Systematic Review and Meta-Analysis

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Minocycline in depression not responding to first-line therapy

A systematic review and meta-analysis

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Abstract

Background: Major depressive disorder is often resistant to first-line treatment, with around 30% failing to respond to traditional therapy. Treatment-resistant depression results in prolonged hospitalization and healthcare costs. Anti-inflammatory drugs have shown promising results in depression not responding to initial therapy. Minocycline has anti-inflammatory properties and crosses the blood-brain barrier. It has demonstrated varied results in several randomized controlled trials (RCTs).

Methods: We assessed the efficacy of minocycline compared to placebo in depression not responding to one first-line antidepressant via a systematic review and meta-analysis. We performed a comprehensive literature search across PubMed, Cochrane, and Scopus for RCTs. We visualized the results using forest plots and drapery plots. We assessed and explored heterogeneity using I^2, prediction interval, and meta-regression. Then, we rated the certainty of the evidence.

Results: Four RCTs revealed a non-significant difference in depression severity [–3.93; 95% CI: –16.14 to 8.28], rate of response [1.15; 0.33–4.01], and rate of remission [0.94; 0.44–2.01]. However, the reduction in depression severity is significant at a trend of $P < .1$. The high between-study heterogeneity ($I^2 = 78\%$) for depression severity could be answered by meta-regression ($P = .02$) for the duration of therapy.

Conclusion: There is no significant difference with minocycline compared to placebo for depression not responding to first-line antidepressant therapy. However, the treatment response varies with treatment duration and patients' neuroinflammatory state. Thus, larger and longer RCTs, especially in diverse disease subgroups, are needed for further insight. This is needed to allow greater precision medicine in depression and avoid elevated healthcare expenditure associated with hit-and-trial regimens.

Registration: CRD42023398476 (PROSPERO).

Abbreviations: CRP = C-reactive protein CRP, DALYs = disability-adjusted life years, GRADE = Grading of Recommendations Assessment, Development, and evaluation, MDD = major depressive disorder, NSAIDs = non-steroidal anti-inflammatory drugs, PRISMA = preferred reporting items for systematic reviews and meta-analyses, RCTs = randomized controlled trials, SD = standard deviation, SRMA = systematic review and meta-analysis, TRD = treatment resistant depression.

Keywords: antidepressants, antidepressive agents, anti-inflammatory agents, depressive disorder, depressive disorder, treatment resistant

MAS, SM, & PD contributed equally to this work.

The authors have no funding and conflicts of interest to disclose.

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

It is not applicable here since it is a systematic review and meta-analysis of publicly available data.

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1. Introduction

Depressive disorders constitute a major health issue with a rapidly increasing burden. Its prevalence has increased by over 60%, from 170.8 million in 1990 to 279.7 million in 2019. Mental disorders constituted the 13rd highest contributor of disability-adjusted life years (DALYs) in 1990 at 80.8 million DALYs comprising just over 3% of the global DALYs. The burden has increased to 125.3 million DALYs in 2019, now comprising almost 5% of the global burden, representing an over 50% increase. Depressive disorders are the biggest contributor (37.3%) to the burden of mental disorders.[1] The World Health Organization estimated that by 2030, major depressive disorder (MDD) would overtake all other diseases as the third leading contributor to the global burden of diseases.[2] And it is currently the leading cause of disability globally,[3] more so in war-torn countries.[4] Among the most prevalent psychiatric conditions in both specialized and general medical practice are major depressive disorder (MDD) and related mood syndromes. These syndromes manifest at various stages of life and with diverse combinations of symptoms. There is a high variability in vulnerability, age of onset, predisposing conditions, clinical features, and comorbidity status. As a result, MDD is a highly varied disorder,[5] with around 30% of patients resistant to traditional therapy.[6]

Over 100 million people are expected to suffer from treatment resistant depression (TRD). The estimate of TRD could go even higher if more comprehensive criteria with patient-reported outcomes are considered.[7] Compared to MDD, TRD is associated with more outpatient visits, emergency visits,[8] admissions, duration of hospitalization,[9] all-cause deaths, and suicide-specific deaths,[10] along with a worse quality of life.[11] It is also associated with higher healthcare expenditure[12] and healthcare resource utilization.[12] Hospitalizations and healthcare expenditure show a linear trend as the number of failed antidepressants for a patient increases.[13] Absenteeism contributes to nearly 70% of the total cost during a major depressive episode in a patient with TRD.[14] The classical therapy targeting monoaminergic neurotransmitters fails in many patients. Treatment-resistant depression (TRD) occurs when a patient with unipolar depression fails to respond to sufficient antidepressant therapy. The definition for TRD varies, with some defining it as failure of one first-line option, and some defining it as failure of 2 first-line options. A clearer definition is required.[15] However, depression not responding to initial therapy can result in prolonged and costly inpatient hospitalization.[16] The continued agony from these symptoms can also impair their quality of life and work productivity. And treatment failure is so common in depression that in this landmark trial, more than 50% of the patients did not respond to the first-line therapy.[17] It is seen that psychiatric conditions are the primary driver of mortality in TRD patients.[18] Along with the previously described burden of TRD, caregivers of patients with TRD had a better quality of life if the patients remitted than if they were symptomatic. Moreover, the caregivers experienced various work, performance, and cognition issues. Treatment of these patients helped the caregivers.[19] Given these public health implications of TRD and its treatment, optimal management of TRD is an important health concern.

