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

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

Abstract

Introduction: Evidence suggests a role for CNS 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 (CENTRAL), MEDLINE, and EMBASE from their inception until the date the searches are run to identify relevant randomized controlled trials. The reference lists of retrieved studies, as well as online trial registries, will also be searched. Randomized, 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 (RR) and number needed to treat (NNT) or harm (NNH). The quality of evidence will be assessed using GRADE.

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: This protocol is being submitted for registration in the PROSPERO review registry.

Word Count: 1,867 (excluding abstract)

Keywords
pain, chronic pain, acute pain, postsurgical pain, glia, microglia, analgesic therapy, clinical trials, systematic review

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Strengths and limitations of the 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 synthesized will provide insight into which pain conditions are most responsive to treatment with glial-modulating drugs
- This review is limited to evidence from randomized trials and the inclusion of only English language studies.

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Introduction

Pain, in particular related to pathological clinical conditions, is well recognized 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.[3,6,8,23,24] The difficulty to treat pain, and its complex neurobiology, have emphasized the need for extensive and thoughtful translational research,[1,14,18,33] which has spanned over decades with a huge financial investment. One important area of pain research has involved characterizing the critical role of glia in the nervous system and how glia modulates pain transmission, and also, opioid effects.[4,11,16,25,32]

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.[7,13,15,29,30,31] 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.[16,32] 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.[10,12,17,28] 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.

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Methods

This protocol is developed in accordance with best practices for systematic review reporting[20] and with PRISMA-P guidelines[19,34] and will be registered in the PROSPERO register (protocol number pending).

Sources of evidence:

We will conduct a detailed search on Cochrane 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) specializing in literature searches (Appendix 1).

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

Report selection:

Types of studies
The review will include randomized, 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 minimize 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.[27]

Types of interventions
We will focus on glial-modulating drugs as outlined in the search strategy (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 standardized 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 (IMMPACT) definitions for moderate and substantial benefit in chronic pain studies.[5] 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 (e.g., 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 (e.g., sedation).

Search methods for identification of studies

Electronic searches

A detailed search will be conducted on the Cochrane Central Register of Controlled Trials (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 (Appendix 1).

Searching other resources

We will also review the bibliographies of any randomized controlled trials identified for relevance, search clinical trial databases (ClinicalTrials.gov), and the World Health Organization

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(WHO) International Clinical Trials Registry Platform (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 base on full-text review will be reported.

Data extraction and management

Data from selected studies will be extracted independently by two reviewers using standardized 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.[9] 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 GRADE approach indicated below.

Measures of treatment effect

We will use dichotomous data to calculate the risk ratio (RR) and risk difference (RD) with 95% confidence intervals (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 (RD). 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 utilize the intention-to-treat (ITT) analysis. The ITT population will include randomized 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.[2,21,22]

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], Version 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-effects 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 Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach,[26] and presented by using a 'summary of findings' table.

Progress

The protocol was submitted to PROSPERO and is currently being assessed. The

electronic database search strategies are currently being developed and modified. The entire review is expected to be completed by November 2021.

Patient and Public Involvement
No patient involved

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Discussion

Completion of this review is expected to identify available high-quality evidence describing the efficacy and safety of glial-modulating drug in the setting of pain treatment or opioid administration. This review will serve to 1) identify which glial-modulating drugs are safest and most efficacious; 2) identify which pain conditions are most responsive to treatment with glial-modulating drugs; and 3) identify current gaps in this research field and guide continued research efforts.

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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.

Footnotes

Contributors: I.G. is the study principal investigator and the guarantor of the review. All authors (I.G., M.ZX.X., M.B., M.C., N.G., M.W.S., M.R.H., D.E.M., R.A.M., and A.RW.) contributed to the conception, design and writing of this protocol manuscript. M.ZX.X and M.B 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 of the authors have competing interests to declare.

