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Conflicts of interest:
None declared.

Conservative Primary Care Management for Recent Onset Cervical Radiculopathy – a Systematic Review & Meta-analysis Protocol

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Review question / Objective: **To investigate the effectiveness of conservative management available in primary care for adults with recent onset (less than 12 weeks) cervical radiculopathy. Conservative management will be compared to any available comparator i.e. no treatment, placebo or any treatment.**
Eligibility criteria: **Inclusion criteria – trials (as defined in item 15) investigating any conservative management (e.g. exercise, advice, manual therapy, traction, acupuncture, pharmacology etc), involving adults with single level CR (as defined in item 10) of any aetiology, with symptom duration of 12 weeks or less, and including 1 or more of the following outcomes i.e. pain, disability, overall improvement or satisfaction with intervention, quality of life or participation restriction. Exclusion criteria – full text not available, not a randomised controlled trial, trials not involving CR (e.g. cervicobrachial pain, neck pain only), trials involving chronic CR, multilevel or bilateral CR (polyradiculopathy) or radiculomyelopathy, major or systemic pathology, post-surgery interventions, trials of surgery or spinal injection only, or involving a paediatric population or not in English language.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 13 February 2022 and was last updated on 13 February 2022 (registration number INPLASY202220047).

INTRODUCTION

Review question / Objective: **To investigate the effectiveness of conservative management available in primary care for adults with recent onset (less than 12 weeks) cervical radiculopathy. Conservative management will be compared to any available comparator i.e. no treatment, placebo or any treatment.**

Rationale: During the World Health Organisation's Bone & Joint Decade (2000-2010), the Taskforce on Neck Pain (TNF) brought attention to the research gap that existed for the optimal management of people with cervical radiculopathy (CR), despite the high levels of pain and activity limitation often associated with this condition. People with CR present to primary carers seeking diagnosis, reassurance and treatment for a condition thought to have a favourable natural history of recovery over weeks and months (Wong et al., 2014, Alentado et al., 2014). The research gap highlighted by TNF is most evident for the first 12 weeks of the condition, making evidence-based clinical decision-making a challenge for primary carers. A significant increase in CR-focused systematic reviews has also occurred in the last decade investigating epidemiology and diagnostic classification (Lam et al., 2021, Mansfield et al., 2020, Thoomes et al., 2017, Wong et al., 2014), conservative treatment (Borrella-Andrés et al., 2021, Kuligowski et al., 2021, Colombo et al., 2020, Romeo et al., 2018, Gross et al., 2016, Zhu et al., 2016, Gross et al., 2015, Thoomes et al., 2013, Lin et al., 2012, Boyles et al., 2011, Leininger et al., 2011) and surgical management (Alomar et al., 2021, Broekema et al., 2020, Zhang et al., 2020, van Middelkoop et al., 2013) of CR. There has also been recent growth in publication of review protocols (Mansfield et al., 2021, Xue et al., 2021, Zhou et al., 2021, Taso et al., 2020) or review registrations with PROSPERO; all of which signposts increased momentum of enquiry in this population. Manual therapy (mobilisation and/or manipulation) has been the dominant focus of physiotherapy treatment reviews to date, with 8 being undertaken since 2011 (Borrella-Andrés et al., 2021, Kuligowski et al., 2021, Thoomes, 2016, Zhu et al., 2016, Lin et al., 2012, Boyles et al., 2011, Leininger et al., 2011), including a Cochrane review of mechanical neck disorders (Gross et al., 2015). Two additional reviews have focused on effectiveness of traction (Colombo et al., 2020, Romeo et al., 2018). Less individual attention has been given to exercise, other than in a single Cochrane review of mechanical neck disorders (Gross et al., 2016), although it has featured in reviews of all conservative treatment (Thoomes et al., 2013). Kjaer et al. (2017) have highlighted that long-lasting or chronic CR should be considered very different from recent onset CR and although recent clinical practice guidelines (CPG) have provided recommendations for recent-onset CR (Blanpied et al 2017, Côté et al 2016 Kjaer et al 2017), they have done so based on consensus and a small evidence base. Previously published systematic reviews have not considered this temporal delineation, except for Cochrane reviews; which were last updated over 5 years ago (Gross et al, 2015, Gross et al 2016). This systematic review aims to inform the primary carer in shared-decision making with their patient presenting with recent-onset cervical radiculopathy.

