# Nonoperative management of degenerative cervical radiculopathy: protocol of a systematic review

Joshua Plener, DC[1,2]
Carlo Ammendolia, DC, PhD[2,3,4]
Sheilah Hogg-Johnson, MMath, PhD[5,6,7,8]

Background: *Degenerative cervical radiculopathy (DCR) is a common condition which, due to the aging global population, is expected to worsen over time. For the majority of patients with DCR, surgical intervention is not required as nonoperative management is sufficient for symptom improvement. However, there are significant gaps within the literature as the majority of past systematic reviews assessing conservative interventions are outdated, or omit relevant studies due to strict inclusion/exclusion criteria. Therefore, an updated understanding of the effectiveness of noninvasive nonoperative management for DCR is required.*

Prise en charge non opératoire de la radiculopathie cervicale dégénérative : protocole d'un examen systématique.

Contexte : *la radiculopathie cervicale dégénérative (DCR) est une affection courante qui, en raison du vieillissement de la population mondiale, devrait s'aggraver avec le temps. Pour la majorité des patients atteints de DCR, une intervention chirurgicale n'est pas nécessaire, car la prise en charge non opératoire est suffisante pour l'amélioration des symptômes. Cependant, il existe des lacunes importantes dans les publications scientifiques, car la majorité des examens systématiques antérieurs évaluant les interventions conservatrices sont obsolètes ou omettent des études pertinentes en raison de critères d'inclusion et exclusion stricts. Par conséquent, une compréhension actualisée de l'efficacité de la prise en charge non invasive et non opératoire de la DCR est nécessaire.*

[1]  Division of Graduate Studies, Canadian Memorial Chiropractic College
[2]  Institute for Health Policy Management and Evaluation, University of Toronto
[3]  Department of Medicine, Mount Sinai Hospital, Toronto, Canada
[4]  Department of Surgery, University of Toronto, Toronto, Canada
[5]  Department of Research and Innovation, Canadian Memorial Chiropractic College
[6]  Dalla Lana School of Public Health, University of Toronto
[7]  Institute for Disability and Rehabilitation Research
[8]  Faculty of Health Sciences, Ontario Tech University

Corresponding author: Joshua Plener, Canadian Memorial Chiropractic College, 6100 Leslie Street, Toronto, ON, M2H 3J1
Tel: 416-482-2340
E-mail: jplener@cmcc.ca

Methods: *We will search MEDLINE, CENTRAL, Embase, PsycINFO, and CINAHL from inception, as well as hand-search reference lists of included studies and previous systematic reviews, to identify peer-reviewed randomized controlled trials on this topic.*

Discussion: *The results of this review will provide an understanding of the effectiveness of various nonoperative interventions. The quality of evidence will also be assessed using the GRADE approach.*

Systematic review registration: PROSPERO CRD42021249699

Méthodologie : *nous effectuerons des recherches dans MEDLINE, CENTRAL, Embase, PsycINFO et CINAHL depuis le début, et entreprendrons des recherches manuelles dans les listes de références des études incluses et des examens systématiques précédents, afin de déterminer les essais contrôlés randomisés et évalués par des pairs sur ce sujet.*

Discussion : *les résultats de cet examen permettront de comprendre l'efficacité de diverses interventions non opératoires. La qualité des preuves sera également évaluée à l'aide de l'approche GRADE.*

Enregistrement d'examen systématique : PROSPERO CRD42021249699

## Background

Cervical radiculopathy from degenerative disorders, termed degenerative cervical radiculopathy (DCR), is defined 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".[1,2] This condition can result from degenerative changes to the intervertebral disc and uncovertebral and facet joints, leading to disc herniations and bone hyperplasia, which can cause nerve root compression.[2-5] Despite the generally favourable natural history of DCR, with significant improvements within four to six months, patient symptoms can include severe pain, paresthesia and motor weakness, which can lead to significant morbidity and disability, resulting in poorer quality of life (QOL).[2,6-8] Current epidemiological data suggests that DCR has an incidence between 0.83 to 1.79 per 1000 person-years and a point prevalence of 1.21 to 5.8 per 1000.[9-12] These numbers are expected to increase as a result of the aging population and a rise in degenerative spinal conditions.[13,14]