Studies have tried to find neuro-biological evidence for TRD. More recently, there has been a great focus on the neuroimmunology of depression. Many studies have repeatedly linked the emergence of depression and resistance to depression with enhanced immune system activity.[20] Among biological predictors, improved immune system activity has been repeatedly linked to the emergence of MDD and TRD. Pro-inflammatory immunological markers have been found in depression patients.[21] Treatment with a proinflammatory marker (Interferon-alpha) has been linked to the emergence of depression in several studies. Patients with inflammatory disorders are also more likely to suffer from depression.[22] Furthermore, longitudinal studies show that elevated plasma levels of the pro-inflammatory cytokine predispose to depressive symptoms.[23,24] Innovative depression treatments should boost neuroprotective mechanisms and the compensatory immune-regulatory system. They can decrease the activation of oxidative, neuro-progressive, and immunological pathways.[25,26] Patients responding to antidepressants have lower neuroinflammatory markers compared to non-respondents.[27] These are just some of the findings hinting towards a link between peripheral inflammatory markers and response to antidepressant drugs.

Building up on these studies, recent clinical trials have explored the possible role of anti-inflammatory drugs in depression. Anti-inflammatory medications (e.g., Non-steroidal Anti-inflammatory Drugs (NSAIDs) and cytokine inhibitors) have been tested as monotherapy[28,29] or as adjuvant to antidepressants.[30–32] There is an improvement in depression in several studies.[29,33,34] A systematic review exploring both selective and nonselective cytokine inhibitors like NSAIDs has suggested that anti-inflammatory treatment—particularly celecoxib—improved depression without any particular safety concern..[35] However, the low quality of individual studies and significant heterogeneity was found in the meta-analysis, suggesting further evaluation.[35] Different studies with NSAIDs provided contrasting results, with some showing benefit[30,31] while some showing a lack of benefit.[36]

Despite these findings, we need to exercise extra caution. Patients with depression have a high prevalence of comorbid physical illnesses. In this setting, treatment with anti-inflammatory agents might increase the risk of adverse side effects. This leads to treatment discontinuation.[37] For instance, NSAIDs and cytokine inhibitors are associated with infections,[38] cardiovascular adverse events,[39] and gastrointestinal adverse events.[40] So, research is needed on innovative treatment options targeting the inflammatory aspect of neuroinflammation alternately and more safely.[41]

In this regard, Minocycline has been explored for its potential role in the treatment of TRD. Minocycline is derived from tetracycline, one of the earliest discovered antibiotics. However, minocycline has several structural differences that lead to altered pharmacokinetics and pharmacodynamics. It has higher absorption and a longer half-life. More importantly, for depression, the altered structure also allows blood-brain barrier penetration. Here, it is seen to suppress microglial activation.[42] Depression involves an imbalance between the pro-inflammatory M1 microglia and the anti-inflammatory M2 microglia. Minocycline suppresses M1-phenotypic microglia, restores neurogenesis, and corrects the neuroinflammatory markers. It decreases tumor necrosis factor alpha and interleukin-1-beta.[43] It inhibits the microglial and neuronal release of high mobility group box 1.[44] Minocycline also suppresses several matrix metalloproteases.[45] This decreases ongoing

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neuroinflammatory damage and demyelination.[46] Moreover, it alters pro-apoptotic, anti-apoptotic, and neurotrophic mediators.[47] It also increases neuroprotective retinoid signaling and has overall neuroprotective properties.[48] These potentially beneficial actions of Minocycline led to it being assessed in several diseases involving the central nervous system, including depression.[46]

Apart from this direct action, Minocycline might reduce depression by modulating the gut-brain axis, too.[49] Alongside its action on apoptosis, oxidation, and modulation of glutaminergic and monoaminergic neurotransmission, it directly affects the serotonergic system in several ways.[50–52] It reduces both the production of serotonin[53] and its availability in the synapse[54] by targeting the *P*-38 and the kynurenine pathways, respectively. Given the link between neuroinflammation and treatment resistance, and the effect of minocycline on neuroinflammation, minocycline is a promising option in treatment-resistant depression. Thus, the drug minocycline has been suggested to have potential antidepressant properties. Randomized controlled trials (RCTs) have demonstrated that minocycline has a varying response in treating the depression of MDD patients.[55–57]

Even though the results are promising, they are only preliminary. Moreover, the small sample sizes of these studies, between-study heterogeneity, and variable results restrict direct conclusions from the individual studies. This heterogeneity stems from the patient groups, severity of depression, length, and manner of treatment.

