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ABSTRACT

Introduction Due to the anti-inflammatory, antioxidant and anti-apoptotic properties of minocycline, clinical trials have evaluated the potential of this drug to treat several psychiatric and neurological disorders, including major depressive disorder, schizophrenia, bipolar disorder, stroke and amyotrophic lateral sclerosis. This protocol proposes a systematic review (and potential meta-analysis) that aims to identify and critically evaluate randomised controlled trials of minocycline for treating psychiatric and neurological disorders.

Methods and analysis PubMed, Embase, Cochrane Central Register of Controlled Clinical Trials, PsycINFO and Cumulative Index to Nursing and Allied Health Literature (CINAHL) will be used to identify randomised controlled trials that used minocycline to treat psychiatric and neurological disorders. Double-blind, randomised, controlled, clinical trials of participants aged 18 years or older and written in English will be included in the review. Data will be extracted by two independent reviewers. Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines will be followed and the Cochrane Collaboration's 'Risk of Bias' tool will be used to assess the risk of bias in all studies included in the systematic review. The Grading of Recommendations, Assessment, Development and Evaluation system will be used to access the overall quality of the level of evidence of the studies. If sufficient evidence is identified, a meta-analysis will be conducted using the standardised mean difference approach and reported with 95% CIs. Heterogeneity of evidence will be evaluated using the I^2 model.

Ethics and dissemination This systematic review will evaluate only published data; therefore, ethical approval is not required. The systematic review will be published in a peer-reviewed journal and presented at relevant research conferences.

Trial registration number CRD42020153292.

Strengths and limitations of this study

- This systematic review will update and extend the evidence regarding the effects of minocycline in psychiatric and neurological disorders; this is the first review to present these two fields together.
- Data will be extracted by two independent reviewers.
- Rigorous screening processes and assessment of included studies will allow only for peer-reviewed publications.
- A potential limitation of this systematic review may be the lack of studies in some of the conditions, making it unfeasible to perform a meta-analysis.

INTRODUCTION

Minocycline (7-dimethylamino-6-demethyl-6-deoxytetracycline) is a second-generation semi-synthetic tetracycline antibiotic. It is used to treat several bacterial infections as well as severe acne and rheumatoid arthritis.[1] Minocycline is a highly lipophilic drug and can cross the blood–brain barrier.[2] It is well tolerated in humans with either acute or chronic use.[3]

Minocycline has been proposed as a novel intervention for psychiatric and neurological disorders due to its anti-inflammatory, antioxidant and anti-apoptotic properties, in addition to its ability to promote neurogenesis.[4–6] Several neuropsychiatric and neurologic disorders have been associated with neuroinflammation.[7–12] Minocycline is known to have inhibitory effects on microglial activation.[4] This inhibition aids to attenuate neuroinflammation and may be beneficial in preventing cognitive and behavioural impairments. In addition, the antioxidant properties of minocycline, including free-radical scavenging activity and inhibition of lipid peroxidation, have been described in several studies.[13 14] Minocycline also presents cytoprotective properties by reducing apoptosis. This can be explained at least in part by its effect on the expression of the anti-apoptotic B-cell lymphoma protein-2 (Bcl-2)

and antagonising pro-apoptotic proteins such as Bax, Bak and Bid.[15 16] This, in turn, suppresses the activation of caspases 1 and 3 and the release of apoptotic factors such as cytochrome c from mitochondria, reducing cell death.[15 16] Minocycline additionally enhances neurogenesis in several preclinical models.[17 18]

These aforementioned properties led to several studies designed to evaluate the potential of minocycline to treat several psychiatric and neurological disorders, including major depressive disorder (MDD), schizophrenia, bipolar disorder, stroke and amyotrophic lateral sclerosis (ALS). Regarding the current use of minocycline in psychiatry, there have been recent systematic reviews from Zheng *et al*[19] reporting that adjunctive minocycline treatment improved total symptoms in schizophrenia patients, but failed to demonstrate primary efficacy for bipolar depression and MDD. With respect to MDD, the findings of Zheng *et al* are in contrast to the work of Rosenblat and McIntyre which showed a positive effect of minocycline on depressive symptoms.[20] This can be explained by the fact that Zheng *et al* only included studies with minocycline as monotherapy and Rosenblat and McIntyre included studies where minocycline was an adjunctive treatment. Similarly, secondary outcomes were not explored by Zheng and colleagues. On the other hand Xiang *et al*[21] and Solmi *et al*[22] also demonstrated a potential positive effect of minocycline in schizophrenia.

In neurology, Malhotra *et al*[23] reviewed the effects of minocycline in acute ischaemic stroke (AIS) and acute intracerebral haemorrhage showing efficacy especially in the AIS group. The potential of minocycline in Parkinson's disease, Huntington's disease and ALS has been previously discussed in the literature; however to the best of our knowledge, no systematic review has been conducted to evaluate the effects of minocycline in these conditions.

In animal models, some deleterious effects of minocycline have been reported in the literature. Diguet *et al* suggest that minocycline may have deleterious effects in Parkinson's models according to the mode of administration and dose.[24] Vogt *et al* showed no antidepressant effects at doses from 20 to 40 mg/kg in a C57BL/6 mouse.[25] Minocycline ameliorated brain injury in developing rats, but worsened the injury in the developing C57BL/6 mouse.[26] Pro-apoptotic properties of minocycline were demonstrated in developing mouse brain, raising concerns of its use in children.[27]

There is clear justification to explore the potential use of minocycline across psychiatric and neurological disorders that share dysregulation in inflammation, oxidative pathways, apoptosis and neurogenesis. There are significant overlaps in pathophysiology between many psychiatric and neurological conditions. Minocycline potentially addresses these common factors, such as inflammation and oxidative stress.

