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

Marco Solmi,[1,2,3] * Nicola Veronese,[3,4] Nita Thapa,[5] Silvia Facchini,[4] Brendon Stubbs,[6,7] Michele Fornaro,[8] André F. Carvalho,[9] and Christoph U. Correll[10,11,12,13]

[1] Department of Neurosciences, University of Padova, Padova, Italy
[2] Local Health Unit 17, ULSS 17, Mental Health Department, Padova, Italy
[3] Institute for Clinical Research and Education in Medicine (IREM), Padova, Italy
[4] Department of Medicine (DIMED), Geriatrics Section, University of Padova, Padova, Italy
[5] Kaski Sewa Hospital and Research Centre, Pokhara, Nepal
[6] Physiotherapy Department, South London and Maudsley NHS Foundation Trust, London, United Kingdom
[7] Health Service and Population Research Department, Institute of Psychiatry, Psychology, and Neuroscience, King's College London, London, United Kingdom
[8] New York Psychiatric Institute, Columbia University, New York, New York, USA
[9] Department of Clinical Medicine and Translational Psychiatry Research Group, Faculty of Medicine, Federal University of Ceará, Fortaleza, Ceará, Brazil
[10] The Zucker Hillside Hospital, Psychiatry Research, Northwell Health, Glen Oaks, New York, USA
[11] Hofstra Northwell School of Medicine, Hempstead, New York, USA
[12] The Feinstein Institute for Medical Research, Manhasset, New York, USA
[13] Albert Einstein College of Medicine, Bronx, New York, USA

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 ($CI_{95\%}$) 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 ($SMD = -0.59$; $CI_{95\%} = [1.15, -0.03]$; $p = 0.04$), negative ($SMD = -0.76$; $CI_{95\%} = [-1.21, -0.31]$; $p = 0.001$); general subscale scores ($SMD = -0.44$; $CI_{95\%} = [-0.88, -0.00]$; $p = 0.05$), Clinical Global Impressions scores ($SMD = -0.50$; $CI_{95\%} = [-0.78, -0.22]$; $p < 0.001$); and executive functioning ($SMD = 0.22$; $CI_{95\%} = [0.01, 0.44]$; $p = 0.04$). 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.

* Address correspondence to: Marco Solmi, Department of Neurosciences, University of Padua, Via Giustiniani, 2, 35128 Padova, Italy.
(Email: marco.solmi83@gmail.com)

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,[1–6] a decrease in oxidative and nitrosative stress (O&NS),[2,7] as well as putative anti-inflammatory effects (e.g., a decrease in the production of tumor necrosis factor-α and interferon-γ by activated microglia).[8,9] Minocycline has demonstrated neuroprotective properties in such neurodegenerative disorders as Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis (ALS),[3,4,10] in addition to ischemia.[11]

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

The mechanism of action of minocycline in schizophrenia has been reviewed elsewhere.[27] 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,[28] apoptotic mechanisms,[29] oxidative stress,[30] and glutamate dysfunction,[31] which appear to interact with dopamine- and serotonin-related signaling, thus promoting neuroprogression of this severe mental illness.[12] While second-generation antipsychotics (SGAs) mainly act on positive symptoms modulating dopamine and serotonin pathways with mostly questionable or minor effects on glutamate signaling,[32–34] 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.[35,36]

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.[37,38] 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),[39] the Scale for the Assessment of Negative Symptoms (SANS),[40] and the Clinical Global Impressions–Severity scale (CGI–S),[41] 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.[38] Those conclusions deserve reassessment, as both meta-analyses were preliminary and based on four and two studies, with 330 and 100 patients,[37,38] and as additional studies have become available.[42,43] 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,[44] 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),[40] the Positive and Negative Syndrome Scale (PANSS),[39] the Brief Psychiatric Rating Scale (BPRS),[45] the Clinical Global Impressions Scale (CGI),[41] the Calgary Depression Scale for Schizophrenia (CDSS),[46] the Hamilton Depression Rating Scale (HDRS),[47] the Beck Depression Inventory (BDI),[48] the MATRICS Consensus Cognitive Battery (MCCB),[49,50] the Cambridge Neuropsychological Test Automated Battery,[51] discontinuation rates, frequencies of side

effects, results on extrapyramidal symptom scales (such as the Extrapyramidal Symptom Rating Scale[2] and the Abnormal Involuntary Movement Scale[41]), 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.[53] 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[54] (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[55,56] 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 χ^2 and I^2 statistics, with $p < 0.05$ for χ^2 and $\geq 50\%$ for I^2 indicating significant heterogeneity.[57] We compared end-point 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),[58] investigating the following potential moderator variables: age, sex, study duration, and illness duration.

