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Effectiveness of interventions for middle-aged and ageing population with neck pain: a systematic review and network meta-analysis protocol

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ABSTRACT

Introduction Neck pain (NP) is a common musculoskeletal complaint and is increasing in prevalence. Current clinical practice guidelines and systematic reviews recommended conservative, pharmacological and invasive interventions for individuals with NP. However, optimal management specifically for those who are middle-aged or older adults (≥45 years) is not available; and important considering our ageing population.

Methods and analysis A systematic review with network meta-analysis (NMA) will be conducted following the Cochrane guidelines. Eligibility criteria include randomised controlled/clinical trials evaluating any of acute (<3 months) or chronic (≥3 months) non-specific NP, whiplash associated disorders, cervical radiculopathy and cervicogenic headache. Any interventions and outcome measures detailed within The International Classification of Functioning, Disability and Health domains will be included. Two independent reviewers will search key databases (AMED, CENTRAL, CINAHL, Embase, MEDLINE, PEDro and PsycINFO), grey literature, key journals and reference lists in May 2022. Two reviewers will decide eligibility and assess risk of bias (ROB) of included studies. The kappa statistic will be used to evaluate agreement between the reviewers at each stage. Data will be extracted by one reviewer and checked for accuracy by a second reviewer. Descriptive data and ROB will be summarised and tabulated. Traditional pairwise meta-analysis using random-effect model will be performed for all direct comparisons, and NMA using a frequentist random-effect model then performed based on NP classification where possible. A network of traditional pairwise meta-analysis allows comparisons of multiple interventions from both direct and indirect evidence to provide a hierarchal establishment for enhancing decision making of clinical practitioners.

Ethics and dissemination Ethic approval is not required as the study is a literature review. The findings will be shared with the national and international researchers, healthcare professionals and the general public through publishing in a peer-reviewed journal and presentations at conferences.

PROSPERO registration number CRD42021284618.

Strengths and limitations of this study

- ⇒ The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Protocols was used to report the protocol and the review will be reported in adherence with the PRISMA extension statement for incorporating network meta-analysis (NMA).
- ⇒ Two reviewers will search, select and assess risk of bias of included studies independently.
- ⇒ NMA will be conducted resulting in establishment of a hierarchy of interventions evidence.
- ⇒ Subgroup analysis and quality of the evidence using Grading of Recommendations, Assessment, Development and Evaluation will be considered where possible.

INTRODUCTION

Neck pain (NP) is a common musculoskeletal complaint, affecting 50%–85% of the global population annually.[1] The number of individuals with NP has increased from 164.3 to 288.7 million in the last two decades worldwide.[2] NP along with low back pain was ranked as the fourth leading cause of disability-adjusted life-years (DALYS) globally in 2015.[3 4] It is characterised with recurrent or persistent pain that may extend over a lifetime,[5] not only leading to personal burden in terms of pain, disability and quality of life (QoL)[6 7] but with associated national and international socioeconomic burden.[8] For example, in the USA, costs of treatment for NP accounted for US$88 billion per year from 1996 through 2013.[3] While in the UK, the number of working days lost due to musculoskeletal problems was 30.8 million days in 2017, resulting in lost economic produce.[9]

NP can increase with age, with the highest prevalence being in those 45–54 years and with peaked global annual incidence at 65–69

years.[2] Also, among age 50–75 years, NP was ranked in the top 25 leading causes of DALYS in 2019, rising from the 32 in 1990.[10] Approximately 20% of older adults 70 years and above experience NP once a month,[11] contributing to poorer self-rated health and comorbidities.[12] To promote health and well-being in older age in accordance with World Population Ageing report 2015 by United Nations,[13] addressing management of NP in those aged 45 and older is important.

NP is a complex biopsychosocial disorder and management is challenging.[14] Recent clinical practice guidelines and systemic reviews broadly recommend conservative treatments, medication and invasive treatment for individuals with NP.[14–26] Different classifications (eg, mobility deficits, movement coordination impairment, cervicogenic, radiculopathy) and duration (eg, acute, subacute and chronic) of NP require different treatment approaches.[14] For example, manual therapy is highly recommended for NP with mobility deficits,[14] while NP with neuropathic pain is associated with increased need for medication.[27] However, considering older adults, interventions must be selected cautiously because of possible risks such as drug interactions and comorbidities.[28] Moreover, factors associated with NP in older adults are not only limited to pain, disability, depression,[29] pain catastrophising[30] and QoL but also include impaired balance[31] and memory decline[32] which could be important and frequently overlooked clinical outcomes. As a result, management in this specific population remains unclear. In the absence of population specific guidance, a review focused to individuals with NP age 45 years and above is now needed.

Objective

This review aims to systematically evaluate and synthesise the effectiveness of interventions for middle aged and ageing population aged 45 and older with NP.

