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ORIGINAL PAPER

Minocycline for Depressive Symptoms: a Meta-Analysis of Randomized, Double-Blinded, Placebo-Controlled Trials

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Abstract

Neuroinflammation appears to be associated with the neurobiology of depression, and treatments targeting inflammation have shown promising results in depression. This meta-analysis examined the efficacy and safety of minocycline, an anti-inflammatory drug, for the treatment of depressive symptoms. A systematic electronic literature search was independently conducted by two investigators. Standardized mean differences (SMDs) and risk ratio (RR) with their 95% confidence interval (CI) were calculated using a random-effect model. Four RCTs ($n = 211$) were identified for meta-analysis. Minocycline showed a significant trend of improvement in depressive symptoms compared to placebo [4 RCTs, $n = 190$, SMD: -0.54 (95%CI:-1.12, 0.04), $P = 0.07$; $I^2 = 73\%$]. Subgroup analyses showed that minocycline was superior to placebo in improving depressive symptoms in studies of unipolar depression (3 RCTs, $n = 151$, SMD: -0.77 (95%CI:-1.32, −0.22), $P = 0.006$; $I^2 = 60\%$) and in studies using minocycline monotherapy [SMD: -1.06 (95%CI:-1.68, −0.44), $P = 0.0008$]. The rates of discontinuation due to any reasons [RR: 1.48 (95%CI: 0.79, 2.77), $P = 0.22$, $I^2 = 0\%$] and adverse drug reactions [RR: 0.32 to 1.98 (95%CI: 0.03, 14.74), $P = 0.19$ to 0.84, $I^2 = 0\%$ to 31%] were similar between minocycline and placebo. Minocycline appears to be effective and well-tolerated in ameliorating depressive symptoms in unipolar depression. Future large RCTs with sufficient duration is needed to confirm the positive effects of minocycline in treating depressive symptoms.

Keywords Minocycline · Depressive symptoms · Response · Remission · Meta-analysis

Dong-Bin Cai, Wei Zheng and Qing-E Zhang contributed equally to this work.

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Introduction

Depressive symptoms are common and a major challenge in clinical practice [1]. The Sequenced Treatment Alternatives for the Relief of Depression (STAR*D) trial involving 3,671 outpatients found that the remission rate for major depressive disorder (MDD) was only 36.8% following the first treatment step, and the rate decreased to 13.0% over three subsequent treatment steps [1]. A recent network meta-analysis of 21 antidepressant drugs in acute treatment of MDD only found a small effect size compared to placebo [2], which is similar to the findings of another meta-analysis [3]. Hence, novel treatment agents for depression are urgently needed to improve the outcomes for patients.

Neuroinflammation appears to be associated with the neurobiology of depression and treatments targeting inflammation has shown promising results in depression [4–6]. Studies have found elevated circulating pro-inflammatory cytokines in patients with depressive symptoms [7], while patients with chronic inflammatory and autoimmune disorders frequently have comorbid depressive symptoms [8]. Moreover, inflammatory system dysregulation is associated with more severe course of depressive symptoms [9] and treatment-resistant depression [10].

The tetracycline antibiotic minocycline shows potent anti-inflammatory, anti-apoptotic and anti-oxidant properties, and is associated with the modulation of glutamate and monoamine neurotransmission [11, 12], and thus could have antidepressant effects [12]. The potential neuroprotective and antidepressant-like effects of minocycline have been confirmed in animal studies [13]. Preliminary data from open-label trials of adjunctive minocycline in patients with unipolar [14] and bipolar depression [15–17] also showed clinical efficacy and safety. However, the findings of randomized controlled trials (RCTs) [18–21] of the antidepressant effects of minocycline have been mixed.

A recent meta-analysis [22] of 3 RCTs ($n = 158$) [19–21] of the efficacy and safety of minocycline in the treatment of depressive symptoms found superiority of minocycline over placebo. However, the meta-analysis [22] was limited by the small number of RCTs and sample size, and since the meta-analysis did not include any studies from the Chinese databases.

This updated meta-analysis of RCTs in both English and Chinese databases examined the efficacy and safety of adjunctive minocycline for depressive symptoms, regardless of their primary diagnoses.

Methods

This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement [23] (CRD42018102481; http://www.crd.york.ac.uk/prospero/).