Condition being studied: Cervical radiculopathy of recent onset (less than 12 weeks duration). Cervical radiculopathy (CR) has been defined by the North American Spine Society (NASS) as pain in a radicular pattern in one or both upper extremities related to compression and/or irritation of one or more cervical nerve roots, with signs and symptoms including varying degrees of sensory, motor, and reflex changes in addition to dysesthesia and paraesthesia related to nerve root(s) without evidence of spinal cord dysfunction (myelopathy) (Bono et al., 2011). The Neuropathic Pain Special Interest Group (NeuPSIG) of the International Association for the Study of Pain (IASP) have defined CR as an objective loss of sensory and/or motor function from a conduction compromise to a spinal nerve or its root, which can be experienced as painless, or more commonly, painful (Finnerup et al., 2016). The IASP Taxonomy Working Group (2011) highlighted the variable pain experience of CR, which can include referred or spinal pain, and not just radicular pain (typically lancinating). Thoomes et al (2012) have highlighted the lack of consistency across diagnostic criteria used in research and reviewed the value of physical tests in diagnosis and suggested test clusters for ruling in and

ruling out CR diagnosis (Thoomes et al, 2017). In a recent systematic review, Lam et al (2021) evaluated CR classification schemes and suggested 9 eligibility criteria be considered by future researchers. In the current review, a pragmatic approach to diagnostic criteria has been applied, based on Bono et al (2011) and Thoomes et al (2017) to maximise inclusion of relevant trials. The following diagnostic criteria for cervical radiculopathy will be utilised in this review - Complaints of neck, scapular or neck and arm pain; and / or paraesthesia, numbness or dysaesthesia
AND
a. one or more of dermatomal sensory loss, myotomal paresis and hyporeflexia
OR
b. at least 3 positive tests from - Spurling's test, supine distraction test, upper limb neurodynamic test, ipsilateral rotation* or arm squeeze test (Gumina et al, 2013)
OR
c. concordant positive MRI / CT or nerve conduction studies.
*The first 4 tests represent a clinical prediction rule (CPR) for CR diagnosis (Wainner et al 2003). Positive test findings are 1. 10deg difference elbow extension with contralateral limb OR reduction in symptoms with ipsilateral sideflexion or increase with contralateral sideflexion) , 3. positive Spurling's test (arm symptom provocation) & 4. positive Supine distraction test (arm symptom reduction). Diagnosis in primary care is most often based on clinical assessment alone, with MRI, CT or nerve conduction studies often reserved to confirm diagnosis & aetiology in more severe cases, or in advance of secondary referral. In recent onset CR, access to diagnostic tests may not be necessary or readily available in primary care settings in many countries, and to enhance generalisability of this review's findings, confirmatory diagnostic imaging / nerve conduction will not be required for inclusion.

METHODS

Search strategy: Searching will be performed using a combination of Mesh and free text terms in PubMed (MEDLINE) and tailored search strategies in EMBASE and CINAHL (EBSCOhost) and will follow recommendations from the Cochrane Back and Neck Group (Furlan et al, 2015). Search strategies were designed with Grainne McCabe, Scholarly Communications & Research Support Officer, RCSI. Searches will be undertaken from database inception to January 2022. The search strategy was piloted to ensure it was sufficiently sensitive to identify 4 specific studies. Medline search strategy –
Search: ((("Radiculopathy" [Mesh]) OR (radiculopath*[Title/Abstract]) OR (radicular[Title/Abstract]) OR (nerve root pain[Title/Abstract]) OR ("Brachial Plexus Neuropathies" [Mesh]) OR (Cervicobrachial pain[Title/Abstract]) OR (Neuralgia[Mesh])) AND (("Neck Pain"[Mesh]) OR ("Neck"[Mesh]) OR ("Neck Injuries"[Mesh]) OR (neck[Title/Abstract]) OR (cervical[Title/Abstract])) AND ((("Physical Therapy Modalities"[Mesh]) OR (physiotherapy[Title/Abstract]) OR (physical therapy[Title/Abstract]) OR (rehabilitation[Title/Abstract]) OR ("Musculoskeletal Manipulations"[Mesh]) OR (manual therapy[Title/Abstract]) OR (chiropract*[Title/Abstract]) OR (osteopath*[Title/Abstract]) OR (kinesiol*[Title/Abstract]) OR (acupressure[Title/Abstract]) OR (massage[Title/Abstract]) OR (manipulat*[Title/Abstract]) OR (mobilisation[Title/Abstract]) OR (mobilization[Title/Abstract]) OR (neural mobilisation[Title/Abstract]) OR (dry needling[Title/Abstract]) OR ("Acupuncture"[Mesh]) OR (acupuncture[Title/Abstract]) OR (exercise[Title/Abstract]) OR (stretch*[Title/Abstract]) OR (strength*[Title/Abstract]) OR (motor control[Title/Abstract]) OR (physical activity[Title/Abstract]) OR (endurance[Title/Abstract]) OR (resistance[Title/Abstract]) OR ("Exercise Movement Techniques"[Mesh]) OR ("Exercise"[Mesh]) OR ("Conservative Treatment"[Mesh]) OR (conservative[Title/Abstract]) OR (non-surgical[Title/Abstract]) OR (non surgical[Title/Abstract]) OR (nonsurgical[Title/Abstract]) OR (traction[Title/Abstract]) OR (collar*[Title/Abstract]) OR ("Low-level light