Furthermore, these clinical trials have not yet been thoroughly reviewed. There appear to be few existing syntheses[58–63] of the evidence on minocycline in this domain, but they miss out on most of the included studies,[64–67] which is crucial in an upcoming area where studies are very few. Moreover, there are methodological issues like the lack of a prediction interval to explain clinical utility and the expected variability in response in a clinical setting.[68] There are no graded recommendations to serve as takeaway for clinicians and health professionals. The effect of treatment duration on response has not been studied well enough, thus not adequately addressing or explaining the observed heterogeneity.[69] Thereby, this study aims to conduct a systematic review and meta-analysis to optimally summarize and quantify available evidence on the effect of minocycline in depression not responding to first line treatment.

2. Methods

The systematic review and meta-analysis (SRMA) answers the following research question: "What is the efficacy of minocycline versus placebo in depression not responding to first line therapy?" following the 2020 Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (Annexure 1, http://links.lww.com/MD/K554).[70]

2.1. Study selection criteria

The study answers the following research question: "What is the efficacy of minocycline versus placebo in depression not responding to first line therapy?" following the 2020 Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (Annexure 1, http://links.lww.com/MD/K554).[70] To answer this question, we systematically searched the literature and identified articles based on the eligibility criteria defined in a PICOS format (Annexure 2, http://links.lww.com/MD/K555). We included all studies on patients with depression who did not respond to the first line of antidepressant therapy. One group of patients should have been administered minocycline while the other group should have been administered placebo. There is no restriction on the standard care in both the groups. We only included RCTs, and excluded non-randomized interventional studies, observational studies, and reviews. This study was registered prospectively at an openly accessible registry, with the record ID CRD42023398476.

2.2. Systematic search and data extraction

A systematic search was carried out across 3 databases of published literature: PubMed, Scopus, and Cochrane, on 14.02.2023. MAS prepared the search strategy for PubMed using medical subject headings terms and Boolean operators according to this extension to the PRISMA statement.[71] Another author (SM) reviewed this search strategy per the Peer Review of Electronic Search Strategies checklist.[72] Additionally, we searched the gray literature by searching several preprint servers like Medrxiv, Biorxiv, Arxiv, and SSRN. We supplemented it with a search in Google and Google Scholar. This was complemented by a review of clinical trial registries like ClinicalTrials.gov, International Clinical Trials Registry Platform (World Health Organisation), and Clinical Trials Registry—India. On top of that, we manually screened the references of eligible and other relevant articles. After that, we searched for records by forward citation matching. To ensure accountability and enhance reproducibility, we have reported the search strategy across all 4 databases in Annexure 3, http://links.lww.com/MD/K556. This was built scientifically, including medical subject headings words, keywords, and truncated terms. For managing extracted reports, we used Mendeley Desktop (V1.19.5).

2.3. Screening and data extraction

Two independent authors (MAS & SM) reviewed the title and abstracts. Potentially eligible reports were identified for full-text screening by the same authors. The 4 included reports were taken up for data extraction using a datasheet containing columns on bibliographic information, study characteristics, baseline data, information on intervention, and outcome parameters. In case of any disagreement, the coauthors discussed to build consensus. A PRISMA flowchart summarizes the complete screening report process (Fig. 1).

2.4. Statistical analysis

We have synthesized the evidence on response, remission, and depression severity. The response was defined as a 50% reduction in the depression score, as reported by the study. Remission is the absence of symptoms and is assessed according to the known threshold for validated depression severity scoring systems.

Response and remission are the proportions of participants who have responded or remitted in each arm. These have been described as risk ratios. These were log-transformed and synthesized using the Mantel-Haenszel method.[74]

The severity of depression has been expressed as the mean and standard deviation (SD) of the score in Hamilton Depression Rating Scale. A variable was missing in one of the studies.[64] The mean was available, but the standard deviation of the post-treatment score was not given. However, this was missing in only one of the 4 studies. And the pretreatment SD and mean difference SD were known. So, we imputed the SD following existing guidelines.[75] We synthesized the mean scores using the inverse variance method.[76] The analyses were carried out using meta,[77] and metafor[78] packages in R v4.2.1.[79]

For the assessment of heterogeneity, we focused on demonstrating the prediction interval for the true outcomes.[80] Given the current evidence, this gives us a range into which the results of future studies are expected to fall. We used the Paule-Mandel estimator[81] for estimating tau-squared for risk ratios, restricted maximum likelihood estimator[82] for estimating tau-squared for mean difference, and Q-profile[83] for determining the confidence interval of tau-squared in both the cases. For synthesis, we