Search Strategy

An electronic literature search was independently conducted in both English (PubMed, PsycINFO, EMBASE and the Cochrane Library) and Chinese (Chinese Journal Net and WanFang) databases from their inception date up to June 26, 2018 by two investigators (DBC and WZ), using the following search terms: ("minocycline"[Mesh] OR "minocyline"[Mesh] OR minocyline OR minocycline) AND ("depression"[Mesh] OR

depressive OR depressed OR melancholia). Reference lists of included RCTs [18–21], meta-analyses [22] and reviews [24] were also hand-searched for additional studies.

Study Selection

The eligibility of studies was independently determined by two investigators (WZ and DBC) according to the following ***PICOS*** acronym: (i) ***P***articipants: subjects with depressive symptoms (age ≥ 18 years), regardless of their primary diagnoses [25]. (ii) ***I***ntervention: minocycline monotherapy or minocycline plus treatment as usual (TAU). (iii) ***C***omparison: TAU or TAU plus placebo. (iv) ***O***utcomes: the primary outcome was depressive symptoms measured by standardized rating scales [such as the Hamilton Depression Rating Scale (HAMD), Montgomery-Asberg Depression Rating Scale (MADRS) or Beck Depression Inventory (BDI)]. If one study concurrently used the HAMD and other rating scales on depressive symptoms, the HAMD assessment was preferred. The key secondary outcomes included treatment response, discontinuation due to any reasons and adverse drug reactions (ADRs). (v) ***S***tudy design: double-blinded RCTs with meta-analyzable data.

Data Extraction

Data were independently extracted from the included RCTs, entered into a standardized Microsoft Excel spreadsheet, checked, and analyzed by two investigators (DBC and WZ). Any disagreement was resolved by consensus or by involving a third reviewer (YTX). Whenever essential data were not reported, the first/correspondence authors were contacted for more information.

Statistical Methods

All outcomes were meta-analyzed using the Review Manager (Version 5.3) (http://www.cochrane.org) in case when at least 2 studies provided data for a given outcome as per other meta-analysis [26]. Due to the heterogeneity across studies, the random effects model was used to synthesize outcomes [27]. For continuous and dichotomous data, we calculated standardized mean differences (SMDs) and risk ratios (RRs) with their 95% confidence intervals (CIs).

Study heterogeneity was assessed using the chi-squared and I-squared statistics, with chi-squared $P < 0.10$ and I-squared≥50% suggesting high heterogeneity. When heterogeneity for depressive symptoms (primary outcome) was high, a sensitivity analysis [i.e., removing an outlying study [21] with comorbid Human Immunodeficiency Virus (HIV) infection] was conducted to explore the heterogeneity source. Furthermore, the following two subgroup analyses were conducted: (1) studies with minocycline as monotherapy vs. studies with minocycline as adjunctive therapy; (2) studies on MDD vs. studies on bipolar disorder. Funnel plots and Egger's test [28] for primary outcomes were conducted to evaluate publication bias. All meta-analytic outcomes were 2 tailed, with alpha set at 0.05.

Quality Assessment

Evaluation of methodological quality of each study was independently conducted by two investigators (WZ and DBC) using the Cochrane risk of bias [29] and Jadad scale [30]. The Jadad total score of ≥3 was considered as "high quality" [30]. The grading of

recommendations, assessment, development, and evaluation (GRADE) system [31, 32] was administered to estimate the recommendation level for adjunctive minocycline in treating depressive symptoms.

Results

Results of the Search

Figure 1 shows the PRISMA flow diagram. Out of 855 initial hits from English ($n = 839$) and Chinese ($n = 16$) databases, 851 were excluded: duplicates ($n = 53$), after reading title/abstract ($n = 787$), and full text review ($n = 11$). Finally, 4 RCTs [18–21] in English databases were included.

Study Characteristics

All 4 RCTs ($n = 211$) were double-blind and the weighted mean study duration was 9.2 (range = 6–12 weeks; Table 1). The weighted mean age of the 170 patients in 3 RCTs with available data was 43.3 (range = 35.5–49.4) years; males accounted for 42.9% (range =