Conservative management is considered the first-line treatment for DCR, with surgery reserved for non-responsive cases or significant neurological decline.[2,15] The majority of past systematic reviews have focussed on the effectiveness of single unimodal conservative interventions. Zhu et al.[16] identified three trials that demonstrated a significant short-term improvement in pain with cervical manipulation compared to computer traction. Romeo et al.[17] and Colombo et al.[18] found that the effectiveness of cervical traction for cervical radiculopathy has mixed results, demonstrating statistically but not clinically significant improvements.[17,18] Liang et al.[19] assessed exercise in patients with cervical radiculopathy, finding low quality evidence that exercise significantly improves pain and disability scores.

Despite the range of nonoperative interventions assessed in individual systematic reviews, significant gaps still exist. One reason for this includes the date of completion for some reviews. Systematic reviews assessing exercise and cervical traction have search strategies ending between 2018 to early 2020, but Zhu et al.[16] completed the most recent systematic review assessing the literature on cervical spine manipulation for DCR with a search ending in 2014.[16-19] In addition, the most recent systematic review to assess multiple conservative interventions searched until 2011, and this review found only low to very low quality evidence for any single intervention.[20] Furthermore, clinical practice guidelines with the

most recent search ending in 2016 have cited limited literature, providing varying levels of evidence to support their recommendations.[21-23] Another reason for these gaps in knowledge involves the exclusion of relevant comparative groups required to assess and understand the clinical effectiveness of each treatment. For example, Colombo *et al*.[18] excluded studies assessing cervical traction compared to other passive/active interventions and Liang *et al*.[19] excluded studies that included exercise in both the treatment and control group. As a result of the above limitations of past systematic reviews on this topic, a significant number of studies have not been assessed and included.[24-34] Therefore, an updated comprehensive review examining the effectiveness and quality of evidence for conservative interventions of DCR is urgently needed.

Our objective is to conduct a systematic review to identify, appraise and synthesize the evidence on the effectiveness and safety of noninvasive nonoperative treatments for the management of adults with DCR.

## Methods

### Protocol
This systematic review protocol development was guided using the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P).[35] The subsequent systematic review will be reported based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[36] The systematic review protocol has been registered through the International Prospective Register of Systematic Reviews (PROSPERO) database (CRD42021249699).

### Eligibility criteria

### PICO question
Are noninvasive nonoperative interventions associated with short-term and long-term improvements in pain, associated symptoms such as numbness and weakness, disability, functional status, and quality of life compared to other interventions, placebo/sham interventions, or no intervention for the management of adults with DCR?

### Population
Our systematic review will include studies examining adults aged 18 years or older with DCR of any duration

(i.e. acute/recent, chronic/persistent) secondary to degenerative disorders, which are the most common causes of cervical radiculopathy. As it is clinically difficult to identify the pathoanatomical cause for an individual's cervical radiculopathy, included studies will involve participants with disc herniations and bone hyperplasia in isolation or in combination.[7] Studies will be excluded if major structural or serious pathology is present such as fractures, tumor, infection, major trauma, neurodegenerative disease or inflammatory arthritides. Furthermore, post-surgical studies will be excluded.

The diagnostic criteria used for participant inclusion in conservative intervention studies is heterogenous, with a history based diagnosis such as radiating arm pain being the most common.[37] Concurrent diagnostic modalities including a neurological examination (sensory, motor and/or reflex deficits), physical examination tests (i.e., Spurling's and/or upper limb nerve tension tests) and/or imaging are used less frequently.[8,37,38] In particular, imaging is recommended for interventional and/or surgical procedures, and as a result may be utilized less in patient populations receiving conservative care.[1,37] Since this systematic review will be assessing nonoperative interventions, a diagnosis based on clinical findings and/or diagnostic findings would be appropriate.