Patient consent for publication: Not required

Ethics approval and consent to participate: Not applicable

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Appendix 1: Systematic review of clinical trials of glial-modulating drugs to treat pain - Search strategy

Treatment terms (each of the 8 following search sets to be combined with 'Pain Terms' and 'Trial Terms'):

1. (glia or glial OR microglia)
2. minocycline
3. pentoxifylline
4. propentofylline
5. ibudilast OR av411 OR av-411
6. slc022
7. av333
8. OR 1-7

Pain terms

9. Exp Pain/
10. Exp fibromyalgia/
11. Exp arthritis/
12. Exp headache disorders/
13. Fibromyalgia or musculoskeletal pain or dysmenorrhea or neuralgi* or neuropath*.mp.
14. headache* or cephalgi* or cephalalgi* or migrain* or neuropath*.mp.
pain or painful.mp.
15. postoperative or 'post operative'.mp.
16. opioid* OR opiate* OR morphine OR oxycodone OR hydromorphone OR heroin OR fentanyl
17. OR 9-16

Trial terms

18.-randomized controlled trial.pt.
19. -controlled clinical trial.pt.
20.-randomized.ab.
21.-placebo.ab.
22.-drug therapy.fs.
23.-randomly.ab.
24.-trial.ab.
25.-groups.ab.
26. OR 18-25
27. AND 8,17,26

PRISMA 2020 Main Checklist

Topic	No.	Item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 4, Paragraph 2
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 4, Paragraph 3
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 5, 'Report selection'
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 5, 'Sources of evidence'
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 17, 'Appendix'
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 5-6, 'Data collection, extraction, and management' & Page 7 'Data collection and analysis'
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 5-6, 'Data collection, extraction, and management' & Page 7 'Data collection and analysis'

Topic	No.	Item	Location where item is reported
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 6, 'Types of outcome measures'
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 6, 'Primary outcomes' & 'Secondary outcomes'
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 7, 'Assessment of risk of bias in included studies'
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 7-8, 'Measures of treatment effect'
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item 5)).	Page 7, 'Data collection and analysis'
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 8, 'Dealing with missing data'
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 8, 'Data synthesis and analysis of outcomes'
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 8, 'Data synthesis and analysis of outcomes'
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Page 8, 'Assessment of heterogeneity'
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Page 8, 'Data synthesis and analysis of outcomes'

Topic	No.	Item	Location where item is reported
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Page 8, 'Assessment of reporting bias'
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Page 8, 'Quality of evidence'
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	N/A
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	N/A
Study characteristics	17	Cite each included study and present its characteristics.	N/A
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	N/A
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	N/A
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	N/A
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	N/A
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	N/A
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	N/A
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	N/A

Topic	No.	Item	Location where item is reported
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	N/A
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	N/A
	23b	Discuss any limitations of the evidence included in the review.	N/A
	23c	Discuss any limitations of the review processes used.	N/A
	23d	Discuss implications of the results for practice, policy, and future research.	N/A
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 8, 'Progress'
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	The protocol for the systematic review will be submitted to BMJ Open
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 16, 'Funding'
Competing interests	26	Declare any competing interests of review authors.	Page 16, 'Conflicts of interest'
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	N/A

PRIMSA Abstract Checklist

Topic	No.	Item	Reported?
TITLE			
Title	1	Identify the report as a systematic review.	Yes
BACKGROUND			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	Yes
METHODS			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	Yes
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	Yes
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	Yes
Synthesis of results	6	Specify the methods used to present and synthesize results.	Yes
RESULTS			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	No
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	No
DISCUSSION			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	No
Interpretation	10	Provide a general interpretation of the results and important implications.	No
OTHER			
Funding	11	Specify the primary source of funding for the review.	No
Registration	12	Provide the register name and registration number.	No

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. MetaArXiv. 2020, September 14. DOI: 10.31222/osf.io/v7gm2. For more information, visit: www.prisma-statement.org

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

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Secondary Subject Heading:	Neurology
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Glial-modulating agents for the treatment of pain: Protocol for a systematic review

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

Abstract

Introduction: Evidence suggests a role for CNS 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 (CENTRAL), MEDLINE, and EMBASE from their inception until the date the final searches are run to identify relevant randomized controlled trials. The reference lists of retrieved studies, as well as online trial registries, will also be searched. English language, randomized, 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 (RR) and number needed to treat (NNT) or harm (NNH). The quality of evidence will be assessed using GRADE.

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: This protocol has been registered in the PROSPERO review registry (CRD42021262074).