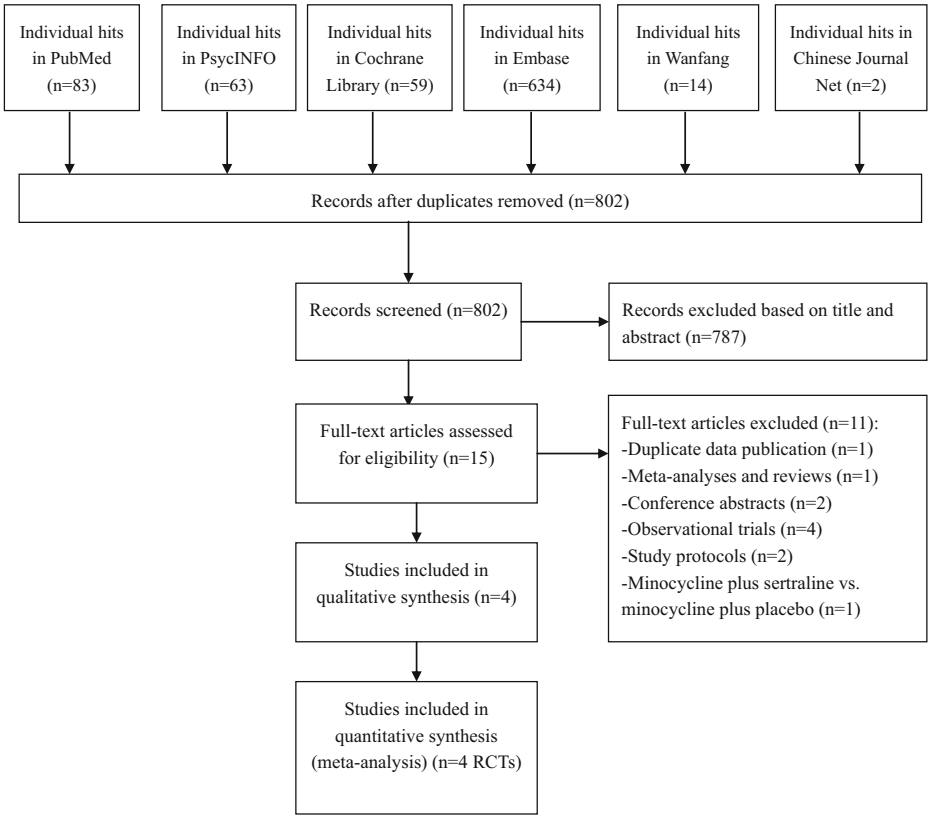

Fig. 1 PRISMA flow diagram

28.6%–65.2%) of the 211 patients. The weighted mean illness duration was 9.8 years (range = 3.9–14.0) in 2 RCTs with available data. The given dose of minocycline was 200 mg/day in all RCTs.

Quality Assessment

All four RCTs were rated as low risk in terms of selective bias, attrition bias, and reporting bias (Supplemental Fig. 1). The weighted mean score of the Jaded scale was 5 and all included RCTs were considered as high quality (Table 1). Using the GRADE approach, the overall evidence levels for 12 outcomes ranged from "low" (8.3%; 1/12) to "moderate" (91.7%; 11/12) (Supplemental Table 1).

Depressive Symptoms

Meta-analysis of depressive symptoms measured by HAMD (2 RCTs) and MADRS (2 RCTs) showed that minocycline had a significant trend of improving depressive symptoms compared to placebo [4 RCTs, $n = 190$, SMD: -0.54 (95%CI:-1.12, 0.04), $P = 0.07$; $I^2 = 73\%$, Fig. 2]. The marginal significance disappeared [SMD: -0.37 (95%CI:-1.03, 0.29), $P = 0.27$; $I^2 = 71\%$] after removing one study [21] with comorbid HIV infection. Subgroup analyses showed that minocycline was significantly superior to placebo in studies on unipolar depression (3 RCTs, $n = 151$, SMD: -0.77 (95%CI:-1.32, −0.22), $P = 0.006$; $I^2 = 60\%$) and in studies using minocycline monotherapy [SMD: -1.06 (95%CI:-1.68, −0.44), $P = 0.0008$]. Meta-analysis of response (≥50% reduction in HAMD or MADRS score) did not find any group differences [3 RCTs, $n = 133$, RR: 1.94 (95%CI: 0.93, 4.04), $P = 0.08$, $I^2 = 12\%$; Table 2].

Discontinuation Rate and ADRs

Meta-analysis of all-cause discontinuations did not find any group differences [RR: 1.48 (95%CI: 0.79, 2.77), $P = 0.22$, $I^2 = 0\%$; Table 2]. Meta-analysis of ADRs including abdominal pain, diarrhea, dizziness, headache, fast/irregular heartbeat, insomnia, myalgia, nausea, and rash [RR: 0.32 to 1.98 (95%CI: 0.03, 14.74), $P = 0.19$ to 0.84, $I^2 = 0\%$ to 31%; Table 2] also did not show any group differences.

Publication Bias

Four RCTs were meta-analyzed, which is less than the minimum 10 RCTs to perform funnel plot or Egger's test. Thus, publication bias was not assessed for depressive symptoms ($n = 4$ RCTs).