For this systematic review, diagnostic imaging reported in any included study will be used as supplemental information. If imaging is present and an isolated etiology of radiculopathy can be ascertained, study results will be stratified according to the etiology. This will provide the opportunity to assess the effectiveness of nonoperative interventions depending on the cause of symptoms, which has been demonstrated to be important in other degenerative cervical spine disorders.[39]

### Intervention
Studies that assess at least one treatment arm of noninvasive nonoperative management will be included. Examples of treatment can include physical therapy, medications (e.g. NSAIDs, muscle relaxants, gabapentin/pregabalin), collars, cervical manipulation/mobilization, acupuncture, cervical traction, and multimodal care.[16,19,20] Nonoperative treatments will be categorized based on the Ontario Protocol for Traffic Injury Management (OPTIMa) Collaboration which includes manual therapy (e.g. manipulation, mobilization, traction), soft tissue ther-

apy, exercise, patient education, acupuncture and passive physical modalities.[22,40] In addition, a category of pharmacological interventions will be used in this review as interventions such as medications will be included.

## Comparators

Studies may include no treatment/observation, operative treatment, nonoperative treatment and/or placebo/sham treatment. These are similar to comparators other systematic reviews have utilized when assessing the effects of nonoperative treatment for degenerative spinal conditions.[41,42]

## Outcomes

The following outcomes for DCR will be targeted: (1) Disability scores (e.g., neck disability index (NDI)[43,44]), (2) pain intensity (e.g., neck and arm pain[44]), (3) functional status (e.g., patient specific functional scale[44,45]), (4) quality of life (e.g., SF-36, EuroQol[46]), (5) psychological impact (e.g., Fear-Avoidance Beliefs Questionnaire (FABQ)[47]), and (6) global success of treatment (e.g., global perceived effect scale[46], global rating of change[1]). When available, adverse events and/or complications will be recorded. Clinical outcomes unrelated to the conservative treatment of DCR will be excluded, such as qualitative studies describing patient experiences, surgical outcomes (e.g., blood loss), health care utilization, and cost-effectiveness outcomes.

## Time

Following similar protocols utilized when evaluating the nonoperative management of lumbar spinal stenosis[42], treatment outcomes will be analyzed according to: immediate (up to one week following the intervention), short-term (between one week and three months), intermediate (between three months and one year) and long-term (one year or longer) post-treatment. This will help inform the effect of nonoperative treatments on DCR with regards to short-term compared to long-term symptom relief.

## Study designs/characteristics

Eligible studies targeting the population, intervention and outcomes listed above must meet the following criteria: 1) English language; 2) randomized controlled trial; 3) at least one treatment arm is nonoperative and noninvasive;

4) mixed population studies must report DCR subjects separately; 5) included studies must have participants diagnosed with symptomatic DCR confirmed through positive clinical examination tests and/or diagnostic tests; and 6) at least one of the outcomes listed above has to be measured. The following will be excluded: 1) case reports, case series, cohort studies, and case-control studies; 2) cadaveric or animal studies; 3) studies assessing degenerative cervical myelopathy; 4) DCR caused by major structural or serious pathology such as fractures, tumor, infection, neurodegenerative disease or inflammatory arthritides; 5) post-surgical studies; and 6) qualitative studies.

## Information sources and search strategy

MEDLINE (Ovid), Cochrane Controlled Register of Trials (CENTRAL), CINAHL (EBSCO), Embase (Ovid), PsycINFO (Ovid) will be searched from database inception to April 30, 2021. The search strategy will be developed with the assistance of a Health Sciences Librarian, with a second librarian peer reviewing the final search strategy using the Peer Review of Electronic Search Strategies (PRESS) Checklist.[48] The search strategy will be constructed in Ovid MEDLINE (Appendix 1) and adapted to the other databases listed. Search terms will include subject headings (e.g. MeSH in MEDLINE) and free text words to capture key concept DCR, and retrieve randomized controlled trials. EndNote X9 will be used as an electronic reference manager to identify duplicate references across databases, and record the number of duplicates identified. In addition, reference lists of included studies and previous systematic reviews on this topic will be hand searched to ensure all relevant studies are identified.

