

## ORIGINAL REPORT

## EFFECTIVENESS OF MULTIMODAL REHABILITATION INTERVENTIONS FOR MANAGEMENT OF CERVICAL RADICULOPATHY IN ADULTS: AN UPDATED SYSTEMATIC REVIEW FROM THE ONTARIO PROTOCOL FOR TRAFFIC INJURY MANAGEMENT (OPTIMA) COLLABORATION

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**Objective:** To update the systematic review from the Ontario Protocol for Traffic Injury Management (OPTIMA) Collaboration and to evaluate the effectiveness of multimodal rehabilitation interventions for the management of adults with cervical radiculopathy.

**Study design:** Systematic review and best-evidence synthesis.

**Methods:** Eligible studies (from January 2013 to June 2020) were critically appraised using the Scottish Intercollegiate Guidelines Network and Risk of Bias 2.0 criteria. The certainty of the evidence was assessed according to Grading of Recommendations Assessment, Development, and Evaluation.

**Results:** Four RCTs were deemed acceptable and 1 RCT was considered low quality. In adults with recent-onset cervical radiculopathy, multimodal rehabilitation was associated with a trivial and non-clinically important reduction in neck pain compared with mechanical cervical traction; no differences in disability were reported (1 study, 360 participants, low certainty of the evidence). In adults with cervical radiculopathy of any duration, (i) multimodal rehabilitation may be more effective than prescribed physical activity and brief cognitive-behavioural approach; specifically, a small reduction in arm pain and in function was found (1 study, 144 participants, low certainty of the evidence); (ii) no difference in pain reduction was found between multimodal rehabilitation interventions compared with an epidural steroid injection (1 study, 169 participants, low certainty of the evidence); and (iii) compared with surgery combined with neck exercises, multimodal rehabilitation interventions lead to similar arm pain reduction and improvement in function (1 study, 68 participants, low certainty of the evidence).

**Conclusion:** The evidence suggests that some multimodal rehabilitation care may provide small and trivial reduction in neck pain or improvement in function to patients with cervical radiculopathy.

## LAY ABSTRACT

Cervical radiculopathy refers to neck and arm pain associated with neurological signs and symptoms. Management of this condition involves clinical rehabilitation as the first line of treatment. A systematic review of the literature was performed to evaluate the effectiveness of multimodal interventions for management of cervical radiculopathy. This review suggests that multimodal interventions that include manual therapy to the cervical spine or neck-specific exercises, education, and a cognitive behavioural approach are associated with trivial benefits to patients with cervical radiculopathy. The review also found that adding medication (gabapentin), education, electrical stimulations, ultrasound, massage, and exercise to epidural steroid injection leads to similar outcomes as an epidural steroid injection alone. Finally, the evidence suggests that multimodal rehabilitation (exercises and education) leads to similar outcomes to surgery combined with neck exercises, pain coping, self-efficacy, and stress management strategies.

**Key words:** cervical radiculopathy; multimodal rehabilitation; grade III NAD; disc herniation.

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Cervical radiculopathy refers to radicular arm pain associated with neurological signs and symptoms including decreased deep tendon reflexes, weakness, or sensory deficits (1). Patients with cervical radiculopathy often present with high-intensity neck and arm pain and limited functioning (2). A recent systematic review suggests that the incidence of cervical radiculopathy ranges from 0.83 per 1,000 person-years

in the general population to 1.79 per 1,000 person-years in US military personnel (3). The same review reported that the prevalence ranged from 0.13% in Bombay, India to 0.35% in Sicily, Italy (3). Finally, the incidence of cervical radiculopathy related to disc protrusion/herniation has been estimated at 0.055 per 1,000 person-years, and to peak between the ages of 45 and 54 years (4).

Management of cervical radiculopathy involves clinical rehabilitation as the first line of treatment (5). However, evidence about the effectiveness and safety of most rehabilitation interventions is lacking. In 2008, The Bone and Joint Decade 2000–2010 Task Force on Neck Pain and Its Associated Disorders defined multimodal interventions as a combination of single treatments, rehabilitation programmes, or packages of care (4, 6). Their systematic review concluded that there was no evidence that rehabilitation interventions led to clinically important benefits in patients with cervical radiculopathy (6).