Discussion

This updated meta-analysis of 4 RCTs with 211 subjects with depressive symptoms found that minocycline was superior to placebo in studies on unipolar depression and studies using minocycline monotherapy. The efficacy and safety of minocycline in depression appears to be consistent with effect of minocycline in the treatment of schizophrenia [26, 33].

Table 1 Study, patient and treatment characteristics

Study	Blinding	Analyses	Trial duration (wks)	Setting (%)	Diagnosis (%)	Diagnostic criteria	Illness duration
Dean et al., 2017 (Australia)	DB	ITT	12	Outpatients (100)	MDD (100)	DSM-IV	14[b] yrs
Emadi-Kouchak et al., 2016 (Iran)	DB	OC	6	Outpatients (100)	MDD (100) with documented HIV infection	DSM-IV-TR	3.5 yrs
Husain et al., 2017 (Pakistan)	DB	ITT	12	Outpatients (100)	MDD (100)	DSM-5	NR
Savitz et al., 2018 (USA)	DB	OC	6	Psychiatric clinics (100)	BP-I (43);BP-II (49);BP-NOS (8)	DSM-IV-TR	NR

Study	Mean Age[a]: yrs (range)	Sex[a]: male (%)	Intervention versus control Dose (mg/d); Number of patients	Primary outcome measure	Jadad score
Dean et al., 2017 (Australia)	49.4 (NR)	33.8	1. TAU+MINO (200; FD); $n = 36$ 2. TAU+Pbo; $n = 35$	MADRS	5
Emadi-Kouchak et al., 2016 (Iran)	35.5 (18–55)	65.2	1. HAART+MINO (200; FD); n = 25 2. HAART+Pbo; $n = 25$	HAMD-17	5
Husain et al., 2017 (Pakistan)	37.6 (median) (18–65)	48.8	1. TAU+MINO (200; range from 100 to 200); n = 21 2. TAU+Pbo; $n = 20$	HAMD-17	5
Savitz et al., 2018 (USA)	42.4 (NR)	28.6	1. MINO (200; FD); n = 19 2. Pbo; $n = 30$	MADRS	5

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

[b] Duration of illness since diagnosis

Abbreviations: *BP-I* Bipolar I disorder, *BP-II* Bipolar II disorder, *BP-NOS* Bipolar disorder not otherwise specified, *DB* double blind, *DSM-IV* Diagnostic and Statistical Manual of Mental Disorders 4th edition, *DSM-IV-TR* Diagnostic and Statistical Manual of Mental Disorders 4th edition, Text Revision, *DSM-5* Diagnostic and Statistical Manual of Mental Disorders 5th edition, *FD* fixed dosage, *HAART* Highly Active Antiviral Therapy, *HIV* human immunodeficiency virus, *HAMD-17* Hamilton Depression scores 17-item, *ITT* intent to treat, *MADRS* Montgomery–Äsberg Depression Rating Scale, *MDD* major depressive disorder, *MINO* Minocycline, *NR* not report, *OC* observed cases, *Pbo* placebo, *T* total, *TAU* treatment as usual, *TRD* treatment-resistant depressive symptoms, *wks* weeks, *yrs*. years

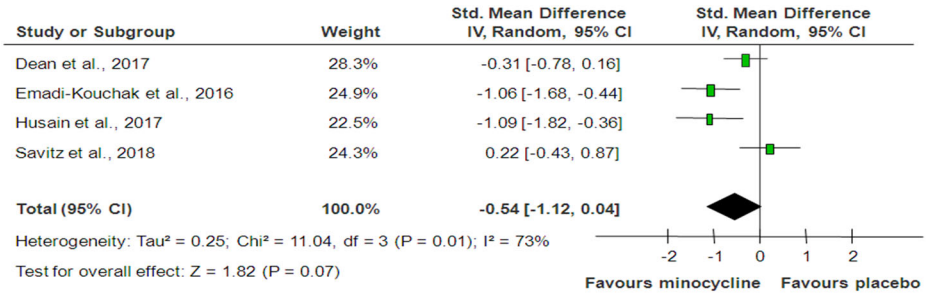

Fig. 2 Minocycline for depressive symptoms: Forest plot for depressive symptoms

The potential antidepressant mechanism of minocycline could be attributed to its anti-inflammatory and neuroprotective effects [34]. Biological mediators of stress (such as glucocorticoids) and peripheral inflammation are associated with the activation of neuroinflammatory processes [35], in which microglia associated with the release of inflammatory mediators, such as pro-inflammatory cytokines, exert an important role [36]. Minocycline could modulate microglial activation [12, 37] and reduce pro-inflammatory cytokines (i.e. tumour necrosis factor (TNF)-α, interleukin-1β and glucocorticoids), which is associated with the improvement of depressive and anxiety symptoms [38].