METHODS

Design

A systematic review and NMA will be conducted in accordance with guidelines in the Cochrane Handbook.[33] The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Protocols was used to report the protocol,[34] and the review will be reported in adherence with the PRISMA extension statement for incorporating network meta-analysis (NMA).[35]

Eligibility criteria

The Population Intervention Comparison Outcome Study Design (PICOS) framework was used to develop eligibility criteria.[36] Selected included studies should meet the following criteria:

Population

Participants aged 45 years and older with NP with or without pain referred into the upper limb(s) that lasts for at least 1 day[37] will be included. Also, individuals with any of the four common classifications of NP[14] will be included, defined as (1) non-specific (or idiopathic or mechanical) NP; (2) traumatic NP or whiplash associated disorder (WAD); (3) NP with radicular pain or cervical radiculopathy and (4) NP with headache or cervicogenic headache (CGH). For each category, duration of NP less than 3 months will be defined as acute,[38–40] while pain equal or more than 3 months will be defined as for chronic.[41 42]

Interventions

Interventions may comprise:

- Conservative interventions, for example: cognitive—behavioural therapy[24] exercise,[43] manual therapy,[21] massage,[25] patient education[19] and multidisciplinary approaches.[22]
- Pharmacological Interventions, for example: antidepressant, non-steroidal anti-inflammatory drugs, opioids, muscle relaxants, paracetamol and topical agents (non-opioids).[28]
- Invasive interventions, for example: anterior or posterior surgical approaches for cervical spine[18] and cervicothoracic sympathectomy.[44]

Comparator

Comparators can include alternative treatment options or a control condition such as placebo/sham, usual care, standard intervention or no-intervention.

Outcome measures

Both patient-reported and performance-based clinical outcomes using a reliable and valid instrument measure for this specific population will be included. Outcome measures detailed within physical, psychological, social and cultural contexts based on a framework from The International Classification of Functioning, Disability and Health will be included.[36]

Study design

Only randomised controlled trials or randomised clinical trials or randomised controlled clinical trials (RCTs) will be included.

Studies will be excluded if:

1. It did not focus on the effectiveness of interventions as key outcomes.
2. It has not evaluated NP separately from other musculoskeletal disorders, resulting in differential effectiveness of the interventions strategies of interest.
3. It considered a participant with specific underlying pathologies that requires specific approaches such as tumours, infection, inflammatory disorders, fibromyalgia or widespread pain disorder, neck injury that resulted in a spinal dislocation and fracture, osteoporosis, rheumatological condition or ankylosing spondylitis.
4. It was not published in English.

Information sources

The systematic search will be conducted in databases from inception: Allied and Complementary Medicine Database

(AMED), Cochrane Central Register of Controlled Trial (CENTRAL), Cumulative Index to Nursing and Allied Health (CINAHL), Excerpta Medica Database from Elsevier (Embase), Medical Literature Analysis and Retrieval System Online (MEDLINE), Physiotherapy Evidence Database (PEDro) and Psychological Information Database (PsycINFO).

Additional searches in key journals will be performed manually including, for example, Geriatric Rehabilitation, Journal of Aging and Health, Advances in Aging Research, European Spine Journal, Journal of Orthopaedic and Sports Physical Therapy, Physiotherapy, BMC Musculoskeletal Disorders, Musculoskeletal Science and Practice and Neurosurgery. To avoid publication bias and overestimation of treatment effects,[45] grey literature (eg, Zetoc, OpenGrey and Google Scholar) and unpublished literature (WHO International Clinical Trials Registry Platform (ICTRP)) will be explored. Potentially eligible studies will be considered from relevant systematic review and the reference lists of the included studies.

Search strategy

The strategy is informed by the PICOS criteria based on groups of search terms including: (1) NP (one of four common classifications); (2) middle-aged and ageing population and (3) RCTs. Different interventions, comparators and outcome measures are included in this review, no search terms will be used for those to avoid exclusion of potentially relevant studies. The examples of search terms and search strategies used are provided in the example below.

Search string for Ovid MEDLINE(R) 1946 to August week 4 2021.