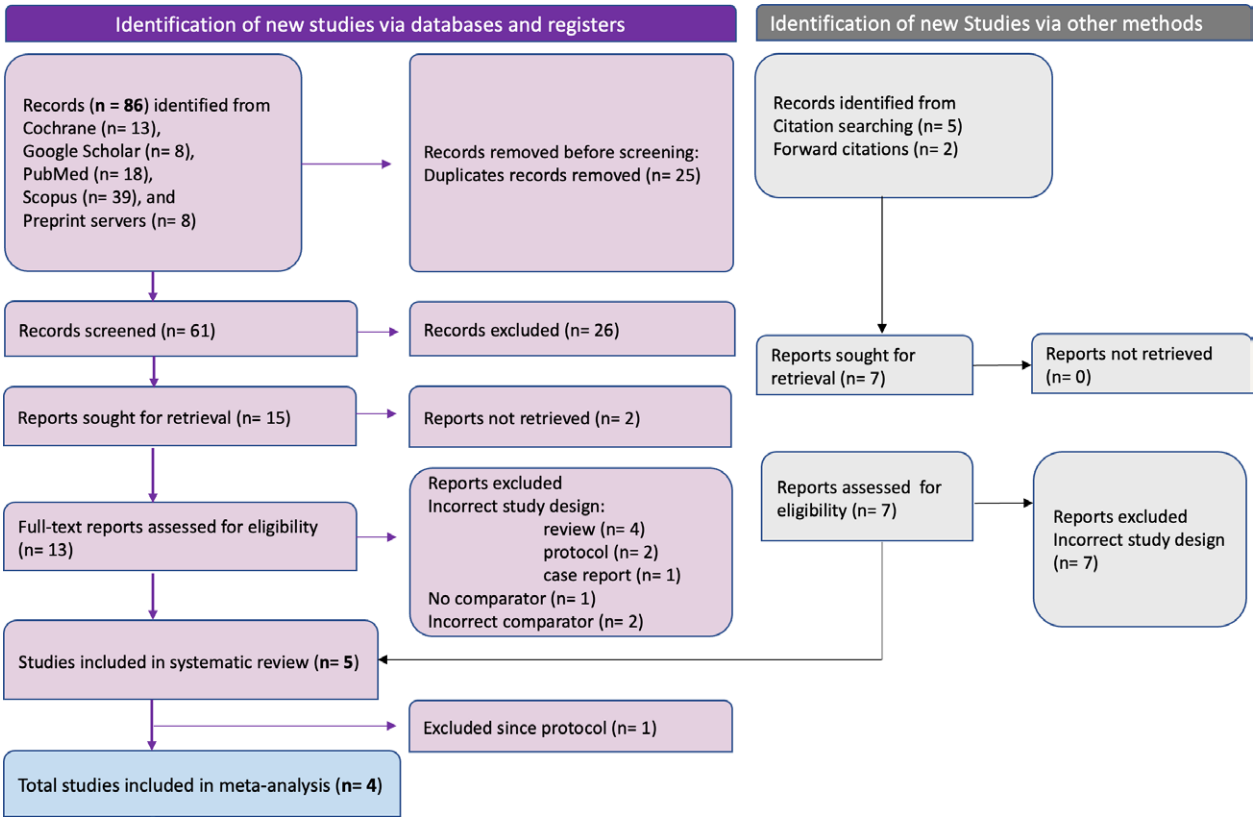

Figure 1. PRISMA flow chart detailing the literature search, and providing reasons for exclusion of studies. PRISMA = preferred reporting items for systematic reviews and meta-analyses.

employed a fixed-effects or a random-effects model depending on the data and the between-study heterogeneity. In the case of a random-effects model, Knapp-Hartung adjustments[84] help control the uncertainty in estimating between-study heterogeneity, reducing false-positivity[81] with less studies.[81]

The pooled estimate has been expressed using forest and drapery plots. Forest plots are the conventional and more commonly interpreted method of summarizing the results of a meta-analysis. Drapery plots complement the inference drawn from a forest plot.[85] The limitation of the former is that they only display the result at a single fixed threshold for the level of significance, usually $P < .05$. We can avoid this controversial sole reliance on a single level[86] and instead use *P*-value functions. This helps us visualize the results across a wide range of confidence intervals corresponding to diverse p-values. Moreover, the studies are presented in a logical sequence, and the overall trend can be easily observed, along with assessing small-study effects and heterogeneity.

We have used a trim-and-fill imputed,[87] contour-enhanced funnel plot for a more precise idea of publication bias and small-study effects. We use contours of different colors (shades of gray) to assess the funnel plot at different levels of significance, that is, 0.90, 0.95, 0.99, corresponding to *P* values of .1, .05, and .01, respectively.[88] The trim-and-fill method removes the outlying studies by trimming them and then imputes the purported missing studies.

We intended to perform a sensitivity analysis by omitting the studies with a moderate or higher risk of bias. Moreover, we performed another sensitivity analysis by the leave-one-out method.

