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Glial-modulating agents for the treatment of pain: protocol for a systematic review

Ian Gilron ,[1] Maggie Z X Xiao ,[1] Marielle Balanaser,[1] Meg Carley ,[1] Nader Ghasemlou ,[1,2] Michael W Salter ,[3] Mark R Hutchinson ,[4] Dwight E Moulin,[5] R Andrew Moore,[6] Amanda Ross-White [7]

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For numbered affiliations see end of article.

Correspondence to
Dr Ian Gilron;
gilroni@queensu.ca

ABSTRACT

Introduction Evidence suggests a role for Central nervous system glia in pain transmission and in augmenting maladaptive opioid effects. Identification of drugs that modulate glia has guided the evaluation of glial suppression as a pain management strategy. This planned systematic review will describe evidence of the efficacy and adverse effects of glial-modulating drugs in pain management.

Methods and analysis A detailed search will be conducted on the Cochrane Central Register of Controlled Trials, Medline, and Embase from their inception until the date the final searches are run to identify relevant randomised controlled trials. The reference lists of retrieved studies, as well as online trial registries, will also be searched. English language, randomised, double-blind trials comparing various glial-modulating drugs with placebo and/or other comparators, with participant-reported pain assessment, will be included. Two reviewers will independently evaluate studies for eligibility, extract data and assess trial quality and potential bias. Risk of bias will be assessed using criteria outlined in the *Cochrane Handbook for Systematic Review of Interventions*. Primary outcomes for this review will include any validated measure of pain intensity and/or pain relief. Dichotomous data will be used to calculate risk ratio and number needed to treat or harm. The quality of evidence will be assessed using Grading of Recommendations Assessment, Development and Evaluation.

Ethics and dissemination This systematic review does not require formal ethics approval. The findings will be disseminated through peer-reviewed publications and conference presentations.

PROSPERO registration number CRD42021262074.

Strengths and limitations of this study

- This systematic review protocol follows the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols guidelines.
- To the best of our knowledge, this proposed systematic review will be the first to critically evaluate the available evidence describing the efficacy and safety of glial-modulating drugs to treat pain.
- Evidence synthesised will provide insight into which pain conditions are most responsive to treatment with glial-modulating drugs.
- This review is limited to evidence from randomised trials and the inclusion of only English language studies.

INTRODUCTION

Pain, in particular related to pathological clinical conditions, is well recognised to be a major health problem given its high prevalence, negative impact on quality of life, economic burden, and severely limited number of highly effective treatments.[1–5] The difficulty to treat pain, and its complex neurobiology, have emphasised the need for extensive and thoughtful translational research,[6–9] which has spanned over decades with a huge financial investment. One important area of pain research has involved characterising the critical role of glia in the nervous system and how glia modulates pain transmission, and also, opioid effects.[10–14]

Hundreds of preclinical studies have shown that nerve injury, surgical incision and opioid administration can lead to the proliferation of microglia in the central nervous system as well as upregulation of various receptors, including P2X(4) purinoceptors and toll-like receptor 4, and, enhanced signalling via p38 mitogen-activated protein kinase and heat shock protein-90, among several other receptors and mediators of microglial activation.[15–20] Of relevance to pain, the proliferation, and activation of microglia have further been shown to be responsible, in part, for the facilitation of nociception and pain.[12 14] The recognition of inhibition of microglial activation as a potential pain treatment strategy has pointed to several drugs identified as glial inhibitors, including minocycline, propentofylline and ibudilast.[21–24] Subsequently, a growing number of clinical trials are emerging to evaluate the analgesic efficacy

of these agents in the setting of acute and chronic pain management. Thus, the aim of the proposed systematic review is to evaluate emerging clinical evidence describing the efficacy and adverse events of glial-modulating drugs relevant to pain treatment.

OBJECTIVES

The objective of this systematic review is to evaluate clinical trials of glial modulators in the setting of pain treatment or opioid administration so as to evaluate analgesic efficacy, opioid-related outcomes, and adverse effects of treatment.

METHODS AND ANALYSIS

This protocol is developed in accordance with best practices for systematic review reporting[25] and with Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidelines,[26] with similar methods to our previous review protocols,[27] and has been registered in the PROSPERO register (CRD42021262074).