1. exp neck pain/
2. (ache, neck or aches, neck or cervical pain or cervical pain, posterior or neckache or neckaches or posterior or cervical pain or posterior neck pain or idiopathic neck pain or neck pain with mobility deficits).mp.
3. (pain neck shoulder or myofascial neck pain or non-specific neck pain or NSNP or acute non-specific neck pain or acute neck pain or chronic neck pain or chronic non-specific neck pain or CNSNP or neck pain with mobility deficits or cervical spondylosis).mp.
4. 1 or 2 or 3
5. exp Radiculopathy/
6. (cervical radiculopathy or neck pain with radicular pain or nerve root avulsion or nerve root compression or nerve root disorder or nerve root inflammation or cervical disc herniation or herniated disc or cervical stenosis or cervical spondylolysis or cervical spondylolisthesis).mp.
7. Neck pain with radiation.mp.
8. referred pain.mp.
9. 5 or 6 or 7 or 8
10. exp neck injuries/
11. exp Whiplash Injuries/
12. (Acute whiplash or acute whiplash injury or acute whiplash associated disorder or acute WAD or chronic whiplash or chronic whiplash injury or chronic whiplash associated disorder or chronic WAD or WAD or traumatic neck disorder).mp.
13. 10 or 11 or 12
14. exp Post-Traumatic Headache/
15. Cervicogenic Headache.mp.
16. (Neck pain with headache or secondary headache or secondary headache disorder).mp.
17. 14 or 15 or 16
18. 4 or 9 or 13 or 17
19. exp Aged/
20. (aged or elderly or aging or elder or senior or old or older or pre-aging or pre-elderly).mp.
21. exp Middle Aged/
22. 19 or 20 or 21
23. exp "Randomized Controlled Trials as Topic"/
24. (clinical trials, randomized or controlled clinical trials, randomized or "randomized controlled trials as topic" or trials, randomized clinical).mp.
25. randomi?ed.ab.
26. 23 or 24 or 25
27. 18 and 22 and 26

Study records

Data management

Microsoft Endnote will be used to store the imported search results, remove duplicates and manage bibliographies.

Selection process

Two reviewers (UB and NP) will independently search and screen[1] titles and abstracts[2] full texts and exclude studies not meeting the criteria; reporting all reasons for exclusion. The potentially eligible papers will be classified as eligible/not eligible/unclear and then compared between the two reviewers after the searching process. The two reviewers will meet and discuss if there are possible differences. A third reviewer (TW) will resolve disagreements at any stage through discussion. The process of study selection will be reported using a PRISMA flow diagram.

Data collection process

The data for each paper will be extracted by the first reviewer (UB) and checked for accuracy by the second reviewer (NP) using the Cochrane 'Data collection forms for intervention reviews: RCTs only'.[46] The form will be piloted by the first reviewer and checked by the second reviewer on five random eligible studies. A third reviewer (TW) will mediate any disagreements.

Both dichotomous and continuous outcomes data will be extracted. The outcome data (eg, means and SD) will be extracted to investigate time points of follow-up that could be divided into short-term (<3 months), medium-term (3–12 months) and long-term effects (≥12 months).[26] In a case of available data of participants with

a variety of age ranges or unavailable data, data will be recoded from only participants age over 45 if possible, or trial authors will be contracted once for further information via email. A reminder email will be sent 2 weeks after. If there are no responses within 3 weeks, we will assume that the data is not available or we will estimate the mean and SD following Cochrane recommendations.

Data items

The extracted information will be recorded in a 'characteristics of included studies' table to further investigate statistical analysis.[47] This includes:

1. Study identifiers (eg, trial authors, publication date).
2. Study characteristics (eg, study setting, location, source of financial support).
3. Participant information (eg, age, gender ratio, sample size, clinical conditions, duration and severity of NP).
4. Intervention data (eg, type of intervention used, duration of treatment, dosage).
5. Clinical outcomes (eg, measurements used, follow-up period, main results).

Risk of bias assessment of individual studies

The risk of bias assessment tool used in this review is the revised Cochrane risk of bias tool for randomised trials (ROB 2.0) which is suitable for assessing biases of relative effects of two interventions (experimental and comparator interventions) on a particular outcome in RCTs.[48] Studies will be evaluated according to the following response options for the signalling questions: 'no' or 'probably no' (considered as high risk of bias), 'yes' or 'probably yes' (considered as low risk of bias) and no information (indicated some concerns). The overall risk of bias will be assessed based on five domains at each stage including the randomisation process, deviations from intended interventions, missing outcome data, measurement of the outcome and selection of the reported result.[49]

The risk of bias of all included studies will be independently evaluated by two reviewers (UB and NP). The kappa statistic will be used to evaluate agreement between the two reviewers, where>0.75 is excellent agreement, 0.60–0.74 is good agreement and 0.40–0.59 is fair agreement.[48 50] Calibration exercise for the risk of bias assessment and kappa analysis will be piloted on five excluded studies to assess inter-rater reliability.[51] The third reviewer will resolve any conflicts through discussion as needed.

Data synthesis

Our approaches to data synthesis utilises multiple stages of a general framework from Cochrane Recommendation.[52] To determine which studies are similar enough to be grouped and what data are available for synthesis, descriptive data will be presented in a table of key characteristics of included eligible studies illustrating summaries of key study and participants' characteristics, interventions, patient-reported and performance-based outcomes and risk of bias assessment. The numbers and process of including/excluding papers will be reported on a PRISMA flow chart.