More recently, in 2016, the Ontario Protocol for Traffic Injury Management (OPTIMA) Collaboration recommended that clinicians consider a course of supervised strengthening exercises and structured patient education to manage patients with recent onset (<3 months) cervical radiculopathy (5). The literature search for the OPTIMA systematic review ended in 2013; an update is therefore warranted.

The objective of this systematic review is to determine the effectiveness and safety of multimodal rehabilitation interventions compared with other interventions, placebo/sham interventions, or no intervention in the management of adults with cervical radiculopathy. The review focuses on multimodal rehabilitation because clinical care typically involves combining more than one type of intervention when managing patients (5).

## METHODS

### Registration

The review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) on 28 August 2019 (CRD42019138058). The review deviated from the protocol by the conduction of a sensitivity analysis to assess whether the validity of the results was dependent on the critical appraisal method used in the review. Therefore, we re-evaluated the quality of all eligible randomized controlled trials (RCTs) using the Cochrane Risk of Bias Tool for Randomized Trials version 2 (RoB 2) tool (7).

### Population

The review targeted studies of adults (aged  $\geq 18$  years) with cervical radiculopathy of traumatic (e.g. related to

traffic collisions) or non-traumatic nature. Studies that recruited surgical populations at baseline, studies of neck pain without radiculopathy, and studies of neck pain due to major structural pathology (e.g. fractures, dislocations, spinal cord injury, or neoplasms) were excluded.

### Inclusion and exclusion criteria

Eligible studies had to fulfil the following inclusion criteria: (i) published in a peer-reviewed journal; (ii) English or French language; (iii) RCTs, cohort studies and case-control studies; and (iv) at least 30 participants per treatment arm for RCTs, or 100 subjects per group for cohort studies. For RCTs, a sample size of 30 per study group is conventionally considered the minimum needed for non-normal distributions to approximate the normal distribution. In cohort and case-control studies, a sample of 100 is conventionally considered the minimum needed to effectively control for multiple confounding variables (8–11).

The following publications were excluded: (i) guidelines, letters, editorials, commentaries, unpublished manuscripts, dissertations, government reports, books and book chapters, conference proceedings, meeting abstracts, lectures and addresses, consensus development statements, guideline statements; (ii) pilot studies, cross-sectional studies, case reports, case series, qualitative studies, non-systematic and systematic reviews, clinical practice guidelines, biomechanical studies, laboratory studies, studies not reporting on methodology; and (iii) cadaveric or animal studies; (iv) studies that included participants with severe injuries or pathologies (spinal cord injuries, moderate and severe traumatic brain injuries, amputations, blindness, fracture, injuries resulting in a complete or partial joint dislocation, myelopathy, neoplasm, or systemic disease).

### Interventions

For this study, “rehabilitation” was defined according to the World Health Organization (WHO) as a “set of interventions designed to optimize functioning and reduce disability in individuals with health conditions in interaction with their environment” and “multimodal rehabilitation” was defined as “an approach that includes at least 2 different therapeutic modalities” (12). Multimodal rehabilitation may include a combination of acupuncture, education, exercise, manual and soft-tissue therapies, passive physical modalities, psychological interventions, and pharmacological interventions (Appendix I). These interventions can be provided by 1 or more healthcare provider. Studies of surgical interventions alone and studies that investigated the effectiveness of a single intervention were excluded.

### Comparison groups

Studies that compared multimodal rehabilitation with other interventions (single rehabilitation interventions, pharmacological or non-pharmacological treatments), placebo/sham interventions, or no intervention were eligible for the review.

### Outcomes

The review focused on the following outcomes: (i) functioning (e.g. disability, return to activities, work, or school); (ii) self-rated recovery (e.g. global perceived recovery); (iii) clinical outcomes (e.g. pain, health-related quality of life); (iv) psychological outcomes (e.g. depression, anxiety, stress); (v) administrative outcomes (e.g. time on benefits); or (vi) adverse events. Outcomes related to costs and cost-effectiveness were excluded from this review.

### Search strategy and information sources

The search strategy was developed with a health sciences librarian (Appendix II). The search strategy was reviewed by a second librarian for completeness and accuracy using the Peer Review of Electronic Search Strategies (PRESS) Checklist (13). The following electronic databases were systematically searched from 1 January 2013 to 22 June 2020: PubMed, MEDLINE, Embase, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Index to Chiropractic Literature, PEDro, APA PsycInfo, SportDiscus, and the Cochrane Central Register of Controlled Trials. Databases were searched from 1 January 2013, because the literature search for the systematic review by the OPTIMA Collaboration ended on 16 May 2013. The search strategy was first developed in MEDLINE and subsequently adapted to the other databases. The search terms included subject headings (e.g. MeSH in MEDLINE) and free-text words relevant to cervical radiculopathy and Neck Associated Disorders grade III. For feasibility reasons, grey literature was not searched.