Finally, funnel plots were visually inspected, and Egger's test[59] and Begg–Mazumdar Kendall's tau[60] were utilized to determine if a publication bias was likely, and if it was part of the trim-and-fill procedure,[61] 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,[62] 2 because they were meta-analyses,[37,38] and 2 were trial protocols.[63,64] Among the remaining 10 studies, 6 RCTs were included in the quantitative meta-analysis.[42,43,65–68] Out of the four studies included in the systematic review, one was an open-label study [69] and three were case series.[70–72]

Included studies, treatments, and participants (Table 1)

We meta-analyzed 6 placebo controlled RCTs,[42,43,65–68] including 215 patients taking minocycline and 198 patients taking placebo. In the minocycline group, the patients were on average 29.91 ± 10.2 years old, their age of illness onset was 20.24 ± 5.28 years, illness duration was 17.79 ± 12.98 years, duration of education was 10.39 ± 3.6 years, and 67.92 % were male. In the placebo group, patients were 29.88 ± 9.9 years of age, their age of illness onset was 20.3 ± 5.04 years, illness duration was 20.18 ± 14.69 years, duration of education was 10.21 ± 3.79 years, and 73.4% were male. The mean
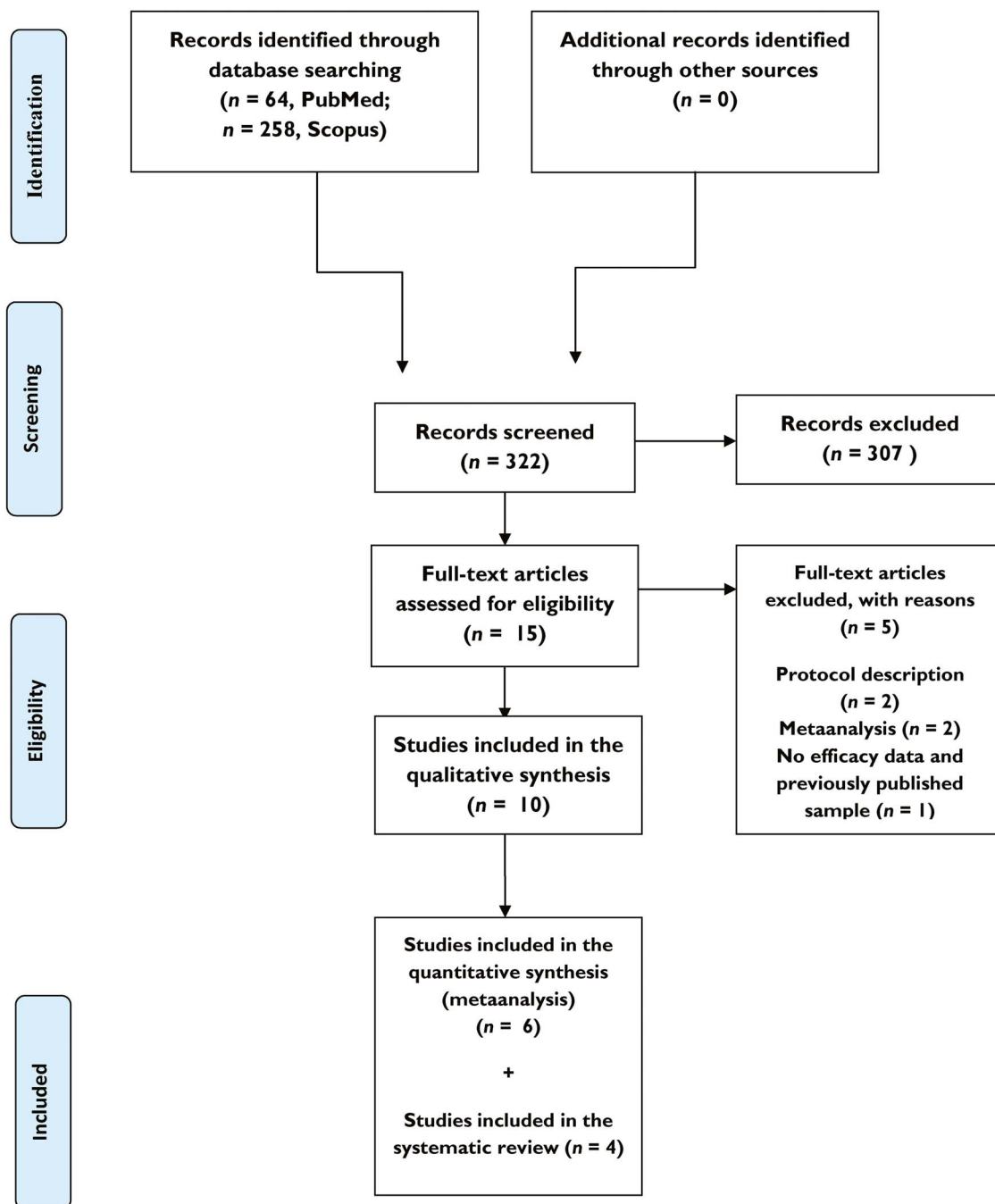
FIGURE 1. PRISMA flowchart.