The study outcomes were explored for causes of high heterogeneity. We have used a mixed-effects model for the meta-regression, with the duration of therapy as a prespecified suspected moderator.[89]

2.5. Quality, bias, and evidence certainty assessment

Two independent authors (M.A.S. & S.M.) assessed the risk of bias in the eligible reports. For each included outcome in the individual reports, we answered signaling questions. This led to assessing the study quality under 5 distinct domains, as recommended by the Cochrane Risk of Bias v2.0 tool.[73] Ultimately, this produced the judgement for an overall risk of bias. Then, the synthesis was done after integrating these judgements. GRADE (grading of recommendations assessment, development, and evaluation) helps assess the certainty in the synthesized evidence.[89]

2.6. Ethical statement

Ethical review is not applicable here since this is an SRMA of publicly available data.

3. Results

The literature screening process can be visualized in the PRISMA flowchart (Fig. 1). After a systematic search according to the search strategy (Annexure 3, http://links.lww.com/MD/K556), we searched for literature across 4 databases, gray literature, and clinical trial registries. Then, we retrieved 15 full texts and selected 5 for the systematic review. One is an ongoing randomized controlled trial (RCT); thus, the remaining 4 are considered for quantitative evidence synthesis.[64–67]

Amongst other studies, a cluster RCT compared minocycline to celecoxib in a factorial trial.[90] And a study in the USA was a single-group interventional study with no comparator group.[91] Researchers in Italy published a case report of 2 patients with TRD.[92] So, we excluded these studies. http://links.lww.com/MD/K572

3.1. Study characteristics

We have included 4 blinded RCTs from 2017 to 2022 and 1 ongoing study. The RCTs are from Canada,[64] Germany,[65] Pakistan,[67] and the United Kingdom,[66] and their sample sizes range from 21 to 139. The ongoing study[93] is also taking place in Canada, headed by the researcher who published the pilot study[67] from Pakistan. We have summarized the studies' baseline characteristics and outcomes in Table 1.

3.2. Pooled estimate

We have pooled 3 outcomes reported in multiple studies: depression severity (as assessed by Hamilton Depression Rating Scale), response rate, and remission rate. The depression severity is 3.93 points lower [95% CI: 16.14 points lower to 8.28 points higher] in the minocycline group compared to the placebo. The pooled response rate to treatment with minocycline versus placebo (as risk ratio) is 1.15 [95% CI: 0.33–4.01]. The pooled ratio of remission rate with minocycline versus placebo is 0.94 [95% CI: 0.44–2.01]. The other details, including the method of meta-analysis, domain-wise risk of bias assessment, and the prediction intervals, are summarized in Figure 2. The wide confidence interval can be attributed to the usage of Knapp-Hartung adjustments. Though this reduces the false positive rate,[81] it is also over-conservative with respect to the confidence interval of the pooled estimate.[94]

We have also provided the drapery plots for a better and more comprehensive meta-analysis visualization [Fig. 3, Annexures 4a–4b, http://links.lww.com/MD/K557, http://links.lww.com/MD/K558]. The p-values are plotted along the y-axis, and the effect estimates are plotted along the x-axis. We can visualize the results across a range of significance values. The thin lines represent the individual studies, while the thick line represents the pooled estimate along with its confidence interval at a particular threshold of the significance level. The peak of these lines represents the exact effect size. We can visualize the prediction interval by the shaded region and see its trends at different p-values. We can observe in Figure 3 that the decrease in depression severity may not be significant at the threshold level of 5 % type-1 error, but it is significant on a trend level of $P < .1$.

3.3. Publication bias

We have used trim-and-fill contour-enhanced funnel plots to assess publication bias and small-study effects. (Annexures 5a-5c, http://links.lww.com/MD/K559, http://links.lww.com/MD/K560, http://links.lww.com/MD/K561). We could not detect any outliers for the remission rate. For the outcome of depression severity and response rate, there was some asymmetry due to which studies were imputed in the final funnel plot. However, the number of studies is less; and most studies fall under enhanced contours. We do not suspect small-study effects, publication bias, or treatment fidelity. Moreover, funnel plots are not usually employed when the number of studies is less than ten.

3.4. Sensitivity analysis

We have performed a leave-one-out sensitivity analysis for the outcomes reported in more than 2 studies. This did not lead to any of the effect sizes becoming significant (Annexures 6a-6b, http://links.lww.com/MD/K562, http://links.lww.com/MD/K563).

We did not perform any subgroup analysis because of the smaller number of studies. However, with RCTs answering this research question in the pipeline, we might have greater evidence on this question a few years later.

Table 1

Summary of reports on efficacy of minocycline vs placebo in depression not responding to first line therapy (N = 5).