### Study selection

A 2-phase screening process was used to select eligible studies. In phase 1, pairs of independent reviewers screened titles and abstracts to determine eligibility. Studies were classified as relevant, possibly relevant, or irrelevant. In phase 2, the same reviewers independently reviewed manuscripts of possibly relevant studies to make a final determination of eligibility. Reviewers met to resolve disagreements and reach consensus in both phases. Disagreements were resolved by a third reviewer (PC).

### Assessment of risk of bias

Two independent reviewers (FM and NL) critically appraised the internal validity of eligible studies using the Scottish Intercollegiate Guidelines Network (SIGN) criteria for RCTs, cohort studies and case-control studies (14). Reviewers were trained in the evaluation of studies using the SIGN criteria. The SIGN criteria assist with evaluation of the impact of selection bias, information bias, and confounding on the results of a study. Specifically, the following methodological aspects of an RCT were critically appraised: (i) clarity of the research question; (ii) randomization method; (iii) concealment of treatment allocation; (iv) blinding of patient/treatment provider and of outcome assessor or data analyst (modification from the SIGN criteria); (v) similarity of baseline characteristics between treatment arms; (vi) co-intervention/contamination; (vii) validity and reliability of outcome measures; (viii) attrition; (ix) intention to treat analysis; and (x) comparability of results across study sites (where applicable) (Appendix III).

Consensus between reviewers was reached through discussion. An independent third reviewer was included to resolve disagreements if consensus could not be reached (PC).

Studies were rated as high, acceptable, or low quality using the SIGN criteria. In the sensitivity analysis, studies were also rated as high risk of bias, some concern, or low risk of bias according to the RoB 2 tool (7).

### Data extraction

The data extraction process involved 2 steps. First, the lead author (FM) extracted data from acceptable studies to build evidence tables. Data extracted included author, year, country; subject and setting; description of interventions; description of comparisons; follow-up period; outcome measures; and key findings including: (i) summary statistics for each group (where appropriate) and, (ii) an effect estimate and its precision (e.g. 95% confidence interval; 95% CI). Secondly, 2 reviewers (NL and JW) independently checked the accuracy of the extracted data by referring to the original studies.

### Heterogeneity of RCTs

The study assessed the clinical heterogeneity of eligible RCTs by comparing the characteristics of their samples, interventions, comparators, and outcomes.

### Data synthesis

Evidence from acceptable studies was synthesized according to the Synthesis without Meta-Analysis (SWiM) Guideline (Appendix IV) and reported in



evidence tables (15). Standardized cut-off values were used to determine if clinically important changes were reached in each study for common outcome measures. These include a mean difference of 2/10 on the numerical rating scale (NRS) (16), 10/100 mm on the visual analogue scale (VAS) for neck pain and arm pain change (16), 7/50 on the Neck Disability Index (NDI) (17), 9/24 for the physical subscale of Fear Avoidance Belief Questionnaire (FABQ) and 12/42 for the work subscale of FABQ (18,19), and 1.5/21 points for the Hospital Anxiety and Depression Scale (HADS) (20). Accordingly, the effectiveness of interventions was reported as: (i) superior (associated with a clinically important change compared with its comparator), (ii) equivalent (no clinically important differences between groups), and (iii) inferior (associated with worse outcomes than its comparator). Results were interpreted by considering the direction, magnitude, and precision of effect estimates across studies, impact of risk of bias in sensitivity analyses, and generalizability of findings.

The synthesis was stratified according to duration of the disorder (i.e. recent (<3 months), any (mixed duration), or persistent (>3 months)) and by intervention type. The mean number of visits for each category was computed to estimate the frequency of care related to groups with superior vs inferior outcomes.

#### *Sensitivity analysis*

A post-hoc sensitivity analysis was conducted to assess the potential impact of the method used to assess for risk of bias on the results of the review. Specifically, all eligible studies were critically appraised using RoB 2 (7).