Assessment of heterogeneity

This review will include both pairwise and network comparisons. For the traditional pairwise meta-analysis, the heterogeneity within the studies will be examined by visually screening the forest plots.[52] As there are various types of intervention included, heterogeneity between studies will be assessed with respect to the classification and duration of NP. I^2 statistic will be used to evaluate statistical heterogeneity and interpreted based on Cochrane Handbook for systematic review of Interventions (0%–40%=might not be important, 30%–60%=may represent moderate, 50%–90%=substantial and 75%–100%=considerable heterogeneity).[53] In the event of significant statistical heterogeneity where meta-analysis is not possible, all data will be redetermined for possible sources of heterogeneity and other statistical analysis methods such as combining p value or summary of effect estimates will be considered as appropriate.[52] In contrast, if there is low heterogeneity (I^2 <50%), a quantitative synthesis will be performed as described below.

Methods for pairwise meta-analysis

Meta-analyses using a random-effect model for each specific intervention comparisons will be completed for all available interventions. This will be undertaken for all direct comparisons following Cochrane Handbook guidelines.[53] Dichotomous outcomes will be determined using risk ratio with 95% CI. Continuous outcomes will be analysed by mean difference or standardised mean difference (with 95% CI) in cases of different measurement scales used. The intervention effect estimates will be pooled using weighted mean differences with 95% CI. Tables and a forest plot will be used to report the quantitative data.

Methods for NMA

To investigate the comparative effectiveness of different interventions regarding each NP category, NMA will allow some interventions that were not directly compared with others to be interpreted along with the entire body of the evidence.[54] The effectiveness of interventions can be estimated by using multiple direct and indirect evidence from a generalisation of traditional pairwise meta-analysis.[48 55] In this review, NMA will be performed using a frequentist random-effect model with the methodology of multivariable meta-analysis to assess consistency of the comparative effectiveness of eligible interventions[56 57] using STATA (V.14).

Although there is similarity between network and conventional meta-analysis, key different assumptions are transitivity (influences from effect modifiers on indirect comparisons) and coherence (similarity between direct and indirect effect estimates.[58] Coherence will be explored by comparing direct and indirect evidence using a design by treatment interaction model (Global approach).[58] Global inconsistency will be indicated significant if the

two-sided of the test equal 0.05.[59 60] Moreover, we will use a network diagram and league table to present mixed treatment effect sizes from combining direct and indirect evidence of interventions.[53]

Subgroup analysis and investigation of heterogeneity

Because intervention responses can be affected by participants' characteristics, it is important to identify the possible sources (effect modifiers) in the NMA review. We hypothesise the potential effect modifiers as:

- Clinical conditions: (1) non-specific (or idiopathic or mechanical) NP[61]; (2) traumatic NP or WAD[62]; (3) NP with radicular pain or cervical radiculopathy[63] and (4) NP with headache or CGH.[64]
- Severity of NP: measured by valid and reliable instruments, for example, 11-point Numeric Pain Rating Scale.[65]
- Duration of NP: acute (<3 months) or chronic (≥3 months).[41]
- Duration of follow-up: short-term (<3 months), medium-term (3–12 months) and long-term effects (≥12 months).
- Dosage of treatment: for example, how many sessions per week and the number of treatment sessions.

Confidence in cumulative evidence

Grading of Recommendations, Assessment, Development and Evaluation will be used to report the overall quality of the evidence in NMA.[66] The certainty of evidence will be evaluated for each important outcome based on five domains which are risk of bias, consistency of effect, imprecision, indirectness and publication bias.[66] The quality of evidence can be downgraded up to two levels across the five domains and will be rated as 'very low', 'low', 'moderate', or 'high' quality.[66 67] This will be assessed by the two independent reviewers (UB and NP) for each treatment effect, and a third reviewer (TW) will mediate any disagreement until consensus is reached. The detailed information and certainty of the evidence will be reported in the 'Summary of findings' tables.[67]

Implications

This systematic review will provide evidence for the effectiveness of interventions for middle-aged and ageing population with NP and NMA can rank the most effective interventions statistically.[68] NMA evaluates both direct and indirect evidence so the effect estimates would be more precise than evaluating direct studies alone.[69] The results of this review will evaluate and summarise a quality of the evidence that will be beneficial for researcher to conduct a better study methodology and high quality in reporting results in the future. Furthermore, in clinical practice, practitioners can be supported by the establishment of a hierarchy of interventions evidence for better decision making.[70 71]

ETHICS AND DISSEMINATION

Ethic approval is not required for this review as the study is literature review, and direct contact with patients or concerns related to patient privacy are not involved. The results of this review will be disseminated through publication in a peer-reviewed scientific journal and presented at conferences for sharing with the national and international scientific community, healthcare professionals and the general population.

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