Sources of evidence

We will conduct a detailed search on Cochrane Cochrane Central Register of Controlled Trials (CENTRAL), Medline and Embase from their inception until the date the searches are run. The search will include terms relating to known glial-modulating drugs, pain conditions and opioid administration. The search strategies have been developed in consultation with our library scientist (AR-W) specialising in literature searches (online appendix 1).

We will also review the bibliographies of any randomised controlled trials identified for relevance, as well as search clinical trial databases (ClinicalTrials.gov) and the WHO International Clinical Trials Registry Platform (ICTRP) to identify additional published or unpublished data.

Report selection

Types of studies

The review will include randomised, double-blind, controlled trials that evaluate the efficacy of glial-modulating drugs in the setting of pain treatment or opioid administration. Studies with fewer than 30 participants will be excluded to minimise small study bias.

Types of participants

We will include studies with human adults aged 18 years and over, reporting any type of pain or receiving opioids. Initial pain should be of at least moderate intensity to ensure assay sensitivity, and use only pain scores reported by participants.[28]

Types of interventions

We will focus on glial-modulating drugs as outlined in the search strategy (online appendix 1) administered by any route or dose.

Comparators

Eligible studies must compare the glial-modulating drug to placebo and/or another active comparator treatment.

Data collection, extraction and management

Two reviewers will independently evaluate studies for eligibility. Screening will be performed on titles and abstracts, and full-text review will be performed on citations identified as potentially eligible. Disagreements between the reviewers will be resolved by discussion and consensus. If necessary, a third reviewer will be consulted.

Data from selected studies will be extracted independently by two reviewers using standardised extraction forms. The forms will capture information about the pain conditions of participants, study intervention details, primary and secondary outcome measures, and other study characteristics.

Types of outcome measures

Participant-reported measures of pain intensity or pain relief using validated methods and, in studies of opioid administration, measures of opioid consumption and/or opioid-related adverse effects.

Primary outcomes

The primary outcomes for this review will include any validated measure of pain intensity and/or pain relief. We will focus on the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials definitions for moderate and substantial benefit in chronic pain studies.[29] In studies of opioid administration, primary outcomes may include measures of opioid consumption and/or opioid-related adverse effects.

Secondary outcomes

1. Any pain-related outcome indicating some improvement (eg, improved function).
2. Withdrawals due to lack of efficacy, adverse events, and for any cause.
3. Participants experiencing any adverse event.
4. Participants experiencing any serious adverse event.
5. Specific adverse events (eg, sedation).

Search methods for identification of studies

Electronic searches

A detailed search will be conducted on the CENTRAL, Medline and Embase from their inception until the date the searches are run. The search will be limited to studies published in English. The search will include terms relating to the glial-modulating drugs, pain and clinical trials. The search strategy for Ovid Medline was developed in consultation with a librarian with expertise in literature searches (online appendix 1).

Searching other resources

We will also review the bibliographies of any randomised controlled trials identified for relevance, search clinical trial databases (ClinicalTrials.gov), and the WHO ICTRP to identify additional published or unpublished data.

Data collection and analysis

Selection of studies

Search results will be exported to the Covidence screening tool and duplicates will be removed. Two reviewers will independently evaluate studies for eligibility. Screening will be performed on titles and abstracts, and full-text screening will be performed on citations identified as potentially eligible. Studies that clearly do not satisfy the inclusion criteria will be removed. Disagreements between the reviewers will be resolved by discussion and consensus. If necessary, a third reviewer will be consulted. The screening and selection process will be presented using a PRISMA flow chart and reasons for exclusion based on full-text review will be reported.

Data extraction and management

Data from selected studies will be extracted independently by two reviewers using standardised data extraction forms. The forms will capture information about the pain condition, number of participants treated, participant characteristics, inclusion and exclusion criteria, type of drug used, dose and frequency and route of administration of the glial-modulating drug and other study drugs, study duration and follow-up, study design, primary and secondary outcome measures, and results.