#### *Assessment of evidence*

The certainty of the evidence was assessed according to Grading of Recommendations Assessment, Development, and Evaluation (GRADE) and reported as high, moderate, low, or very low (21). Each outcome is assessed separately and can be downgraded for each of risk of bias, imprecision, inconsistency, indirectness, and publication bias (21).

#### *Statistical analyses*

Agreements among reviewers for the screening of articles were computed and the kappa coefficient ( $\kappa$ ) reported (22, 23). The percentage agreement was calculated for classifying studies into high quality, acceptable or low quality following independent critical appraisal. The mean difference (difference in mean change between groups) was computed and its 95% CI to quantify effect sizes, where applicable. Computation of the 95% CI for the difference in mean change assumed that the pre- and post-intervention outcomes were correlated ( $r=0.8$ ) (24, 25).

We considered conducting a random effect meta-analysis if the RCTs were homogeneous. Specifically, a random effects meta-analysis would be conducted using the effect estimate (e.g. mean differences for continuous data, odds ratio, or risk ratio for dichotomous data) when at least 2 studies were deemed homogeneous. However, due to the clinical heterogeneity of the studies, no meta-analysis was performed (25).

#### *Reporting*

This review complies with the Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Appendix V) (26).

## RESULTS

#### *Study selection*

A total of 3,306 articles were retrieved and 589 duplicates excluded. Titles and abstracts of 2,717 articles were screened for eligibility and 76 articles were screened in full text (Figure I). During full-text screening, 63 citations were excluded due to ineligible study design or publication type (39 citations) (27–65), sample size (9 citations) (66–74), language (10 citations) (75–84), population (3 citations) (85–87), or intervention (2 citations) (88–89) (Appendix VI).

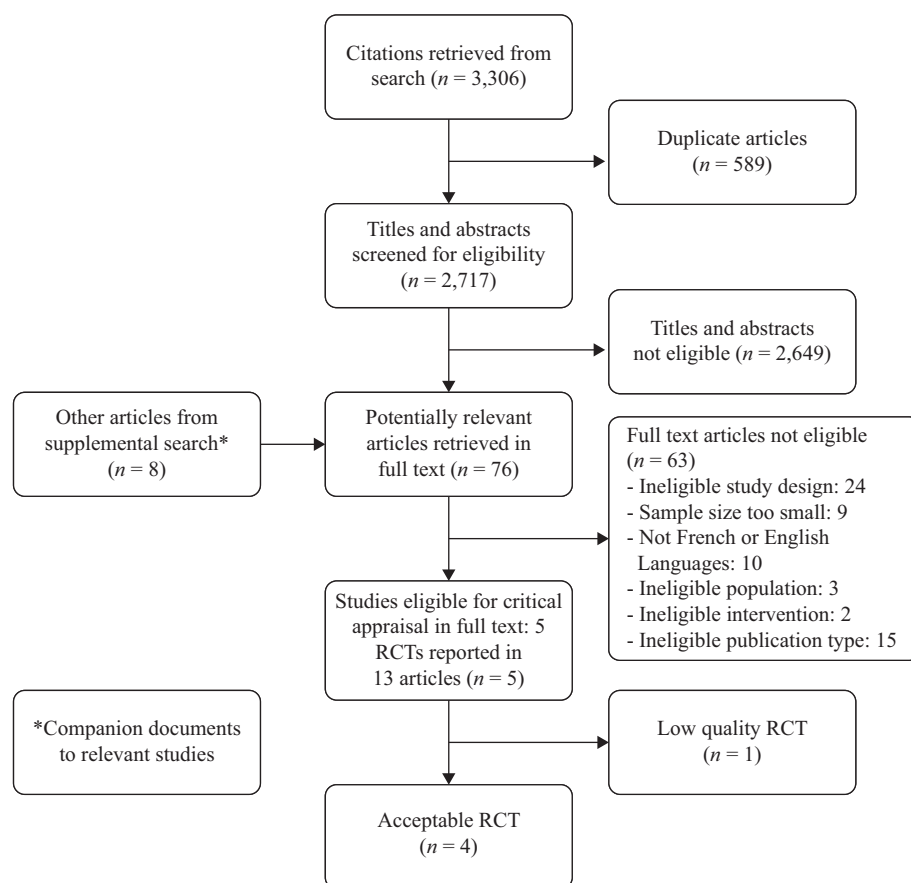
In addition to using the SIGN checklist for risk of bias assessment, a sensitivity analysis was conducted, in which the included studies were appraised using RoB 2 (7). Using the RoB 2 tool, 1 RCT was deemed to be at high risk of bias (95) (with companion documents (95–102)) and was excluded from the synthesis. Four articles were considered acceptable (90–93) and were included in the synthesis.

