amisulpride 100 mg/day over 6 months, with high CRP; after 3 months minocycline 200 mg/day was added, and SANS and CRP improved			Case 2			23-yo male, paranoid schizophrenia, with positive symptoms responding to risperidone 4 mg/day, then switched to aripiprazole, with high CRP; after 2 months, minocycline 200 mg/day was added, and SANS and CRP improved
Kelly <i>et al.</i> (2011), <sup>70</sup> USA	2 case reports	Case 1	36-yo Korean-American male, sine age 17 history of illness, DSM–IV catatonic schizophrenia; failed to respond to 6 years of clozapine, augmented for 4 to 6 weeks with topiramate 100 mg, risperidone 4 mg, olanzapine 15 mg, lithium >0.74 mEq/L, lamotrigine 200 mg; aripiprazole 15 mg yielded some benefit; six months after, he was started with minocycline 100 mg/day, with BPRS, SANS, and self-reported improvements at week 10; continued for 4 years			Case 2			26-yo Caucasian male, DSM–IV catatonic schizophrenia since age 18; failed to respond to 3 years of 350 mg/day clozapine, and started on minocycline titrated to 100 mg/day after 4 weeks;.16 weeks after, BPRS, SANS, and CDRS improved; complained of mild nausea, abdominal pain and constipation, but wanted to continue

BPRS = Brief Psychiatric Rating Scale; CDRS = Calgary Depression Rating Scale; CRP = C-reactive protein; DB = double blind; mcy = minocycline; NOS = not otherwise specified; OL = open-label; PC = placebo-controlled; PLC = placebo; R = randomized; SANS = Scale for Assessment of Negative Symptoms; SGA = second-generation antipsychotic.

two cases in each report described changes on several rating scales in patients with schizophrenia.

### Quality assessment (Supplementary Table2) or randomized placebo controlled studies

According to Cochrane Collaboration's tool for assessing risk of bias,<sup>53</sup> two studies had an unclear risk of bias,<sup>42,68</sup> while each of the others had a low risk of bias.

### Meta-analysis: efficacy

All primary and secondary outcome results are provided in Table 2. The minocycline group had lower endpoint scores compared to placebo in PANSS total score ( $SMD = -0.59$ ;  $CI_{95\%} = [-1.15, -0.03]$ ;  $p = 0.04$ ); PANSS negative score ( $SMD = -0.76$ ;  $CI_{95\%} = [-1.21, -0.31]$ ;  $p = 0.001$ ); SANS score ( $SMD = 0.60$ ;  $CI_{95\%} = [-0.94, -0.27]$ ;  $p < 0.001$ ); PANSS general score ( $SMD = -0.44$ ;  $CI_{95\%} = [-0.88, -0.00]$ ;  $p = 0.05$ ); CGI-S ( $SMD = -0.50$ ;  $CI_{95\%} = [-0.78, -0.22]$ ;  $p < 0.001$ ) and higher (better) executive functioning scores ( $SMD = 0.22$ ;  $CI_{95\%} = [0.01, 0.44]$ ;  $p = 0.04$ ). Results were significantly heterogeneous for the three PANSS-based findings, but not for the remainder of the outcomes that favored minocycline (Table 2).

Endpoint PANSS positive symptom scores ( $p = 0.13$ ), depression rating scale scores ( $p = 0.43$ ), attention ( $p = 0.47$ ), memory ( $p = 0.52$ ), and motor speed processing ( $p = 0.50$ ) did not significantly differ from placebo before the trim-and-fill procedure. These nonsignificant findings were not significantly heterogeneous, with the exception of the results for motor speed and memory (Table 2). All-cause discontinuation ( $p = 0.56$ ), discontinuation due to inefficacy ( $p = 0.99$ ), discontinuation due to intolerability ( $p = 0.51$ ), and discontinuation due to death ( $p = 0.32$ ) did not differ between the minocycline and placebo groups.

### Meta-analysis: publication bias and trim-and-fill (Table 2)

Publication bias test and trim-and-fill procedures did not show any bias in our results. However, the failsafe number was one, suggesting a weak consistency of this result.

