INPLASY PROTOCOL

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Corresponding author:
Kesava Kovanur Sampath

kesava.sampath@wintec.ac.nz

Author Affiliation:
Waikato Institute of Technology.

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None declared.

miRNAs that are dysregulated and/or dysfunctional in chronic neuropathic pain: A scoping Review

Kovanur Sampath, K[1]; Hale, J[2]; Tumilty, S[3]; Farrell, G[4]; Thomson, O[5]; Gisselman, A[6]; Belcher, S[7]; Katare, R[8].

Review question / Objective: **What are the miRNAs that are dysregulated and/or dysfunctional in chronic neuropathic pain? Objective: To identify miRNAs that are dysregulated in neuropathic pain.**
Eligibility criteria: **Inclusion criteria: Participants: Studies undertaken in people with CRPS or DPN will be included in this review. Intervention: N/A Comparison: N/A Outcomes: Any studies where miRNAs were the biomarker/outcome of interest will be included in this review. Setting: Studies should have taken place only in health care (medicine, nursing, physiotherapy, etc.) and/or laboratory-based setting. Limiters: Due to unavailability of language translators, only studies published in the English language will be included in this review. Exclusion criteria: Studies will be excluded if: (1) they were not conducted on humans; (2) study done in other chronic pain conditions such as cancer, MSK pain (e.g. arthritis); (3) the study design is one of the following: expert opinion, editorial, letter to the editor, and commentary; (4) non-peer reviewed studies and (4) non-English studies.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 24 July 2022 and was last updated on 24 July 2022 (registration number INPLASY202270103).

INTRODUCTION

Review question / Objective: **What are the miRNAs that are dysregulated and/or dysfunctional in chronic neuropathic pain? Objective: To identify miRNAs that are dysregulated in neuropathic pain.**

Background: **Chronic pain is a major clinical issue with an incidence of 20–25% amongst the adult population worldwide, often reducing the quality of social and work life (Breivik, Collett, Ventafridda, Cohen, & Gallacher, 2006). The establishment of chronic pain can arise due to physiochemical changes at any level of**

pain pathways making them hypersensitive, commonly referred to as central sensitization (Ligon, Moloney, & Greenwood-Van Meerveld, 2016). Adding complexity to these physiochemical changes is inflammatory dysregulation commonly noted in chronic neuropathic pain conditions such as diabetic painful neuropathy (DPN) and complex regional pain syndrome (CRPS). Neuroinflammatory signatures and pathological neuro-immune communications have been identified as critical components of DPN and CRPS (Pabreja, Dua, Sharma, Padi, & Kulkarni, 2011; Vincent, Callaghan, Smith, & Feldman, 2011). This may explain why in most patients with CRPS the symptoms resolve, however, in 30% of cases the pain persists or even intensifies making it challenging to manage (Marinus et al., 2011). At a molecular level, the neuro-immune changes in the peripheral nervous system and the central nervous system results in altered regulation of gene expression. Gene expression can be modulated by different regulators acting at both the transcriptional and the translational level. Members of the non-coding RNA (ncRNA) family, specifically the short, 22 nucleotide microRNAs (miRNAs) as regulators of gene expression act as master switches orchestrating both immune and neuronal processes (Kalpachidou, Kummer, & Kress, 2020). Specifically, ncRNAs may regulate neuro-immune communication signals in the pain pathway by controlling macromolecular complexes in neurons, glia and immune cells. Pain conditions such as DPN and CRPS have been associated with deregulated miRNA expression (Baron, Förster, & Binder, 2012; Shahar Barbash, 2012).

Rationale: miRNAs may act as essential modulators of processes for the establishment and maintenance of neuropathic pain (Kalpachidou et al., 2020). Therefore, understanding the role and concerted function of miRNA in chronic neuropathic pain may be considered timely. This will help us identify appropriate targets in the management of neuropathic pain.

METHODS

Strategy of data synthesis: Information source - The lead investigator (KKS) in consultation with an experienced subject librarian identified the following electronic databases: PubMed, EBSCO, CINAHL, Cochrane Library, and SCOPUS. Furthermore, two reviewers will independently screen the reference list and citations of the included full-text articles for any additional citations.