The inter-rater agreement for screening of articles was  $\kappa=0.91$  (95% CI 0.9–1.0). The agreement for classifying studies into high-quality, acceptable and low-quality was 86%. The third reviewer was not needed to reach consensus.

#### *Study characteristics*

All acceptable studies were RCTs (90–93). One trial investigated recent cervical radiculopathy (91) and 3 targeted cervical radiculopathy of mixed duration (90, 92, 93). No studies focused on persistent cervical radiculopathy.

The multimodal rehabilitation programmes incorporated a range of interventions including education, exercise, Shi-style cervical manipulations, traction, acupuncture, prescribed medication, and corticosteroid injection (Table I). The most investigated interventions were exercise (3/4 studies), education (3/4 studies), manipulation (2/4 studies) and soft tissue therapy (2/4



**Figure 1.** Identification and selection of articles on the effectiveness of conservative interventions in adults with cervical radiculopathy. RCT: randomized controlled trial.

studies). The interventions were delivered by physiotherapists and physicians.

### Risk of bias assessment

All acceptable studies used clear research questions, valid and reliable outcome measures, and achieved similarity at baseline across groups (Table II). Most studies adequately fulfilled the following criteria: reported method of randomization (3/4), proper allocation concealment (3/4), and reported an intention to treat analysis (3/4).

The follow-up rate was above 75% in all acceptable studies (90–94). Blinding of participants and treatment providers could not be done in any of the RCTs due to

the nature of the rehabilitation interventions (90–93). All studies used self-reported outcome measures (90–93).

One study was low quality (94) and was excluded from the evidence synthesis because of important methodological limitations: (i) differences between groups at baseline; (ii) deviations from the intended interventions; (iii) missing outcome data; and (iv) unreported reasons for loss to follow-up.

### Sensitivity analysis

The sensitivity analysis suggests that the results of this review were not impacted by the use of the SIGN tool to critically appraise studies. Using RoB 2 (Table III),

**Table 1.** Combinations of interventions in multimodal care reported in acceptable randomized controlled trials

Author, year	Treatment provider	Number of visits	Treatment period	Education	Cognitive/behavioural approach	Electrical stimulation	Exercise	Manipulation	Mobilization	Soft-tissue therapy	Medication	Injection
Cohen et al. MD 2014 (90)		Variable	Variable	Y		Y	Y	Y		Y	Y	Y
Cui et al. PT, MD 2017 (91)		12	2 weeks					Y	Y	Y		
Dederling et al. 2018 (92)	PT	36	3 months	Y	Y		Y					
Engquist et al. 2013 (93)	PT, MD	24	3 months	Y			Y					

MD: medical doctor; PT: physiotherapist; Y: yes

**Table II.** Risk of bias rating for randomized controlled trials based on the Scottish Intercollegiate Guidelines Network (SIGN) Criteria (14)

Author, Year	Research question	Randomization	Concealment	Blinding of patient/treatment provider	Blinding of outcome assessor or data analyst	Similarity at baseline	Similarities between arms	Outcome measurement	Percent drop-out (at each follow-up)	Intention to treat	Multiple sites
Cohen et al. 2014, (90)	Y	Y	CS	N	N <sup>a</sup>	Y	CS	Y	1 month CTT intervention: 1/59 = 1.70% ESI intervention: 1/55 = 1.82% CTY intervention: 4/55 = 7.27% 3 months CTT intervention: 2/59 = 3.39% ESI intervention: 5/55 = 9.09% CTY intervention: 0/55 = 0% 6 months CTT intervention: 1/59 = 1.70% ESI intervention: 2/55 = 3.64% CTY intervention: 1/55 = 1.82%	CS	CS
Cui et al. 2017 (91)	Y	Y	Y	N	N <sup>a</sup>	Y	Y	Y	2 weeks SCM intervention: 6/179 = 3.35% Traction intervention: 4/180 = 2.22% 4 weeks SCM intervention: 0/179 = 0% Traction Intervention: 0/180 = 0% 3 months SCM Intervention: 1/179 = 0.56% Traction intervention: 0/180 = 0% 6 months SCM intervention: 11/179 = 6.15% Traction intervention: 15/180 = 8.33%	Y	CS
Dederding et al. 2018 (92)	Y	Y	Y	N	N <sup>a</sup>	Y	CS	Y	3 months NST intervention: 21/72 = 29.16% PPA intervention: 28/72 = 38.88% 6 months NST intervention: 6/72 = 8.33% PPA intervention: 7/72 = 9.72% 12 months NST intervention: 2/72 = 2.77% PPA intervention: 3/72 = 4.16% 24 months NST intervention: 2/72 = 2.77% PPA intervention: 2/72 = 2.77%	Y	N/A
Enquist et al. 2013 (93)	Y	CS	Y	N	N <sup>a</sup>	Y <sup>b</sup>	N	Y	6 months SG intervention 735 = 20% NSG intervention 6/33 = 18.2% 12 months SG intervention 5/35 = 14.3% NSG intervention 3/33 = 9.09% 24 months SG intervention 4/35 = 11.4% NSG intervention 1/33 = 3.03%	Y	N/A