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,[42,66,67] clozapine in one study,[43] and mixed antipsychotics in two studies.[65,68] Two studies were conducted in Iran,[42,66] and one each in the United States,[43] China,[67] Brazil and Pakistan,[65] and Israel.[68] Two studies allowed inclusion of patients with schizoaffective disorder.[43,65] All studies except one[43] used the PANSS, four studies used the CGI,[43,65,67,68] four

studies used the SANS,[42,43,67,68] four used rating scales for depression,[42,43,66,68] and three studies assessed cognitive functioning.[43,67,68]

The open-label study conducted in Japan[69] lasted 4 weeks and included 22 patients with schizophrenia, with a mean age of 31.2 ± 5.5 years, mean age of illness onset of 22.8 ± 9.73 years, and illness duration of 3.4 ± 2.3 years, with 63.6% being male.

Three case series–one from the United Kingdom,[72] one from India,[71] and one from the United States[70]–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	n mcy	n control	Funding
					Randomized controlled trials				
Kelly et al. (2015),[53] NCT#01433055, 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 et al. (2014),[42] 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 et al. (2014),[67] 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 et al. (2014),[66] 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 et al. (2012),[65] 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 et al. (2010),[68] 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.
Total	3 augmenting risperidone, 1 augmenting clozapine, 2 augmenting standard treatment.	2 in- + outpatients, 1 inpatient, 1 outpatient, 2 not declared.	2 schizophrenia or schizoaffective, 4 schizophrenia	19,67	200 mg/day	3 risperidone, 1 clozapine, 2 other antipsychotics	215	198	No drug sponsorship
					Open-label studies				
Miyaoka et al. (2008),[69] 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		
					Case reports				

TABLE 1. Continued

Study	Design	In/ outpatients	Inclusion criteria	Duration (weeks)	Minocycline dose	Other drug dose	n mcy	n control	Funding
Qurashi et al. (2014),[72] 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 et al. (2013),[71] 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 et al. (2011),[70] 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,[53] two studies had an unclear risk of bias,[42,68] 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 Myn	No. of participants PLC	Meta-analysis SMD	Meta-analysis $CI_{95\%}$		Meta-analysis p value	Heterogeneity I^2 (%)	Other analyses Egger bias and p value		Other analyses Classic failsafe n
PANSS total	5[42,65–68]	**156**	**144**	**−0.59**	**−1.15**	**−0.03**	**0.04**	81	−3.32	0.48	25
PANSS neg		**156**	**144**	**−0.76**	**−1.21**	**−0.31**	**0.001**	69	−0.93	0.83	52
PANSS pos		156	144	−0.22	−0.50	0.06	0.13	29	−2.79	0.25	1
PANSS general	3[43,67,68]	**156**	**144**	**−0.44**	**−0.88**	**−0.00**	**0.05**	69	−3.61	0.31	14
Attention		102	81	0.09	−0.16	0.34	0.47	28	Not possible		
Executive functions		**102**	**81**	**0.22**	**0.01**	**0.44**	**0.04**	42	Not possible		
Memory		102	81	0.15	−0.31	0.62	0.52	79	Not possible		
Motor speed processing	2[67,68]	75	58	−0.16	−0.62	0.31	0.50	64	Not possible		
CGI	4[43,65,67,68]	**148**	**129**	**−0.50**	**−0.78**	**−0.22**	**<0.0001**	23	−3.85	0.12	18
SANS	4[42,43,67,68]	**117**	**99**	**−0.60**	**−0.94**	**−0.27**	**<0.001**	29	7.5	0.01	14
Depression	4[42,43,66,68]	98	79	−0.12	−0.42	0.18	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	β	$CI_{95\%}$		p value	R^2
PANSS total						
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
PANSS negative						
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
PANSS general						
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
Baseline values as moderators for each respective endpoint						
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 $n = 2$, $p = 0.79$),[65,68] pigmentation (studies $n = 2$, $p = 0.53$),[65,68] loss of appetite (studies $n = 3$, $p = 0.99$),[43,65,67] dizziness (studies $n = 3$, $p = 0.55$),[43,65,67] vomiting (studies $n = 2$, $p = 0.43$),[43,65] nausea (studies $n = 3$, $p = 0.70$),[43,65,67] extrapyramidal symptoms both as reported by investigators (studies $n = 3$, $p = 0.95$)[43,65,67] and measured with the Extrapyramidal Symptoms Rating Scale[52] (studies $n = 2$, $p = 0.72$),[66,68] constipation (studies $n = 3$, $p = 0.68$),[43,67,68] and dry mouth (studies $n = 2$, $p = 0.56$).[43,67] However, headache was significantly more frequent in the placebo group (studies $n = 2$, $p = 0.01$).[43,65]