Authors	Yr	Country	Dosage schedule	Duration of therapy (wk)	Outcomes			
					Post-treatment HAMD-17 score (mean ± SD)	Reduction in HAMD-17 score (mean ± SD)	Proportion of patients partially responded	Proportion of patients responded	Proportion of patients remitted
Attwells et al	2021	Canada	50 mg once per d (wk 1), 50 mg twice per d (wk 2), 100 mg twice per d (wk 3–8)	8	M: 14.5 P: 14.2	M: 5.7 P: 7.1	-	M: 2/12 P: 3/9	M: 1/12 P: 2/9
Hellmann-Regen et al	2022	Germany	100 mg twice per d	6	M: 13.1 ± 5.9 P: 14.2 ± 6.7	M: 6.9 P: 6.1	-	M: 14/81 P: 21/87	M: 10/81 P: 10/87
Husain et al	2017	Pakistan	100 mg daily (wk 1–2) 200 mg daily (wk 3–12)	12	M: 15.1 ± 13.2 P: 32 ± 11.8	M: 18.3 ± 16.4 P: 0.2 ± 16.1	-	M: 10/16 P: 4/18	Odds ratio of 7.3 (M v/s P)
Nettis et al	2021	United Kingdom	200 mg once per day	4	M: 13.44 ± 5.17 P: 14.1 ± 5.59	M: 5.62 P: 2.9	M: 8/18 P: 9/21	M: 3/18 P: 2/21	-
Husain et al	2020	Canada	100 mg daily (wk 1) 200 mg daily (wk 2–12)	12	This is the protocol for an RCT currently enrolling participants, and is expected to be complete by April, 2023 [NCT03947827].				

HAMD-17 = Hamilton Rating Scale for Depression, M = minocycline, P = placebo, SD = standard deviation, RCT = randomized controlled trial.

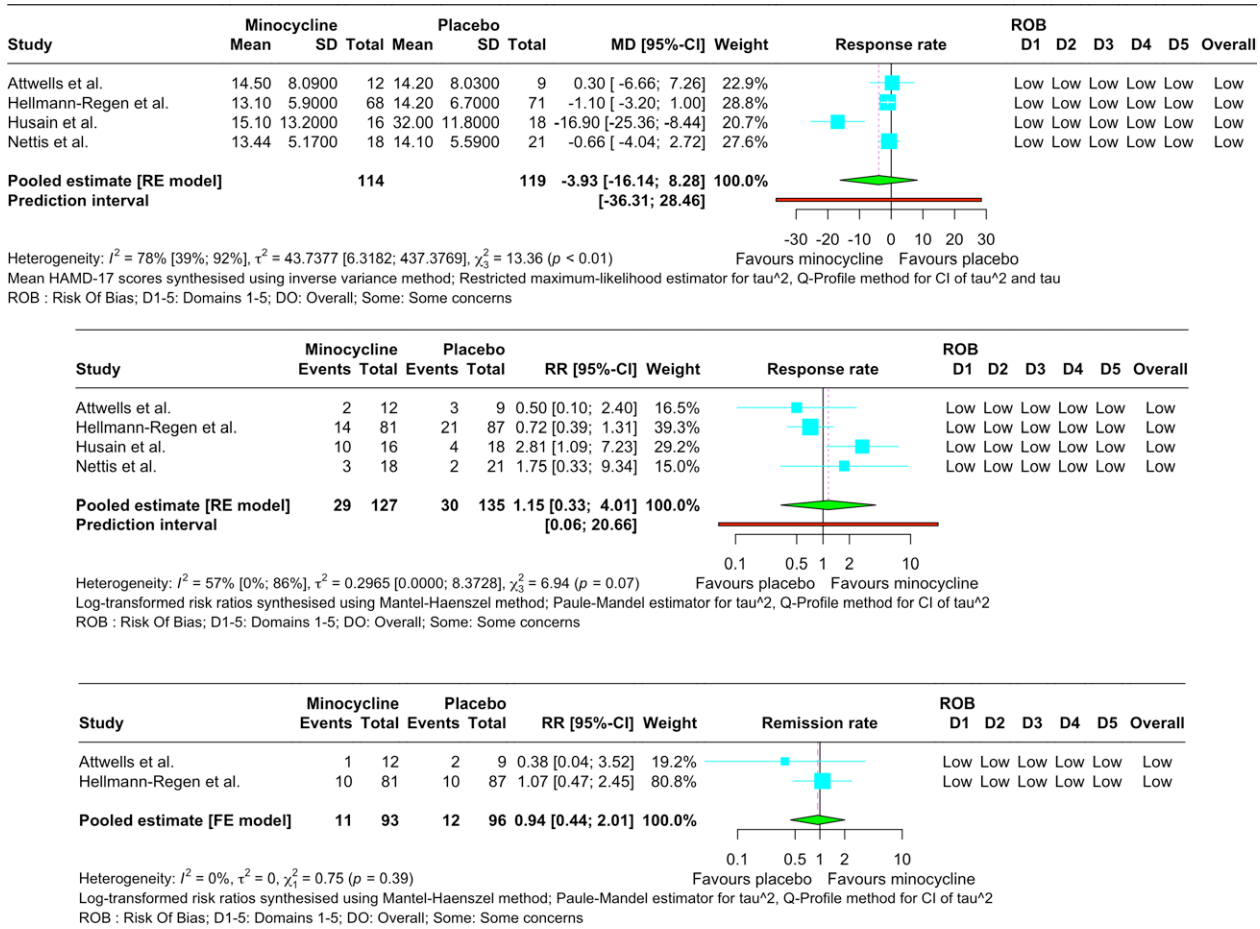

Figure 2. Forest plot showing the pooled outcome measures with minocycline versus placebo in depression not responding to first line therapy.