Since the publication of earlier reviews[6 28] more data are available that may enhance the understanding of the clinical utility of minocycline across neuropsychiatry. More studies allow for exploration of secondary outcomes and subgroups, especially in disorders with high clinical heterogeneity such as depression. As mentioned earlier, there is no systematic evaluation of the use of minocycline in neurology; thus given its use in this field, bringing together the current evidence would be both timely and valuable. Therefore, there is value in exploring the evidence regarding the use of minocycline across fields to better understand its potential clinical usefulness.

OBJECTIVES

This systematic review aims to identify and critically evaluate randomised controlled trials of minocycline for treating psychiatric and neurological disorders. A comprehensive understanding of the current level of evidence in the literature will help clarify the clinical utility of minocycline in each disease and inform future research.

METHODS AND ANALYSIS

This systematic review will be conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[29] The Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) checklist is attached as online supplementary file 1. It will include randomised controlled trials of minocycline of any size and duration in adult populations (≥18 years). The design of the studies can be placebo or active-controlled, parallel group or cluster design. Studies which have included more than one pharmacological intervention will also be included, with the data being pooled when possible. Only studies published in English will be included. Additional information will be requested from the study authors if insufficient details are provided in the manuscript. All studies conducted to the present will be included.

The primary outcome of this systematic review will be improvement in core psychiatric or neurological symptoms after treatment with minocycline. Secondary outcomes include assessing the effects of minocycline treatment on quality of life, functioning, cognition, anxiety, disability, survival time and time to relapse. Adverse drug reactions and discontinuation rates will also be evaluated.

Search strategy

The PICO (Patient/Problem/Population, Intervention, Comparison/Control, Outcome) framework was used to develop the search strategy for this review. PubMed, Embase via embase.com, Cochrane Central Register of Controlled Clinical Trials via cochranelibrary.com, PsycINFO via EBSCO and CINAHL Complete via EBSCO will be used to search for the relevant literature up to March 2020. The appropriate index terms for each database will be used. The online supplementary file 2 shows the full search strategy for PubMed and will be adapted to fit with other databases. The references cited in the

included publications will be searched for additional studies. Studies published since journal inception to the date the searches are run will be included. The searches will be re-run prior to the final analyses and any further studies identified will be retrieved for inclusion.

The studies extracted from the search will be checked for eligibility based on a selection of criteria. First, the titles and abstracts will be assessed to determine if the study is a randomised controlled trial, investigating an intervention with minocycline and has been conducted on participants with a psychiatric or neurologic disease. Subsequently, the full-text papers will be reviewed. A second reviewer will evaluate all articles at each stage of screening. If there is disagreement regarding eligibility, a third independent reviewer will determine the conclusive decision.

Data management

An online reference management database, Covidence,[30] will be used to manage the data. Covidence allows abstracts and full text screening, handling of duplicate data, assessment of the risk of bias and extraction of the study outcomes based on inclusion and exclusion criteria.

Data will be extracted by two reviewers and it will include: (a) study identification details, (b) study design, (c) population characteristics, (d) intervention details, (e) outcome measurements, (f) information for assessment of the risk of bias. Authors will be contacted where substantial outcomes of interest are not reported and/or clarification about study design is required.

Assessment of methodological quality

The Cochrane Collaboration's 'Risk of Bias' tool will be used to assess the risk of bias in all studies included in this review.[31] This tool covers six domains of bias: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias and scores the randomised trials as low, high or unknown risk of bias. The overall quality of the level of evidence of the studies will be measured with the Grading of Recommendations, Assessment, Development and Evaluation system.[32]

Data synthesis and statistical analysis

A narrative synthesis of the findings will be reported, including population characteristics, type of outcome and intervention details.

If sufficient data are available, a meta-analysis will be performed for each diagnostic category.[30–33] For continuous data, mean differences or standardised mean differences with 95% CIs will be calculated. Dichotomous data will be analysed using risk ratios with 95% CIs. Mean differences will be used when the treatment outcome has been measured by the same scale. Standardised mean differences will be used when the treatment outcome has been measured by different scales in different studies. Sample size, SD and p values will be reported. Significance will be set at $\alpha \leq 0.05$.

To assess the statistical heterogeneity of evidence, I^2 will be used in accordance with the suggestions from the Cochrane Handbook for Systematic Reviews of Interventions 5.1.[34] Studies will be scored as low (I^2 value of 25%), moderate (I^2 value of 50%) or high (I^2 value of 75%).

Sensitivity analysis will be performed to evaluate the robustness of the meta-analysis outcome.

Subgroup analysis

The following subgroup analyses will be performed if sufficient data are available:

- Trial treatment duration.
- Effect of treatment at different doses.
- Patient demographics (age, gender and illness severity).
- Biomarkers of inflammation and oxidative stress.

Presentation and reporting of results

This review will follow the PRISMA-P guidelines[35] for reporting data. A PRISMA-P flow chart will describe study selection and numbers excluded at each stage of the process (and the appropriate reasons for exclusion).

Ethics and dissemination

Ethical approval is not required since this review will only include published data which already received ethical approval prior to publication. This review has been registered on PROSPERO. The results of this systematic review will be published in a peer-reviewed journal and presented at relevant scientific conferences.

No patient and public involvement

This research was done without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

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