therapy"[Mesh]) OR (LLLT[Title/Abstract]) OR (low level laser therapy[Title/Abstract]) OR ("Cryotherapy"[Mesh]) OR (cryotherapy[Title/Abstract]) OR (thermal[Title/Abstract]) OR (taping[Title/Abstract])) OR (("Prescription Drugs"[Mesh]) OR ("Nonprescription Drugs"[Mesh]) OR (prescription drugs[Title/Abstract]) OR (non-prescription drugs[Title/Abstract]) OR (nonprescription drugs[Title/Abstract]) OR (non prescription drugs[Title/Abstract]) OR (over-the-counter drugs[Title/Abstract])) OR (("Health Education"[Mesh]) OR (education[Title/Abstract]) OR (promotion[Title/Abstract]) OR (advice[Title/Abstract]))) AND ((((((((((randomized controlled trial[pt]) OR controlled clinical trial[pt]) OR randomized[tiab]) OR placebo[tiab]) OR clinical trials as topic[mesh:noexp]) OR randomly[tiab]) OR trial[tiab]) NOT (animals[mh] NOT humans[mh])))))).

Participant or population: Adults with single-level cervical radiculopathy of recent onset (12 weeks or less of symptoms) treated in any setting. A clinical diagnosis of CR (as defined in item 10) will be required. Participants with major structural pathology e.g. fracture, dislocation, spinal cord injury, infection, neoplasm & systemic disease (Wong et al 2016) or post-surgery will be excluded. Given the narrow focus of this review on recent-onset radiculopathy, if symptom duration is not specified in studies, authors will be contacted to establish whether this data was collected and can be shared, in order to establish eligibility. In studies that include only a subset of eligible participants, if separate grouping of data is not available within the full text, authors will be contacted requesting access to this data. If the majority of published data in a trial includes eligible participants, all of that trial's data will be included in this review if no contact can be made with the authors. In all other cases, if data is not available or no contact can be made, studies will subsequently be excluded. A sensitivity analysis will explore the impact of inclusion of mixed study data on meta-analysis findings.

Intervention: Conservative management available in a primary care setting e.g. advice, education, pharmacology, exercise, manual therapy, collar, low level laser therapy (LLLT), dry needling, acupuncture etc. The type, intensity, dosage, frequency and duration of all interventions included in the review will be explicitly described, aligning with TIDier checklist (Hoffman et al 2014).

Comparator: Any i.e. no treatment / placebo / other conservative treatment / invasive treatment e.g. surgery or spinal injections.

Study designs to be included: Only randomised controlled trials (RCTs) will be included, as the agreed gold-standard methodology to investigate intervention effectiveness. Identification of RCTs will follow the criteria recommended by the current Cochrane Handbook for Systematic Reviews version 6.2 (Higgins et al, 2021), established by Oxman et al (1994).

Eligibility criteria: Inclusion criteria – trials (as defined in item 15) investigating any conservative management (e.g. exercise, advice, manual therapy, traction, acupuncture, pharmacology etc), involving adults with single level CR (as defined in item 10) of any aetiology, with symptom duration of 12 weeks or less, and including 1 or more of the following outcomes i.e. pain, disability, overall improvement or satisfaction with intervention, quality of life or participation restriction. Exclusion criteria – full text not available, not a randomised controlled trial, trials not involving CR (e.g. cervicobrachial pain, neck pain only), trials involving chronic CR, multilevel or bilateral CR (polyradiculopathy) or radiculomyelopathy, major or systemic pathology, post-surgery interventions, trials of surgery or spinal injection only, or involving a paediatric population or not in English language.

Information sources: Electronic searching of the following databases will be undertaken - Medline (via Pubmed), Cinahl (via EBSCOhost), Embase and and the Cochrane Central Register of Controlled

Trials (Central). Grey literature will be searched using Open Access Theses & Dissertations (OATD) and Web of Science to identify theses from repositories and conference proceedings. Conference proceedings will be used to identify additional studies not found in database searching, but only full text articles will be eligible for inclusion. Scopus will be used for citation searches. Reference lists of included studies and any relevant systematic reviews will also be checked for additional studies.