### Meta-analysis: meta-regression Analyses (Table 3)

No significant moderators of primary and secondary outcomes with at least four studies contributing data emerged, including baseline values of each rating scale, country of the study (Asia vs. others), trial duration, baseline antipsychotic (risperidone vs. others), and difference of mean age between the minocycline and placebo groups.

TABLE 2. Meta-analysis and publication bias of efficacy and cognitive outcomes

Analysis	No. of studies	No. of participants		Meta-analysis			Heterogeneity		Other analyses	
		Myn	PLC	SMD	$CI_{95\%}$	$p$ value	$I^2$ (%)	Egger bias and $p$ value	Classic failsafe $n$	
PANSS total	5 <sup>42,65-68</sup>	156	144	-0.59	-1.15	0.04	81	-3.32; 0.48	25	
PANSS neg		156	144	-0.76	-1.21	0.001	69	-0.93; 0.83	52	
PANSS pos		156	144	-0.22	-0.50	0.13	29	-2.79; 0.25	1	
PANSS general		156	144	-0.44	-0.88	0.05	69	-3.61; 0.31	14	
Attention	3 <sup>43,67,68</sup>	102	81	0.09	-0.16	0.47	28	Not possible		
Executive functions		102	81	0.22	0.01	0.04	42	Not possible		
Memory	2 <sup>67,68</sup>	102	81	0.15	-0.31	0.62	79	Not possible		
Motor speed processing	4 <sup>43,65,67,68</sup>	75	58	-0.16	-0.62	0.31	64	Not possible		
CGI	4 <sup>42,43,67,68</sup>	148	129	-0.50	-0.78	<0.0001	23	-3.85; 0.12	18	
SANS	4 <sup>42,43,67,68</sup>	117	99	-0.60	-0.94	<0.001	29	7.5; 0.01	14	
Depression	4 <sup>42,43,66,68</sup>	98	79	-0.12	-0.42	0.43	0	-3.8; 0.06	0	

CGI = Clinical Global Impression Scale; PANSS = Positive and Negative Syndrome Scale; SANS = Scale for Assessment of Negative Symptoms; SMD = standardized mean difference; Depressive scores include data from the Calgary Depression Scale, the Hamilton Depression Rating Scale, and the Beck Depression Inventory. Significant results in bold.

TABLE 3. Meta-regression analysis of the heterogeneous findings

Moderator	Number of comparisons	$\beta$	$CI_{95\%}$	$p$ value	$R^2$
<b>PANSS total</b>					
Country (Asia vs. others [ref.])	6	0.14	-1.17 1.43	0.84	0.00
Duration (weeks)	6	-0.002	-0.004 0.03	0.92	0.00
Other drug (mixed vs. risperidone [ref.])	6	0.36	-0.80 1.52	0.54	0.00
Differences in mean age	4	-0.32	-1.29 0.65	0.52	0.00
<b>PANSS negative</b>					
Country (Asia vs. others [ref.])	6	0.21	-0.85 1.27	0.70	0.00
Duration (weeks)	6	0.001	-0.02 0.03	0.46	0.00
Other drug (mixed vs. risperidone [ref.])	6	0.45	-0.43 1.33	0.32	0.00
Differences in mean age	4	-0.22	-1.03 0.60	0.60	0.00
<b>PANSS general</b>					
Country (Asia vs. others [ref.])	6	-0.25	-1.38 0.82	0.66	0.00
Duration (weeks)	6	-0.01	-0.04 0.02	0.52	0.00
Other drug (mixed vs. risperidone [ref.])	6	0.04	-0.91 1.00	0.93	0.00
Differences in mean age	4	-0.06	-0.60 0.48	0.82	0.00
<b>Baseline values as moderators for each respective endpoint</b>					
PANSS TOT baseline difference	6	-0.07	-0.28 0.14	0.53	0.00
PANSS POS baseline difference	6	0.53	-0.39 1.45	0.26	0.00
PANSS NEG baseline difference	6	0.07	-0.16 0.30	0.54	0.00
PANSS GEN baseline difference	6	-0.14	-0.74 0.47	0.65	0.00
CGI baseline difference	5	-0.83	-2.66 0.99	0.37	0.00

CGI = Clinical Global Impression Scale; PANSS = Positive and Negative Syndrome Scale.