3.5. Meta-regression

We performed meta-regression for depression severity and rate of response based on the effect of the duration of therapy. This was a significant moderator (P < .05) for the change in depression severity, and it accounted for 77.69% of the heterogeneity. The duration of therapy, however, could not explain the variability in the response rate (test of moderators: P = .31).

We visually demonstrated the findings through a bubble plot (Fig. 4, Annexure 7, http://links.lww.com/MD/K564). A detailed summary of the meta-regression can be found in Annexure 8, http://links.lww.com/MD/K565.

3.6. Risk of bias

In both the outcomes of this study,[66] we answered the first 2 signaling questions under the third domain negatively. This is because of some missing data. However, we judged this missingness to be independent of the true outcome value. Thus, this constituted a low risk of bias. There was a low overall risk of bias for all the outcomes.

Traffic-light plots demonstrate the domain-wise assessments in Annexures 9a-9c, http://links.lww.com/MD/K566, http://links.lww.com/MD/K567, http://links.lww.com/MD/K568. A summary of the risk of bias assessments is attached in Annexures 10a-10c, http://links.lww.com/MD/K569, http://links.lww.com/MD/K570, http://links.lww.com/MD/K571.

3.7. GRADE assessment

We have summarized the recommendations using GRADEpro.[95]

The recommendations are displayed as a summary of findings in Annexure 11, http://links.lww.com/MD/K572. There is low certainty in the effect of Minocycline versus placebo for treatment-resistant depression.

4. Discussion

Our SRMA aimed to evaluate the effectiveness of Minocycline on depression not responding to first line therapy. This is the first SRMA that summarized data from all published RCTs in a robust manner to assess its efficacy. Four RCTs were included in this meta-analysis. In this study, the change in depression severity [mean difference: −3.93; 95% CI: −16.14 to 8.28], response rate [RR: 1.15, 95% CI: 0.33–4.01] and remission rate [RR: 0.94, 95% CI: 0.44–2.01] were assessed, and none were statistically significant. However, depression severity reduced on a trend of P < .1.

Existing literature on the antidepressant impact of Minocycline on depression and other psychotic diseases revealed that Minocycline demonstrates a significant increase in improvement in depressive symptoms when compared to placebo.[58] However, the results are not replicated in our SRMA. Minocycline isn't significantly better regarding any of the outcomes in treatment-resistant depression. But continuing from our previous discussion on the controversy around choosing an arbitrary significance threshold of 0.5, the study also reports that the pooled estimate of depression severity is lower in the minocycline group compared to the placebo at a significance threshold of P < .1. This suggests that future studies can easily influenced the pooled estimate. Moreover, the wide prediction intervals suggest that further studies shed more light on its utility. This results of this ongoing RCT are awaited and spark a hope for more data and insights.[93]

The included studies differed amongst themselves with varying responses. The only study[67] that shows a positive effect

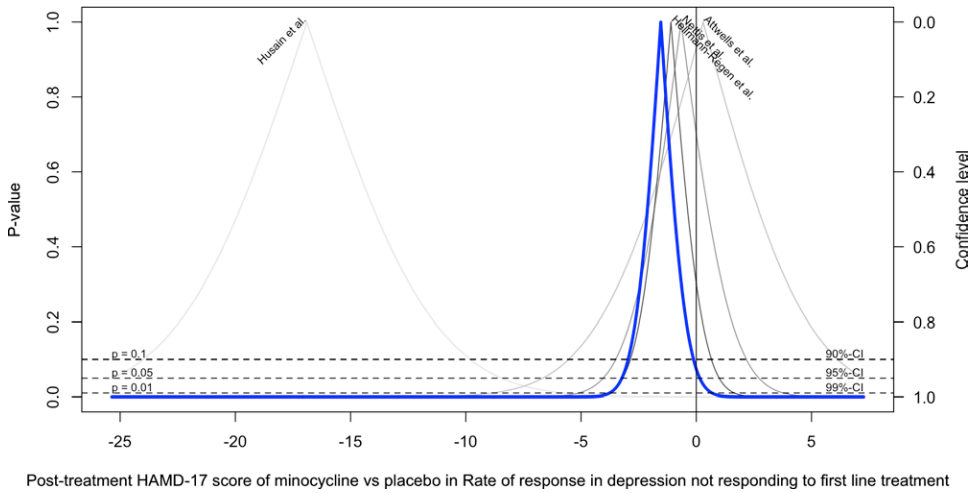

Figure 3. Drapery plot showing the "level of significance"–dependent variation in depression severity with minocycline versus placebo in depression not responding to first line therapy.