Main outcome(s): One or more of neck & arm pain levels, activity limitation (disability), overall improvement or satisfaction with intervention (e.g. global rating of change), quality of life or participation restriction (e.g. work status), as recommended by the Cochrane Back and Neck Review Group (Furlan et al., 2015). Primary outcomes are neck & arm pain levels, and activity limitation (disability). Secondary outcomes are overall improvement or satisfaction with intervention (e.g. global rating of change), quality of life or participation restriction (e.g. work status), in addition to any other clinically useful outcomes reported e.g. ROM. Outcomes will be grouped by time frame of measurement, as appropriate.

Additional outcome(s): Adverse effects will also be reported, if available, as suggested by the Cochrane Back and Neck Review Group (Furlan et al 2015).

Data management: One reviewer (LK) will perform searches and then import & merge results in Endnote. After duplicate removal, title & abstracts will be screened (LK), ahead of progression to full text screening. Two reviewers (LK & AM or MBC) will independently screen full text papers for eligibility based on study design, population, interventions and outcomes. Data will be extracted from included studies by one reviewer (LK) and checked by a second reviewer (AM or MBC), using data extraction template 2.0. Data extraction will include study detail e.g. setting, numbers of participants, randomised & analysed, statistical analysis approach e.g. intention-to-treat; participant characteristics, intervention detail e.g. components and dosage; outcomes at baseline and follow up time-points e.g. mean, SD and n measured per group, point estimates with 95% confidence intervals; co-interventions e.g. medication use & other potential confounders; funding sources, conflict of interests and adverse effects. Risk of bias assessment using Cochrane RoB tool 2.0 will also be performed independently by 2 reviewers (LK & AM or MBC). Disagreements at any stage of data management will be discussed and if not resolved, will be reviewed by an independent reviewer (DM). Inter-rater reliability for screening will be assessed using Cohen's kappa for % agreement. Endnote has been used for database management and Covidence software will be used for screening, data extraction & risk of bias assessment. GRADEPro will be used for quality assessment and RevMan 5.4 will be used for meta-analysis.

Quality assessment / Risk of bias analysis: Cochrane RoB tool 2.0 will be used for risk of bias assessment, within Covidence and following data extraction, GRADE quality assessment will be undertaken through GRADEpro software. Inter-rater reliability for RoB / GRADE Assessment will be assessed using Cohen's kappa for % agreement.

Strategy of data synthesis: Continuous data (e.g. pain scores) and categorical data may be extracted. The data extraction table will be examined by 2 reviewers to consider study heterogeneity of included studies e.g. outcome measures used. Depending on study heterogeneity, a meta-analysis will be performed on primary outcomes, using mean differences (MD) or standardised mean differences (SMD) with 95%CIs. SMD will be used for continuous data where there are differences in interventions being assessed or variation in outcome measures and difference in scales used, across studies. Mean difference (MD) will be used for studies reporting the same outcome measure e.g. NPRS for pain. Fixed effect or random-effects model determination will

be based on heterogeneity. Statistical heterogeneity will be assessed using the inconsistency value (I2). In case of moderate heterogeneity (I2 >/=50% or p < 0.05), subgroup analyses will be conducted to investigate the sources of heterogeneity. Values of 50% or above will indicate use of a random-effects model in the meta-analysis to a random-effects model. When I^2 is less than 50%, a fixed-effect model will be adopted. If a meta-analysis is not possible, a qualitative analysis will be undertaken for primary and secondary outcomes. Publication bias will also be assessed with a funnel plot to explore asymmetry among trial results.

Subgroup analysis: Study comparisons will be sub-grouped by intervention (e.g. conservative treatment vs. no treatment / placebo) and if adequate data are available, for each follow-up time-point separately e.g. short & longer-term. If studies are identified in both primary & secondary care, an additional sub-group analysis will be performed.

Sensitivity analysis: Sensitivity analyses will assess the effect of potential selection & attrition bias on primary outcomes (pain and disability), based on removing studies at high risk of bias from meta-analysis. An additional analysis will explore the impact of inclusion of mixed study data on meta-analysis findings, if the need arises.

Language: English language only.

Country(ies) involved: Ireland.

Keywords: Cervical radiculopathy; neck; conservative treatment; physical therapy modalities; prescription drugs.

Dissemination plans: This systematic review will be published in a peer-reviewed journal.

Contributions of each author:
Author 1 - Louise Keating - Author 1 drafted the protocol and was involved in all elements of data management, synthesis, analysis and dissemination.
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Author 2 - Dr. Ailish Malone - Involved in data management, piloting data extraction template, checking data extraction and analysis of data.
Author 3 - Dr. Maire-Brid Casey - Involved in data management, checking data extraction & analysis of data.
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Author 5 - Dr. Dara Meldrum - Independent third reviewer.
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