Systematic review: efficacy and safety

One open-label study[69] 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[45] in two patients with paranoid schizophrenia,[72] 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,[71] 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.[70] 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.[73] We provide a novel insight into the cognitive effects of minocycline, which are in contrast with a former meta-analysis[38] 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[37] 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%)[42,43] 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,[74] 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.[75] 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;[76–79] 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[37] 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,[37] consisting of an open-label study[69] and several case series.[70–72] 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[63,64] 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

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.

Christoph U. Correll has been a consultant and/or advisor to or has received honoraria from AbbVie, Acadia, Actavis, Actelion, Alexza, Alkermes, the American Academy of Child and Adolescent Psychiatry, Bristol-Myers Squibb, Cephalon, Eli Lilly, Genentech, Gerson Lehrman Group, IntraCellular Therapies, Lundbeck, Medavante, Medscape, Merck, the National Institute of Mental Health, Janssen/J&J, Otsuka, Pfizer, ProPhase, Reviva, Roche, Sunovion, Supermus Takeda, Teva, and Vanda. He has received grant support from BMS, the Feinstein Institute for Medical Research, Janssen/J&J, the National Institute of Mental Health, the National Alliance for Research in Schizophrenia and Depression, Otsuka, and Takeda.

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

REFERENCES:

1. Chaves C, Marque CR, Trzesniak C, *et al.* Glutamate-*N*-methyl-d-aspartate receptor modulation and minocycline for the treatment of patients with schizophrenia: an update. *Braz J Med Biol Res.* 2009; **42**(11): 1002–1014. https://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0027593/. Accessed January 13, 2017.

2. Monte AS, de Souza GC, McIntyre RS, *et al.* Prevention and reversal of ketamine-induced schizophrenia related behavior by minocycline in mice: possible involvement of antioxidant and nitrergic pathways. *J Psychopharmacol.* 2013; **27**(11): 1032–1043. Epub ahead of print Sep 17. http://journals.sagepub.com/doi/pdf/10.1177/0269881113503506. Accessed January 13, 2017.

3. Hashimoto K. Abnormality of cerebral perfusion in the posterior cingulate gyrus of a refractory patient with schizophrenia and minocycline treatment. *Prog Neuropsychopharmacol Biol Psychiatry.* 2010; **34**(6): 1132; author reply 1133–1134. Epub ahead of print Apr 28.

4. Hashimoto K, Ishima T, Fujita Y, Zhang L. Antibiotic drug minocycline: a potential therapeutic drug for methamphetamine-related disorders [in Japanese]. *Nihon Arukoru Yakubutsu Igakkai Zasshi.* 2013; **48**(2): 118–125.

5. Zhang L, Shirayama Y, Iyo M, Hashimoto K. Minocycline attenuates hyperlocomotion and prepulse inhibition deficits in mice after administration of the NMDA receptor antagonist dizocilpine. *Neuropsychopharmacology.* 2007; **32**(9): 2004–2010. Epub ahead of print Jan 17. http://www.nature.com/npp/journal/v32/n9/pdf/1301313a.pdf. Accessed January 13, 2017.

6. Macdonald H, Kelly RG, Allen ES, Noble JF, Kanegis LA. Pharmacokinetic studies on minocycline in man. *Clin Pharmacol Ther.* 1973; **14**(5): 852–861.

7. Hanson E, Healey K, Wolf D, Kohler C. Assessment of pharmacotherapy for negative symptoms of schizophrenia. *Curr Psychiatry Rep.* 2010; **12**(6): 563–571.