Assessment of risk of bias in included studies

Two reviewers will independently assess risk of bias, at the study level, for each study using criteria outlined in the *Cochrane Handbook for Systematic Review of Interventions*.[30] Disagreements between reviewers will be resolved with discussion and consensus. If necessary, a third reviewer will be consulted. The following criteria will be assessed for each study:

1. Random sequence generation to check for possible selection bias.
2. Allocation concealment to check for possible selection bias.
3. Blinding of participants and personnel to check for possible performance bias, and blinding of outcome assessment to check for possible detection bias.
4. Incomplete outcome data to check for possible attrition bias due to amount, nature, or handling of incomplete outcome data.
5. Selective reporting to check for possible reporting bias.
6. Other sources of bias, including small study size.

Risk of bias assessments will, in part, guide assessments of the quality of evidence, as per the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach indicated below.

Measures of treatment effect

We will use dichotomous data to calculate the risk ratio and risk difference (RD) with 95% CIs. A fixed-effect model will be used unless significant clinical heterogeneity is found. We will calculate the number needed to treat (NNT) by taking the reciprocal of the absolute risk reduction (RR). We will calculate number needed to harm (NNH) in the same manner for unwanted effects. We do not plan to use continuous data in any analyses.

Dealing with missing data

For missing data, we will use the intention-to-treat (ITT) analysis. The ITT population will include randomised participants who received at least one dose of assigned study intervention, and provided at least one post baseline assessment. We will assess what (if any) imputation methods are used when participants withdraw from treatment because of the potential for altering effect size.[31–33]

Assessment of heterogeneity

Only studies evaluating similar conditions will be combined for analysis in order to avoid clinical heterogeneity. Clinical heterogeneity will also be assessed visually and by using the I^2 statistic. When the I^2 value is higher than 50%, we will consider possible explanations for this.

Assessment of reporting bias

This review will extract dichotomous data and will not depend on what the authors of the original studies chose to report or not. We will assess for publication bias by using a method that looks for the amount of unpublished data with a null effect needed to make any result clinically irrelevant (usually taken to mean an NNT of 10 or higher).

Data synthesis and analysis of outcomes

Extracted data will be compiled in Microsoft Excel for analysis. Analyses will be carried out using Review Manager (RevMan) (Computer Program), V.5.3, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014. We plan to use a fixed-effect model for meta-analysis. We will use a random-effect model for meta-analysis if it is deemed appropriate to combine heterogeneous studies.

Quality of evidence

The quality of evidence will be rated using the GRADE approach,[34] and presented by using a 'summary of findings' table.

Progress

This protocol has been registered in the PROSPERO review registry (CRD42021262074). The electronic database search strategies is currently being finalised. The entire review is expected to be completed by November 2022.

Patient and public involvement

No patient involved.

Ethics and dissemination

Formal ethical approval is not required as this study is a review of the available literature. Findings will be disseminated through publication in a peer-reviewed journal and conference presentations.

Author affiliations
[1]Anesthesiology & Perioperative Medicine, Queen's University, Kingston, Ontario, Canada
[2]Department of Biomedical & Molecular Sciences, Queen's University, Kingston, Ontario, Canada
[3]The Department of Physiology, University of Toronto, Toronto, Ontario, Canada
[4]Centre of Excellence for Nanoscale BioPhotonics, The University of Adelaide, Adelaide, South Australia, Australia
[5]Clinical Neurological Sciences and Oncology, Western University, London, Ontario, Canada
[6]Department of Anaesthetics, Oxford University, Plymouth, UK
[7]Bracken Health Sciences Library, Queen's University, Kingston, Ontario, Canada

Twitter R Andrew Moore @AndrewMoorepain

Contributors IG is the study principal investigator and the guarantor of the review. All authors contributed to the conception, design and writing of this protocol manuscript. MZXX and MC will conduct article screening, data extraction and perform data analysis. All authors will contribute to the reporting of the review described in this protocol. All authors have reviewed and approved the final version for submission.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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ORCID iDs
Ian Gilron http://orcid.org/0000-0002-5293-8792
Maggie Z X Xiao http://orcid.org/0000-0002-7534-6079
Meg Carley http://orcid.org/0000-0003-2334-0908
Nader Ghasemlou http://orcid.org/0000-0002-1696-7342
Michael W Salter http://orcid.org/0000-0001-6897-6585
Mark R Hutchinson http://orcid.org/0000-0003-2154-5950
Amanda Ross-White http://orcid.org/0000-0003-4737-0968

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