## Data collection and analysis

## Study selection

Screening for eligible studies will occur using pairs of independent reviewers over a two-phase process. In phase 1, title and abstracts will be screened by pairs of independent reviewers to determine study eligibility by denoting studies as possibly relevant or irrelevant. Studies where disagreements arise will automatically move to phase 2.[49] In phase 2, possibly relevant articles will be screened by pairs of independent reviewers to determine

eligibility and studies will be categorized as relevant or irrelevant, with reasons provided for excluding studies. After independent review is completed, reviewers will meet to discuss disagreements and reach consensus for study eligibility. During phase 2, a third reviewer will be consulted if consensus cannot be reached. Missing information will be sought by contacting study authors for information pertinent to screening, risk of bias assessment, and data extraction.

### Data items and data collection process

Pairs of independent reviewers will extract the relevant study data. One reviewer will build evidence tables through data extraction from eligible studies. A second reviewer will independently extract study results (e.g. means and 95% confidence interval) to ensure accuracy, with any disagreements discussed to reach consensus. In addition, a second reviewer will assess the remaining extracted evidence table fields to verify and ensure accuracy and completeness. Disagreements will be discussed to reach consensus, with an independent third reviewer used if needed. Data will be extracted from each study on:

1) **study characteristics** (e.g., author, publication year, number of patients, mean age of participants, country and years of trial conduction, number of trial centres, institution of first author, country where trial was conducted, funding sources, randomization method, blinding method, the use of cross-overs, dropouts and withdrawals, study follow-up, reported prior conservative treatment, study participant demographics, duration of condition, inclusion and exclusion criteria, etiology of cervical radiculopathy, utilization of imaging, co-morbidities);

2) **symptoms** (e.g., neck pain, arm/hand pain, arm/hand symptoms including weakness and sensory deficits);

3) **outcome measures** such as pain scores, disability scores, global success of treatment, well-being (e.g., quality of life measures), participation restriction (e.g., ability to work, mental status), activities of daily living, medication consumption, and adverse events);

4) **interventions and comparisons** (e.g. number

of patients, type, intensity, dosage, frequency and duration);

5) **study results** organized based on immediate (up to one week following the intervention), short-term (between one week and three months), intermediate (between three months and one year) and long-term (one year or longer) post-treatment; and

6) **statistical analysis** (e.g. effect size, confidence intervals, power calculation, intention-to-treat analysis and statistical tests such as ANOVA).

Authors will be contacted if there is missing information in studies and if no response is received, study results will be described based on availability. The data extraction form will be pilot tested on five randomly selected studies with amendments made accordingly.[49]

### Methodological quality and risk of bias appraisal

Pairs of independent reviewers will critically appraise eligible studies for bias using the Cochrane Risk of Bias for Randomized Trials (ROB 2). Established on empirical evidence, bias will be assessed based on five domains; bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported results.[50] Signalling questions within the ROB 2 tool are utilized by reviewers within an algorithm in order to identify a judgement on the risk of bias.[50] The risk-of-bias judgement within each domain will be assigned to one of the three categories: low risk of bias, some concerns or high risk of bias.[50] If a consensus cannot be reached, a third independent reviewer will be used to assist with any disagreement.