8. Liaury K, Miyaoka T, Tsumori T, *et al.* Minocycline improves recognition memory and attenuates microglial activation in Gunn rat: a possible hyperbilirubinemia-induced animal model of schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry.* 2014; **50**: 184–190. Epub ahead of print Jan 2.

9. Seki Y, Kato TA, Monji A, *et al.* Pretreatment of aripiprazole and minocycline, but not haloperidol, suppresses oligodendrocyte damage from interferon-γ-stimulated microglia in co-culture model. *Schizophr Res.* 2013; **151**(1–3): 20–28. Epub ahead of print Oct 4.

10. Zhang W, Narayanan M, Friedlander RM. Additive neuroprotective effects of minocycline with creatine in a mouse model of ALS. *Ann Neurol.* 2003; **53**(2): 267–270.

11. Yrjanheikki J, Tikka T, Keinanen R, Goldsteins G, Chan PH, Koistinaho J. A tetracycline derivative, minocycline, reduces inflammation and protects against focal cerebral ischemia with a wide therapeutic window. *Proc Natl Acad Sci U S A.* 1999; **96**(23): 13496–13500. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC23976/. Accessed January 13, 2017.

12. Davis J, Moylan S, Harvey BH, Maes M, Berk M. Neuroprogression in schizophrenia: pathways underpinning clinical staging and therapeutic corollaries. *Aust N Z J Psychiatry.* 2014; **48**(6): 512–529. Epub ahead of print May 6. http://journals.sagepub.com/doi/pdf/10.1177/0004867414533012. Accessed January 13, 2017.

13. Muller N, Weidinger E, Leitner B, Schwarz MJ. The role of inflammation in schizophrenia. *Front Neurosci.* 2015; **9**: 372. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4612505/. Accessed January 13, 2017.

14. Hu W, MacDonald ML, Elswick DE, Sweet RA. The glutamate hypothesis of schizophrenia: evidence from human brain tissue studies. *Ann N Y Acad Sci.* 2015; **1338**: 38–57. Epub ahead of print Oct 14, 2014. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4363164/. Accessed January 13, 2017.

15. Zink M, Correll CU. Glutamatergic agents for schizophrenia: current evidence and perspectives. *Expert Rev Clin Pharmacol.* 2015; **8**(3): 335–352.

16. Reus GZ, Fries GR, Stertz L, *et al.* The role of inflammation and microglial activation in the pathophysiology of psychiatric disorders. *Neuroscience.* 2015; **300**: 141–154. Epub ahead of print May 14.

17. Shim S, Shuman M, Duncan E. An emerging role of cGMP in the treatment of schizophrenia: a review. *Schizophr Res.* 2015; **170**(1): 226–231. Epub ahead of print Dec 22.

18. Fillman SG, Weickert TW, Lenroot RK, *et al.* Elevated peripheral cytokines characterize a subgroup of people with schizophrenia displaying poor verbal fluency and reduced Broca's area volume. *Mol Psychiatry.* 2015; **21**(8): 1090–1098. Epub ahead of print Jul 21. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4960447/. Accessed January 13, 2017.

19. Xiu MH, Yang GG, Tan YL, *et al.* Decreased interleukin-10 serum levels in first-episode drug-naive schizophrenia: relationship to psychopathology. *Schizophr Res.* 2014; **156**(1): 9–14. Epub ahead of print Apr 22.

20. Tuominen HJ, Tiihonen J, Wahlbeck K. Glutamatergic drugs for schizophrenia: a systematic review and meta-analysis. *Schizophr Res.* 2005; **72**(2–3): 225–234.

21. Ventura J, Subotnik KL, Gitlin MJ, *et al.* Negative symptoms and functioning during the first year after a recent onset of schizophrenia and 8 years later. *Schizophr Res.* 2015; **161**(2–3): 407–413. Epub ahead of print Dec 8, 2014. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4308531/. Accessed January 13, 2017.

22. Remberk B, Bazynska AK, Bronowska Z, et al. Which aspects of long-term outcome are predicted by positive and negative symptoms in early-onset psychosis? An exploratory eight-year follow-up study. *Psychopathology*. 2015; **48**(1): 47–55. Epub ahead of print Dec 2, 2014.

23. Marchesi C, Affaticati A, Monici A, De Panfilis C, Ossola P, Tonna M. Severity of core symptoms in first episode schizophrenia and long-term remission. *Psychiatry Res*. 2015; **225**(1–2): 129–132. Epub ahead of print Nov 11, 2014.