The recent meta-analysis [22] with 3 RCTs ($n = 158$) [19–21] found a significant antidepressant effect of minocycline (SMD = -0.78), which is inconsistent with our findings which included one additional study with 53 patients [18]. This study [18] focused on patients with bipolar depression, which could increase the study heterogeneity. Further, unlike the prior meta-analysis [22], study quality assessment using Jadad scale and the grading of recommendations of meta-analytic outcomes using GRADE analyses were included in this meta-analysis.

The following limitations need to be acknowledged. First, although broad study entry criteria were used, the number of studies and sample sizes were still relatively small, which

Table 2 Secondary outcomes

Variables	Studies (subjects)	RRs (95%CI)	I^2 (%)	P
Response				
(≥50% reduction in HAMD or MADRS score	3 (133)	1.94 (0.93, 4.04)	12	0.08
Discontinuation rate:				
Discontinuation due to any reason	4 (211)	1.48 (0.79, 2.77)	0	0.22
ADRs:				
Abdominal pain	3 (158)	1.96 (0.71, 5.39)	0	0.19
Diarrhea	2 (117)	0.63 (0.15, 2.61)	0	0.52
Dizziness	2 (117)	1.26 (0.55, 2.89)	0	0.59
Fast/irregular heartbeat	2 (112)	1.98 (0.27, 14.74)	0	0.51
Headache	3 (158)	1.29 (0.30, 5.68)	31	0.73
Insomnia	2 (112)	0.32 (0.03, 2.99)	0	0.32
Myalgia	2 (87)	0.88 (0.28, 2.78)	0	0.82
Nausea	3 (163)	1.68 (0.57, 4.96)	0	0.35
Rash	2 (117)	0.88 (0.26, 2.95)	0	0.84

Abbreviations: *ADRs* adverse drug reactions, *CI* confidence intervals, *RRs* risk ratios

limits the capacity to assess publication bias. Second, heterogeneous diagnoses in the four studies (MDD, bipolar disorder and HIV infection) were included. Third, the treatment duration was relatively short (6–12 weeks), thus long-term effects of minocycline could not be examined.

Conclusions

Minocycline appears to be effective and safe in treating depressive symptoms in unipolar depression. Future large RCTs of sufficient duration is needed to confirm the positive effects of minocycline in treating depressive symptoms.

Authors' Contributions Study design: YTX; Data extraction: DBC and WZ; Data analysis: WZ and QEZ; Drafting of the manuscript: DBC, WZ and YTX. Critical revision of the manuscript: CHN and GSU; Approval of the final version for publication: All the author.

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Availability of Data and Material The data of this article are included within the article.

Compliance with Ethical Standards

Ethics Approval and Consent to Participate Not applicable.

Consent for Publication Not applicable.

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

Abbreviations *ADRs,* Adverse drug reactions; *BDI,* Beck Depression Inventory; *BP-I,* Bipolar I disorder; *BP-II,* Bipolar II disorder; *BP-NOS,* Bipolar disorder not otherwise specified; *CI,* Confidence interval; *DB,* Double blind; *DSM-IV,* Diagnostic and Statistical Manual of Mental Disorders 4th edition; *DSM-IV-TR,* Diagnostic and Statistical Manual of Mental Disorders 4th edition, Text Revision; *DSM-5,* Diagnostic and Statistical Manual of Mental Disorders 5th edition; *FD,* Fixed dosage; *GRADE,* grading of recommendations, assessment, development, and evaluation; *HAART,* Highly Active Antiroviral Therapy; *HAMD,* Hamilton Depression Rating Scale; *HAMD-17,* Hamilton Depression scores 17-item; *HIV,* Human Immunodeficiency Virus; *ITT,* intent to treat; *MADRS,* Montgomery-Asberg Depression Rating Scale; *MDD,* Major depressive disorder; *MINO,* Minocycline; *NR,* Not report; *OC,* Observed cases; *Pbo,* Placebo; *PRISMA,* Preferred Reporting Items for Systematic Reviews and Meta-Analyses; *RCTs,* randomized controlled trials; *RR,* Risk ratio; *SMDs,* Standardized mean differences; *STAR*D,* The Sequenced Treatment Alternatives for the Relief of Depression; *T,* Total; *TAU,* Treatment as usual; *TRD,* Treatment-resistant depressive symptoms; *wks,* Weeks; *yrs,* Years

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