### Data synthesis and strength of the evidence

The Grades of Recommendations, Assessment, Development, and Evaluation (GRADE) will be used to assess the overall study quality. GRADE assessments are based on five domains: limitations in design and implementation (risk of bias), inconsistency (heterogeneity), indirectness (inability to generalize), imprecision (insufficient or imprecise data), and publication bias (selective reporting).[49]

*Inconsistency* refers to the heterogeneity of the results measured by $I^2$. While downgrading based on $I^2$ thresh-

olds have been proposed in the literature (<40% is low, 30-60% is moderate, 50-90% is substantial, and 75-100% is considerable[50,51]), for this review significant heterogeneity will be defined as an $I^2 \geq 50\%$.[52] When pooling of studies is not possible, consistency will be defined as $\geq 75\%$ of studies in the same direction (i.e. benefit versus no benefit).[49]

*Indirectness* refers to the representative nature of the population, intervention or outcomes compared to the review's inclusion criteria, with downgrading occurring if deviations from the inclusion criteria occur.[49,53]

*Imprecision* refers to the number of participants, events, and width of confidence intervals.[49] Sufficient sample size and narrow confidence intervals will be required for a classification of precise.[54] Sufficient sample size will be defined as 400 or more.[54]

*Publication bias* refers to the selective publication of trials and selective reporting of outcomes.[49] Selective reporting will be defined as pre-planned outcomes that are not provided in the results section.[49] When at least 10 studies are included in the meta-analysis, a funnel plot will be produced to assess for asymmetry.[49]

For the GRADE approach, RCTs begin as high-quality evidence and are downgraded for each domain not met.[49,55] Evidence for outcomes provided from a single small trial will be considered imprecise and inconsistent and therefore downgraded by at least two levels (Table 1).

Treatment effects for outcomes will be assessed based off statistically significant and clinically important differences. Dichotomous outcomes will be expressed as relative risk and continuous outcomes as mean differences or standard mean differences with 95% CI will be calculated. Clinically important differences between treatment groups will be measured according to published minimal clinically important differences (MCID) in a similar patient population. For outcomes where an MCID is not published, a between group absolute difference of 30% will be used in its place. When using MCIDs, it is important to understand their limitations. For example, MCIDs are sample dependent and therefore different MCIDs may alter the results, such as utilizing patient populations who have undergone conservative versus surgical interventions.[56-59] Despite these limitations, recognizing if between group differences appear to be clinically significant, in addition to statistically significant is important when assessing clinical effectiveness.

When possible, results will be stratified by the type of DCR (i.e., disc herniation; bone hypertrophy), and duration of symptoms (immediate, short-term, intermediate, and long-term post-treatment). If two or more studies are sufficiently homogenous, a random-effects model meta-analysis will be performed. The Cochrane Back and Neck Group recommends using a random-effects model rather than a fixed-effects model as a result of the clinical heterogeneity in the back and neck pain literature.[49] To assess the potential effects of heterogeneity, the following sensitivity analyses will be conducted: 1) methodological quality (risk of bias) impact on study results will be assessed by completing the meta-analysis with all studies (low, some concerns, and high risk of bias), as well as each category separated, 2) DCR etiology, and 3) small sample size bias through a fixed-effect model meta-analysis. If statistical pooling is not possible, the results will be qualitatively described. Results will be interpreted to determine if an intervention is superior, equal or inferior to a comparison group.

### Discussion

The results of this review will provide an updated understanding of the quality of evidence for noninvasive nonoperative treatments for DCR. As mentioned above, there are significant limitations of the previously published DCR systematic reviews, resulting in an incom-

Table 1.
*GRADE quality of evidence and description.*

| Evidence Quality | Description |
| --- | --- |
| High quality | Further research is very unlikely to change our confidence in the estimate of effect |
| Moderate quality | Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate |
| Low quality | Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate |
| Very low quality | Any estimate of effect is very uncertain |

plete understanding of the effectiveness of nonoperative interventions for this condition. With the burden of disability associated with cervical radiculopathy expected to increase, an updated, comprehensive, in-depth understanding of conservative interventions is needed in order to inform clinical practice, and identify research gaps. The results of this review will be relevant to patients, clinicians, and researchers to ensure the best available care is provided to DCR patients and the current state of the literature is understood.