24. Galderisi S, Bucci P, Mucci A, et al. Categorical and dimensional approaches to negative symptoms of schizophrenia: focus on long-term stability and functional outcome. *Schizophr Res*. 2013; **147**(1): 157–162. Epub ahead of print Apr 19.

25. Agid O, Siu CO, Pappadopulos E, Vanderburg D, Remington G.. Early prediction of clinical and functional outcome in schizophrenia. *Eur Neuropsychopharmacol*. 2013; **23**(8): 842–851. Epub ahead of print Nov 7, 2012.

26. Hofer A, Baumgartner S, Bodner T, et al. Patient outcomes in schizophrenia, II: the impact of cognition. *Eur Psychiatry*. 2005; **20**(5–6): 395–402.

27. Zhang L, Zhao J. Profile of minocycline and its potential in the treatment of schizophrenia. *Neuropsychiatr Dis Treat*. 2014; **10**: 1103–1111. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4069141/. Accessed January 13, 2017.

28. Monji A, Kato TA, Mizoguchi Y, et al. Neuroinflammation in schizophrenia especially focused on the role of microglia. *Prog Neuropsychopharmacol Biol Psychiatry*. 2013; **42**: 115–121. Epub ahead of print Dec 13, 2011.

29. Glantz LA, Gilmore JH, Lieberman JA, Jarskog LF. Apoptotic mechanisms and the synaptic pathology of schizophrenia. *Schizophr Res*. 2006; **81**(1): 47–63. Epub ahead of print Oct 14, 2005.

30. Sertan Copoglu U, Virit O, Hanifi Kokacya M, et al. Increased oxidative stress and oxidative DNA damage in non-remission schizophrenia patients. *Psychiatry Res*. 2015; **229**(1–2): 200–205. Epub ahead of print Jul 15.

31. Howes O, McCutcheon R, Stone J. Glutamate and dopamine in schizophrenia: an update for the 21st century. *J Psychopharmacol*. 2015; **29**(2): 97–115. Epub ahead of print Jan 13. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4902122/. Accessed January 13, 2017.

32. Xu S, Gullapalli RP, Frost DO. Olanzapine antipsychotic treatment of adolescent rats causes long-term changes in glutamate and GABA levels in the nucleus accumbens. *Schizophr Res*. 2015; **161**(2–3): 452–457. Epub ahead of print Dec 5, 2014. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4308953/. Accessed January 13, 2017.

33. Goldstein ME, Anderson VM, Pillai A, Kydd RR, Russell BR. Glutamatergic neurometabolites in clozapine-responsive and -resistant schizophrenia. *Int J Neuropsychopharmacol*. 2015; **18**(6): pii: pyu117. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4438552/. Accessed January 13, 2017.

34. Koprivica V, Regardie K, Wolff C, et al. Aripiprazole protects cortical neurons from glutamate toxicity. *Eur J Pharmacol*. 2011; **651**(1–3): 73–76. Epub ahead of print Nov 18, 2010.

35. Millan MJ, Fone K, Steckler T, Horan WP. Negative symptoms of schizophrenia: clinical characteristics, pathophysiological substrates, experimental models and prospects for improved treatment. *Eur Neuropsychopharmacol*. 2014; **24**(5): 645–692. Epub ahead of print Apr 4. http://www.europeanneuropsychopharmacology.com/article/S0924-977X(14)00093-5/pdf. Accessed January 13, 2017.

36. Millan MJ, Agid Y, Brune M, et al. Cognitive dysfunction in psychiatric disorders: characteristics, causes and the quest for improved therapy. *Nat Rev Drug Discov*. 2012; **11**(2): 141–168.

37. Oya K, Kishi T, Iwata N. Efficacy and tolerability of minocycline augmentation therapy in schizophrenia: a systematic review and

meta-analysis of randomized controlled trials. *Hum Psychopharmacol*. 2014; **29**(5): 483–491. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5170618/. Accessed January 13, 2017.

38. Iwata Y, Nakajima S, Suzuki T, et al. Effects of glutamate positive modulators on cognitive deficits in schizophrenia: a systematic review and meta-analysis of double-blind randomized controlled trials. *Mol Psychiatry*. 2015; **20**(10): 1151–1160. Epub ahead of print Jun 16.

39. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull*. 1987; **13**(2): 261–276. https://academic.oup.com/schizophreniabulletin. Accessed January 13, 2017.

40. Andreasen NC. Negative symptoms in schizophrenia: definition and reliability. *Arch Gen Psychiatry*. 1982; **39**(7): 784–788.