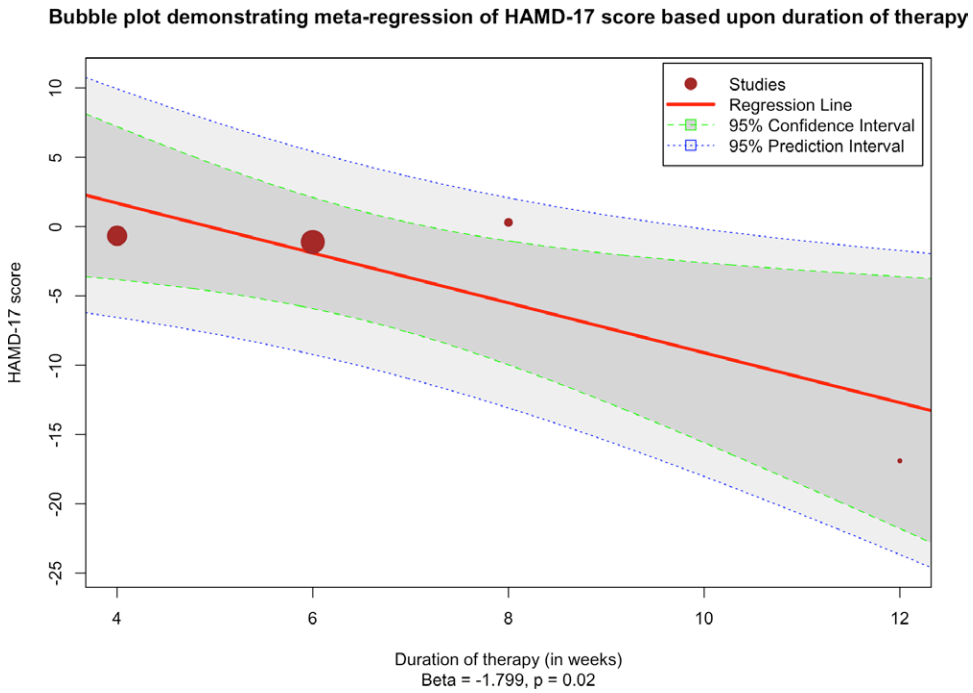

Figure 4. Bubble plot demonstrating the meta-regression of depression severity with minocycline versus placebo in treatment-resistant depression based upon duration of therapy.

also had a much longer duration of therapy (12 weeks) compared to the other 3 studies at 4 to 8 weeks. This finding was reinforced by meta-regression wherein the duration of treatment is seen to moderate the decrease in depression severity.

Here,[66] patients were stratified according to a cutoff of 3 mg/mL serum C-reactive protein (CRP). Though the outcomes weren't positive overall, the response with Minocycline was best in those with higher CRP, suggesting its role in reduction of overall neuro-inflammation and subsequent reduction of depressive symptoms. They further divided the participants into 4 groups based upon intervention (Minocycline or placebo) and CRP level (higher or lower). And the patients receiving Minocycline and having elevated CRP demonstrated the highest reduction in depression severity. The least reduction is in those receiving placebo and having lower CRP. This clearly demonstrates that minocycline may be especially useful in TRD cases with coexisting neuroinflammation. However, other studies have not investigated or evaluated simultaneously inflammatory markers and depressive symptoms. Minocycline response in both aspects cannot be concluded concretely from a single study finding. If further similar studies explore both the length of the disease and the treatment strategy (i.e., corroborating with and without inflammatory markers levels), some interesting insights may be uncovered.

Regarding quality of these studies, all were of good to fair quality. We were not able to report any significant small-study effects or publication bias. However, one must consider the limited number of studies available on this molecule.

We suggest more RCTs with greater sample size are needed to establish the antidepressant efficacy and tolerability of

minocycline in patients with depression not responding to first line therapy. Since a highly personalized treatment plan is preferred in depression,[96] it would be further intriguing to explore if there are any casual or definite link between response of depressive symptoms to minocycline and inflammatory markers response. Future research should also try to examine which patient subgroups are most likely to experience an antidepressant impact from minocycline (such as those with multiple physical comorbidities, patients with recurrent depressive disorder or those with first episode depression). We recommend further investigating the causal connections between the biomarkers and minocycline therapy.

There were few limitations to the present study. The most important drawback was the small sample size, as only 4 RCTs qualified for inclusion in the quantitative synthesis. However, more RCTs are not available, and one is currently ongoing. With more RCTs expected in this topic, updated evidence can refresh the findings. Because of this, our results may only serve as a proof-of-concept for minocycline antidepressant properties. The analysis covered both types of studies where minocycline is used alone or as an add-on agent.

5. Conclusion

Preliminary evidence regarding the efficacy of minocycline in treatment-resistant depression shows a lack of statistically significant difference. Though there is no benefit with response and remission, but depression severity shows a trend of benefit. However, the efficacy depends on the neuroinflammatory status of the patient and duration of therapy. Further trials, with longer duration and in special patient subgroups like those with proven elevated neuroinflammatory markers, can give more insights. This can lead to greater precision medicine for depression, improving patient outcomes, avoiding treatment failure, and reducing unnecessary healthcare expenditure associated with hit-and-trial of different antidepressants.

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