### Meta-analysis: safety and tolerability

No significant difference emerged between minocycline and placebo as concerns suicide (studies  $n = 2$ ,  $p = 0.79$ ),<sup>65,68</sup> pigmentation (studies  $n = 2$ ,  $p = 0.53$ ),<sup>65,68</sup> loss of appetite (studies  $n = 3$ ,  $p = 0.99$ ),<sup>43,65,67</sup> dizziness (studies  $n = 3$ ,  $p = 0.55$ ),<sup>43,65,67</sup> vomiting (studies  $n = 2$ ,  $p = 0.43$ ),<sup>43,65</sup> nausea (studies  $n = 3$ ,  $p = 0.70$ ),<sup>43,65,67</sup> extrapyramidal symptoms both as reported by investigators (studies  $n = 3$ ,  $p = 0.95$ )<sup>43,65,67</sup> and measured with the Extrapyramidal Symptoms Rating Scale<sup>52</sup> (studies  $n = 2$ ,  $p = 0.72$ ),<sup>66,68</sup> constipation (studies  $n = 3$ ,  $p = 0.68$ ),<sup>43,67,68</sup> and dry mouth (studies  $n = 2$ ,  $p = 0.56$ )<sup>43,67</sup>. However, headache was significantly more frequent in the placebo group (studies  $n = 2$ ,  $p = 0.01$ ).<sup>43,65</sup>

### Systematic review: efficacy and safety

One open-label study<sup>69</sup> that included 22 patients affected by schizophrenia resistant to other standard treatments reported that minocycline reduced PANSS positive scores to 40.4% at 8 weeks, PANSS negative scores to 44%, and PANSS general scores to 52.1%. The three case series described improvements in BPRS scores<sup>45</sup> in two patients with paranoid schizophrenia,<sup>72</sup> improvements in SANS scores and C-reactive protein values in one patient with undifferentiated schizophrenia and one with paranoid schizophrenia, both with high C-reactive protein,<sup>71</sup> and improvements in BPRS and SANS scores plus CDSS in one case out of two patients affected by catatonic schizophrenia, who wanted to continue taking

minocycline despite mild nausea, constipation, and abdominal pain.<sup>70</sup> In three of these cases, patients had a history of failing to respond to clozapine.

### Discussion

The results of this, to date largest, systematic review and meta-analysis of the randomized controlled evidence of the efficacy and safety of minocycline for the treatment of schizophrenia suggests a significant beneficial effect of minocycline on several psychopathological and cognitive domains in schizophrenia. Effect sizes were small for the one positive effect on cognition and in the medium range for the significant psychopathology improvements, with a near-large effect size for the PANSS-based negative symptom improvement. The lack of any effect on depression or extrapyramidal symptoms (EPS) ratings strengthens the results regarding improved negative symptoms, which has long been an elusive goal in schizophrenia, as depression and EPS can impose as secondary negative symptoms.<sup>73</sup> We provide a novel insight into the cognitive effects of minocycline, which are in contrast with a former meta-analysis<sup>38</sup> that suggested an effect of minocycline on attention/vigilance in schizophrenia. Notwithstanding the fact that our analyses did not confirm a role of minocycline in improving attention in schizophrenia, we report an improvement in executive functioning. Furthermore, results from a former meta-analysis<sup>37</sup> that indicated beneficial effects of minocycline compared to placebo on the psychopathological domains

of schizophrenia—including efficacy on PANSS total, the negative and general subscales, in SANS score, and CGI-S scores—are now confirmed after adding two more trials (+50%)<sup>42,43</sup> with 83 patients (+25%). However, we suggest that at this stage more well-designed RCTs are necessary to further investigate the effects of minocycline on the positive symptoms of schizophrenia.

Since minocycline has a different pharmacodynamic profile than SGAs and complementary clinical targets, all included trials utilized an “add-on” design, adding minocycline to the SGAs that had yielded insufficient results. Similar to major depressive disorder, where anti-inflammatory agents have been added to antidepressants aimed at improving cognition,<sup>74</sup> a multimodal approach may also help to address unmet treatment needs in schizophrenia.