This review is not without limitations. First, there are no standardized diagnostic criteria for DCR. Therefore, to ensure appropriate conservative management studies are included, this review will utilize a diagnosis based on clinical and/or diagnostic findings. As diagnostic imaging is used infrequently in conservative management studies, there is the possibility of including participants in studies that do not have DCR due to the lack of imaging confirmed findings. Therefore, to mitigate this, studies that include participants based on a clinical diagnosis will be required to include at least one objective finding, as diagnostic studies have demonstrated acceptable psychometric properties for clinical tests such as orthopedic and neurological examination, and it is suggested that only relying on patient reported symptoms can lead to a false positive diagnosis and the inclusion of symptomatically similar conditions.[38,60,61] Second, even though it has been suggested that the etiology of DCR plays a role in prognosis and clinical course, studies do not consistently differentiate the cause of radiculopathy in their included sample. In this review, study results will be stratified according to the cause of symptoms when possible, potentially leading to a better understanding of the impact of etiology on clinical outcomes. Third, following the search, only studies published in English will be included, which will result in any study published in a different language being omitted from the review. Even though it has been demonstrated that limiting included studies to the English language does not result in systematic bias[62], citations for studies that were potentially relevant but in a different language will be provided in the manuscript.

The results of this review will be used in conjunction with current on-going work to develop an evidence-based, patient centered program of care for DCR patients through the use of intervention mapping. Intervention mapping incorporates the best available evidence, along with the application of theories, as well as program implementers and key stakeholders to ensure relevant needs are met.[63] This review will be utilized as one component of the intervention mapping process, as these findings will be vital to inform the current literature of nonoperative DCR interventions.

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Appendix 1.
*Ovid MEDLINE search strategy*

| | |
|---|---|
| 1. Radiculopathy/ | 40. exp Clinical Trials as Topic/ |
| 2. Polyradiculopathy/ | 41. Double-Blind Method/ |
| 3. radiculopath*.mp. | 42. Single-Blind Method/ |
| 4. radiating*.mp. | 43. exp Placebos/ |
| 5. radicular*.mp. | 44. random*.mp. |
| 6. radiculit*.mp. | 45. clinical trial*.mp. |
| 7. polyradiculopathy*.mp. | 46. double* adj2 blind*.mp. |
| 8. poly-radiculopath*.mp. | 47. single* adj2 blind*.mp. |
| 9. neuropath*.mp. | 48. placebo*.mp. |
| 10. NAD grad*.mp. | 49. randomized controlled trial*.pt. |
| 11. grade III NAD.mp. | 50. controlled clinical trial*.pt. |
| 12. pain grade III.mp. | 51. clinical trial.pt. |
| 13. 1-12/OR | 52.  35-51/ OR |
| | |
| 14. exp Cervical Vertebrae/ | 53. 34 AND 52 |
| 15. exp Cervical Plexus/ | 54. Limit 53 NOT (comment or clinical conference |
| 16. Brachial Plexus/ | or congress or consensus development conference |
| 17. cervical*.mp. | or editorial or letter or guideline or practice |
| 18. neck*.mp. | guideline or case reports).pt. |
| 19. c-1*.mp. | 55. 54 NOT (Animals/ NOT Humans/) |
| 20. c-2*.mp. | |
| 21. c-3*.mp. | |
| 22. c-4*.mp. | |
| 23. c-5*.mp. | |
| 24. c-6*.mp. | |
| 25. c-7*.mp. | |
| 26. cervico-gen*.mp. | |
| 27. cervicogen*.mp. | |
| 28. c-spine*.mp. | |
| 29. "c spine".mp. | |
| 30. brachial* adj2 plexus*.mp. | |
| 31. cervicobrachial*.mp. | |
| 32. cervico-brachial*.mp. | |
| 33. 14-32/ OR | |
| | |
| 34. 13 AND 33 | |
| | |
| 35. exp Randomized Controlled Trial/ | |
| 36. exp Randomized Controlled Trials as Topic/ | |
| 37. Controlled Clinical Trial/ | |
| 38. exp Controlled Clinical Trials as Topic/ | |
| 39. exp Clinical Trial/ | |