Word Count: 1,867 (excluding abstract)

Keywords
pain, chronic pain, acute pain, postsurgical pain, glia, microglia, analgesic therapy, clinical trials, systematic review

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

Strengths and limitations of the 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 synthesized will provide insight into which pain conditions are most responsive to treatment with glial-modulating drugs
- This review is limited to evidence from randomized trials and the inclusion of only English language studies.

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

Introduction

Pain, in particular related to pathological clinical conditions, is well recognized 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 emphasized 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 characterizing 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.

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

Methods and analysis

This protocol is developed in accordance with best practices for systematic review reporting[25] and with PRISMA-P guidelines,[26] with similar methods to our previous review protocols,[27] and will be registered in the PROSPERO register (protocol number pending).

Sources of evidence:

We will conduct a detailed search on Cochrane 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) specializing in literature searches (Appendix 1).

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

Report selection:

Types of studies
The review will include randomized, 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 minimize 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 (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 standardized 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 (IMMPACT) 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 (e.g., 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 (e.g., sedation).

Search methods for identification of studies

Electronic searches

A detailed search will be conducted on the Cochrane Central Register of Controlled Trials (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 (Appendix 1).

Searching other resources

We will also review the bibliographies of any randomized controlled trials identified for relevance, search clinical trial databases (ClinicalTrials.gov), and the World Health Organization

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

(WHO) International Clinical Trials Registry Platform (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 base on full-text review will be reported.

Data extraction and management

Data from selected studies will be extracted independently by two reviewers using standardized 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 GRADE approach indicated below.

Measures of treatment effect

We will use dichotomous data to calculate the risk ratio (RR) and risk difference (RD) with 95% confidence intervals (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 (RD). 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 utilize the intention-to-treat (ITT) analysis. The ITT population will include randomized 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], Version 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-effects 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 Grading of Recommendations Assessment, Development and Evaluation (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 finalized. The entire review is expected to be completed by November 2022.

Patient and Public Involvement

No patient involved

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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.

Footnotes

Contributors: I.G. is the study principal investigator and the guarantor of the review. All authors (I.G., M.ZX.X., M.B., M.C., N.G., M.W.S., M.R.H., D.E.M., R.A.M., and A.RW.) contributed to the conception, design and writing of this protocol manuscript. M.ZX.X and M.B 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 of the authors have competing interests to declare.

Patient consent for publication: Not required

Ethics approval and consent to participate: Not applicable

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

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Appendix 1: Systematic review of clinical trials of glial-modulating drugs to treat pain - Search strategy

Treatment terms (each of the 8 following search sets to be combined with 'Pain Terms' and 'Trial Terms'):

1. (glia or glial OR microglia)
2. minocycline
3. pentoxifylline
4. propentofylline
5. ibudilast OR av411 OR av-411
6. slc022
7. av333
8. OR 1-7

Pain terms

9. Exp Pain/
10. Exp fibromyalgia/
11. Exp arthritis/
12. Exp headache disorders/
13. Fibromyalgia or musculoskeletal pain or dysmenorrhea or neuralgi* or neuropath*.mp.
14. headache* or cephalgi* or cephalalgi* or migrain* or neuropath*.mp.
pain or painful.mp.
15. postoperative or 'post operative'.mp.
16. opioid* OR opiate* OR morphine OR oxycodone OR hydromorphone OR heroin OR fentanyl
17. OR 9-16

Trial terms

18.-randomized controlled trial.pt.
19. -controlled clinical trial.pt.
20.-randomized.ab.
21.-placebo.ab.
22.-drug therapy.fs.
23.-randomly.ab.
24.-trial.ab.
25.-groups.ab.
26. OR 18-25
27. AND 8,17,26

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

For: "Glial-modulating agents for the treatment of pain: Protocol for a systematic review"

Section & topic	Item#	Checklist item	Page number
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	Page 1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Pages 2 & 8
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Page 1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Page 10
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	Page 10
Sponsor	5b	Provide name for the review funder and/or sponsor	Page 10
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	Page 10
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	Page 4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Page 4
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Page 5

Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Page 5
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Appendix
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Page 5
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Page 5-6
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Page 5-6
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Page 6
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Page 6
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Page 7
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	Page 7
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	Page 8
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Page 8
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Page 8
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Page 8
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Page 7

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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