Beyond the minocycline efficacy data, its safety and tolerability profile, alongside the increased subjective well-being reported in case reports, suggest that minocycline may also facilitate pharmacological compliance, which indeed is often an object of concern in patients with schizophrenia.<sup>75</sup> However, minocycline has also been associated with triggering or worsening severe autoimmune conditions, such as systemic lupus erythematosus, autoimmune hepatitis, hyperthyroidism, neutropenia, and polyarthritis nodosa;<sup>76–79</sup> hence, patients treated with minocycline should be carefully monitored.

The present work has several strengths. The sample size increased from 173 patients with schizophrenia on minocycline and 157 on placebo<sup>37</sup> to 215 and 198, respectively. Then, we also retested previous evidence controlling for publication bias and potential moderators, suggesting the need for more studies assessing minocycline’s efficacy for positive symptoms of schizophrenia. Moreover, even if our analyses did not suggest any significant moderator of the observed effect sizes, they still conferred more solid and methodologically sound evidence. In addition, our results describe a role for minocycline in enhancing executive functioning in schizophrenia, a core feature of this enduring disease. Finally, we added a descriptive and systematic review of nonrandomized literature, providing further support to our and other colleagues’ conclusions,<sup>37</sup> consisting of an open-label study<sup>69</sup> and several case series.<sup>70–72</sup> Even if these latter reports do not contribute to the evidence as RCTs do, they do provide a valuable contribution in terms of clinical and real-world-based experience.

However, several factors should be considered when interpreting these results. First, although we increased the number of studies and patients considerably, the number of trials and randomized patients is still quite modest. Thus, although the results are more robust than before and although there does not appear to be a

relevant publication bias, additional and larger studies with minocycline and with mechanistically similar molecules are needed. Second, due to the still small evidence base, our subgroup and meta-regression had to remain exploratory. Since several relevant outcomes had a significant heterogeneity of findings, a larger database will be needed to help identify subgroups of patients, and to design features or treatment characteristics that increase the likelihood of benefiting from minocycline. Third, since only one study had clozapine as the baseline antipsychotic, it is unclear from the current data if failure to sufficiently improve to a non-clozapine antipsychotic or to clozapine would yield different outcomes with minocycline augmentation. Fourth, since all RCTs targeted 200 mg of minocycline per day, data are lacking regarding potential dose-response relationships. Finally, studies of add-on minocycline did not assess all relevant cognitive domains. For our analysis of changes in cognitive domain scores, we pooled different cognitive tests assessing similar cognitive domains. Even if this could be considered an approach that accounts for the heterogeneity of cognitive domains definitions, it could be argued that the results have reduced specificity.

## Conclusions

In conclusion, based on the currently available, modest database, minocycline appears to be an effective treatment option for patients with schizophrenia who have had insufficient benefits from antipsychotic treatment, with positive effects on global severity of illness, negative symptoms, general psychopathology, and executive functions, and possibly on positive symptoms. In addition, currently ongoing trials whose protocols have been recently published<sup>63,64</sup> are hoped to add relevant evidence and provide a more detailed picture of minocycline’s clinical, functional, and cognitive effects in patients with schizophrenia. If, in fact, minocycline is a viable adjunctive treatment option for patients with schizophrenia, its various pharmacological mechanisms of actions should stimulate the development of agents that have similar or enhanced properties.

## Statement of Authorship

Marco Solmi, Nicola Veronese, Silvia Facchini, and Nita Thapa conducted literature screening, data extraction, and statistical analyses. Marco Solmi, Nicola Veronese, and Christoph U. Correll ran the statistical meta-analysis. Christoph U. Correll and Marco Solmi prepared the search key and the meta-analysis design, and wrote the paper, which was reviewed and edited by André Carvalho, Nicola Veronese, Brendon Stubbs, and Michele Fornaro.

## Disclosures

Marco Solmi, Nicola Veronese, Silvia Facchini, André F. Carvalho, Brendon Stubbs, Michele Fornaro, and Nita Thapa hereby state that they have nothing to disclose.

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## Conflicts of Interest

The authors hereby declare that they have no conflicts of interest to report.

## SUPPLEMENTARY MATERIAL

To view supplementary material for this article, please visit <https://doi.org/10.1017/S1092852916000638>

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