41. Guy W. *ECDEU (Early Clinical Drug Evaluation) Assessment Manual for Psychopharmacology*. Washington, DC: U.S. Department of Heath, Education, and Welfare Public Health Service Alcohol, Drug Abuse, and Mental Health Administration; 1976. https://archive.org/details/ecdeuassessmentm1933guyw. Accessed January 13, 2017.

42. Ghanizadeh A, Dehbozorgi S, OmraniSigaroodi M, Rezaei Z. Minocycline as add-on treatment decreases the negative symptoms of schizophrenia: a randomized placebo-controlled clinical trial. *Recent Pat Inflamm Allergy Drug Discov*. 2014; **8**(3): 211–215.

43. Kelly DL, Sullivan KM, McEvoy JP, et al. Adjunctive Minocycline in Clozapine-Treated Schizophrenia Patients With Persistent Symptoms. *J Clin Psychopharmacol*. 2015; **35**(4): 374–381. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4485552/. Accessed January 13, 2017.

44. Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Int J Surg*. 2010; **8**(5): 336–341. Epub ahead of print Feb 18. http://www.journal-surgery.net/article/S1743-9191(10)00040-3/pdf. Accessed January 13, 2017.

45. Overall JE, Gorham DR. The brief psychiatric rating scale. *Psychol Rep*. 1962; **10**: 799–812. http://www.statpower.net/Content/312/Homework/OverallGorham1962.pdf. Accessed January 13, 2017.

46. Lancon C, Auquier P, Reine G, Bernard D, Toumi M. Study of the concurrent validity of the Calgary Depression Scale for Schizophrenics (CDSS). *J Affect Disord*. 2000; **58**(2): 107–115.

47. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry*. 1960; **23**: 56–62. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC495331/. Accessed January 13, 2017.

48. Beck AT, Alford BA. *Depression: Causes and Treatment*, 2nd ed. Philadelphia: University of Pennsylvania Press; 2009.

49. Nuechterlein KH, Green MF, Kern RS, et al. The MATRICS Consensus Cognitive Battery, part 1: test selection, reliability, and validity. *Am J Psychiatry*. 2008; **165**(2): 203–213. Epub ahead of print Jan 2. http://ajp.psychiatryonline.org/doi/pdf/10.1176/appi.ajp.2007.07010042. Accessed January 13, 2017.

50. Green MF, Nuechterlein KH. The MATRICS initiative: developing a consensus cognitive battery for clinical trials. *Schizophr Res*. 2004; **72**(1): 1–3.

51. *CANTAB*. Cambridge: Cambridge Cognition Ltd. http://www.cambridgecognition.com/. Accessed January 13, 2017.

52. Chouinard G, Margolese HC. Manual for the Extrapyramidal Symptom Rating Scale (ESRS). *Schizophr Res*. 2005; **76**(2–3): 247–265. Epub ahead of print Apr 18.

53. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011; **343**: d5928. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3196245/. Accessed January 13, 2017.

54. *RevMan 5*. http://tech.cochrane.org/revman. Accessed January 13, 2017.

55. DerSimonian R, Kacker R. Random-effects model for meta-analysis of clinical trials: an update. *Contemp Clin Trials*. 2007; **28**(2): 105–114. Epub ahead of print May 12, 2006.

56. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986; **7**(3): 177–188.

57. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003; **327**(7414): 557–560. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC192859/. Accessed January 13, 2017.

58. *Comprehensive Meta-Analysis* (*CMA*). https://www.meta-analysis.com/?gclid=CO2P5tX3isoCFRThGwodz-8L9A. Accessed January 13, 2017.

59. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997; **315**(7109): 629–634. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2127453/. Accessed January 13, 2017.

60. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics*. 1994; **50**(4): 1088–1101.

61. Duval S, Tweedie R. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics*. 2000; **56**(2): 455–463.

62. Chaves C, Marque CR, Maia-de-Oliveira JP, *et al*. Effects of minocycline add-on treatment on brain morphometry and cerebral perfusion in recent-onset schizophrenia. *Schizophr Res*. 2015; **161**(2–3): 439–445. Epub ahead of print Dec 12, 2014.

63. Lisiecka DM, Suckling J, Barnes TR, *et al*. The benefit of minocycline on negative symptoms in early-phase psychosis in addition to standard care–extent and mechanism (BeneMin): study protocol for a randomised controlled trial. *Trials*. 2015; **16**: 71. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4351843/. Accessed January 13, 2017.