Search strategy

The lead investigator (KKS) developed the initial search strategy which was refined in discussion with an experienced subject librarian. The search strategy was developed to locate studies relevant to two key components of our research question: chronic neuropathic pain and miRNAs. A sample search strategy has been provided below.

1. Exp. Neuropathic pain
2. Exp. Neurogenic inflammation
3. CRPS (MeSH terms)
4. Chronic regional pain syndrome
5. Diabetic neuropathies (MeSH terms)
6. or/ 1-5
7. miRNA
8. miRNA-based diagnostics
9. miRNA expression patterns
10. miRNA-based analgesic
11. extracellular RNA
12. salivary miRNA
13. or/7-12
14. 6 AND 13.

Eligibility criteria: Inclusion criteria: Participants: Studies undertaken in people with CRPS or DPN will be included in this review. Intervention: N/A Comparison: N/A Outcomes: Any studies where miRNAs were the biomarker/outcome of interest will be included in this review. Setting: Studies should have taken place only in health care (medicine, nursing, physiotherapy, etc.) and/or laboratory-based setting. Limiters: Due to unavailability of language translators, only studies published in the English language will be included in this review. Exclusion criteria: Studies will be excluded if: (1) they were not conducted on humans; (2) study done in other chronic pain conditions such

as cancer, MSK pain (e.g. arthritis); (3) the study design is one of the following: expert opinion, editorial, letter to the editor, and commentary; (4) non-peer reviewed studies and (4) non-English studies.

Source of evidence screening and selection: Study selection: Titles and abstracts of the retrieved articles will be screened independently by two reviewers for relevance after removing the duplicates. Before screening, a training session with the reviewers will be undertaken to maximize reliability and agreement. A pilot test will then be done where a random sample of 50 papers will be title and abstract screened, and a >90% inter-rater agreement will be reached between the lead investigator and second reviewer before proceeding further. If this level of agreement is not reached, a discussion will take place with a third reviewer. The inclusion/exclusion criteria will then be revised and modified accordingly. This process will continue until the calibration exercise achieves >90% inter-rater agreement. Following the pilot test, titles, abstracts and full texts will then be screened by two independent reviewers for assessment against the inclusion criteria. All citation details will be exported to Rayann (www.rayyan.ai). Full-text articles that do not meet the inclusion criteria will be excluded, and the reason for exclusion will be provided as a table in the final review. Any disagreements that arise between reviewers at any stage of the selection process will be resolved through discussion; if no agreement can be reached, a third reviewer will be consulted.
Data collection
The research team will collectively create a data charting table/form to standardise the data to be collected. Two independent reviewers will review the extracted data. A third reviewer will be consulted in case of any disagreement. Data that may be extracted from each included study may include study's aim; study design; population, findings and author's conclusions. For qualitative data, the authors' interpretations (presented through themes and categories) will be retrieved. To ensure consistency, the data charting form will be piloted on five studies.

Data management: Articles obtained by the systematic search in the above-mentioned databases will be exported and saved into reference management software (EndNote X9 Thomson Corporation) which will be used throughout the review process.

Reporting results / Analysis of the evidence: A narrative synthesis will be used to synthesise the evidence.

Presentation of the results: The results of the search will be reported in full in the review and reported in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram and a table of included and excluded studies.

Language restriction: English.

Country(ies) involved: New Zealand; Ireland; UK; USA.

Keywords: miRNA, Micro-RNA, Pain, Neuropathic Pain, DPN.

Dissemination plans: The findings of the scoping review will be published in a leading Journal in the field and/or will be presented at national and international conference.

Contributions of each author:
Author 1 - Kesava Kovanur Sampath.
Email: kesava.sampath@wintec.ac.nz
Author 2 - James Hale.
Email: james.hale@wintec.ac.nz
Author 3 - Steve Tumilty.
Email: steve.tumilty@otago.ac.nz
Author 4 - Gerard Farrell.
Email: gerard.farrell@otago.ac.nz
Author 5 - Oliver Thomson.
Email: oliver.thomson@uco.ac.uk
Author 6 - Angela Gisselman.
Email: angela.gisselman@tufts.edu
Author 7 - Suzie Belcher.
Email: suzie.belcher@wintec.ac.nz
Author 8 - Rajesh Katare.
Email: rajesh.katare@otago.ac.nz