64. Fekadu A, Mesfin M, Medhin G, *et al*. Adjuvant therapy with minocycline for schizophrenia (the MINOS Trial): study protocol for a double-blind randomized placebo-controlled trial. *Trials*. 2013; **14**: 406. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4222697/. Accessed January 13, 2017.

65. Chaudhry IB, Hallak J, Husain N, *et al*. Minocycline benefits negative symptoms in early schizophrenia: a randomised double-blind placebo-controlled clinical trial in patients on standard treatment. *J Psychopharmacol*. 2012; **26**(9): 1185–1193. Epub ahead of print Apr 23. http://journals.sagepub.com/doi/pdf/10.1177/0269881112444941. Accessed January 13, 2017.

66. Khodaie-Ardakani MR, Mirshafiee O, Farokhnia M, *et al*. Minocycline add-on to risperidone for treatment of negative symptoms in patients with stable schizophrenia: randomized double-blind placebo-controlled study. *Psychiatry Res*. 2014; **215**(3): 540–546. Epub ahead of print Jan 9.

67. Liu F, Guo X, Wu R, *et al*. Minocycline supplementation for treatment of negative symptoms in early-phase schizophrenia: a double blind, randomized, controlled trial. *Schizophr Res*. 2014; **153**(1–3): 169–176. Epub ahead of print Feb 3.

68. Levkovitz Y, Mendlovich S, Riwkes S, *et al*. A double-blind, randomized study of minocycline for the treatment of negative and cognitive symptoms in early-phase schizophrenia. *J Clin Psychiatry*. 2010; **71**(2): 138–149. Epub ahead of print Nov 3, 2009.

69. Miyaoka T, Yasukawa R, Yasuda H, Hayashida M, Inagaki T, Horiguchi J. Minocycline as adjunctive therapy for schizophrenia: an open-label study. *Clin Neuropharmacol*. 2008; **31**(5): 287–292.

70. Kelly DL, Vyas G, Richardson CM, *et al*. Adjunct minocycline to clozapine treated patients with persistent schizophrenia symptoms. *Schizophr Res*. 2011; **133**(1–3): 257–258. Epub ahead of print Aug 26.

71. Jhamnani K, Shivakumar V, Kalmady S, Rao NP, Venkatasubramanian G. Successful use of add-on minocycline for treatment of persistent negative symptoms in schizophrenia. *J Neuropsychiatry Clin Neurosci*. 2013; **25**(1): E06–E07. http://neuro.psychiatryonline.org/doi/pdf/10.1176/appi.neuropsych.11120376. Accessed January 13, 2017.

72. Qurashi I, Collins J, Chaudhry I, Husain N. Promising use of minocycline augmentation with clozapine in treatment-resistant schizophrenia. *J Psychopharmacol*. 2014; **28**(7): 707–708. Epub ahead of print Mar 19. http://journals.sagepub.com/doi/pdf/10.1177/0269881114527358. Accessed January 13, 2017.

73. Carbon M, Correll CU. Thinking and acting beyond the positive: the role of the cognitive and negative symptoms in schizophrenia. *CNS Spectr*. 2014; **19**(Suppl. 1): 38–52; quiz 35–37, 53.

74. Carvalho AF, Miskowiak KK, Hyphantis TN, *et al*. Cognitive dysfunction in depression: pathophysiology and novel targets. *CNS Neurol Disord Drug Targets*. 2014; **13**(10): 1819–1835.

75. Kane JM, Kishimoto T, Correll CU. Non-adherence to medication in patients with psychotic disorders: epidemiology, contributing factors and management strategies. *World Psychiatry*. 2013; **12**(3): 216–226. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3799245/. Accessed January 13, 2017.

76. Tehrani R, Nash-Goelitz A, Adams E, Dahiya M, Eilers D. Minocycline-induced cutaneous polyarteritis nodosa. *J Clin Rheumatol*. 2007; **13**(3): 146–149.

77. Ramakrishna J, Johnson AR, Banner BF. Long-term minocycline use for acne in healthy adolescents can cause severe autoimmune hepatitis. *J Clin Gastroenterol*. 2009; **43**(8): 787–790.

78. Benjamin RW, Calikoglu AS. Hyperthyroidism and lupus-like syndrome in an adolescent treated with minocycline for acne vulgaris. *Pediatr Dermatol*. 2007; **24**(3): 246–249.

79. Ahmed F, Kelsey PR, Shariff N. Lupus syndrome with neutropenia following minocycline therapy: a case report. *Int J Lab Hematol*. 2008; **30**(6): 543–545.