**Table II (Continues).** Risk of bias rating for randomized controlled trials based on the Scottish Intercollegiate Guidelines Network (SIGN) Criteria (14)

Author, Year	Research question	Randomization	Concealment	Blinding of patient/treatment provider <sup>a</sup>	Blinding of outcome assessor or data analyst	Similarity at baseline	Similarities between arms	Outcome measurement	Percent drop-out (at each follow-up)	Intention to treat	Multiple sites
Ludvigsson et al. 2015; and companion articles (94–102)	Y	Y	Y	N	N <sup>b</sup>	N	N	Y	3 months NSE intervention: 12/76 = 15.79% NSEBA intervention = 5/71 = 7.04% PA intervention: 11/69 = 15.9% 6 months NSE intervention: 17/76 = 22.4% NSEBA intervention = 14/71 = 19.71% PA intervention: 10/69 = 14.49%	CS	CS

<sup>a</sup>Used patient-reported outcome measures.<sup>b</sup>Mean age differed, but did not correlate with any differences in outcome when additional analyses were conducted.

Y: yes; N: no; CS: can't say; N/A: not applicable; NST: neck-specific training; PPA: prescribed physical activity; SCM: Shi-style cervical manipulation; CTT: conservative treatment; EST: epidural steroid injection; CTY: combination therapy; NSE: neck-specific exercise; NSEBA: neck-specific exercise with a behavioural approach; PA: physical activity; NSG: Non Surgical group; SG: Surgical group.

**Table III.** Risk of bias for acceptable randomized controlled trials based on the Cochrane Cochrane Risk of Bias Tool for Randomized Trials version 2 (RoB 2) tool used in sensitivity analysis (7)

Author, Year	Bias arising from the randomization process				Bias arising from intended intervention				Bias owing to missing outcome data				Bias in the measurement of the outcome					Bias in selection of reported results					Overall RoB					
	1.1	1.2	1.3	ROB	2.1	2.2	2.3	2.4	2.5	2.6	2.7	ROB	3.1	3.2	3.3	3.4	ROB	4.1	4.2	4.3	4.4	4.5		ROB	5.1	5.2	5.3	ROB
Cohen et al. 2014, (90)	Y	NI	N	SC	Y	Y	Y	Y	Y	Y	NA	SC	Y	NA	NA	NA	L	N	Y	Y	Y	N	SC	Y	N	N	L	SC
Cui et al. 2017 (91)	Y	Y	N	L	Y	Y	N	NA	NA	Y	NA	L	Y	NA	NA	NA	L	N	N	Y	Y	N	SC	Y	Y	N	H	H/SC*
Dederig et al. 2018 (92)	Y	Y	N	L	Y	Y	N	NA	NA	Y	NA	L	Y	NA	NA	NA	L	N	N	Y	Y	N	SC	Y	N	N	L	SC
Enquist et al. 2013 (93)	NI	Y	N	L	Y	Y	Y	Y	N	Y	NA	SC	Y	NA	NA	NA	L	N	N	Y	Y	N	SC	Y	N	N	L	SC
Ludvigsson et al. 2015 (94)	Y	PY	Y	SC	Y	Y	PY	Y	PN	PY	NA	H	PN	N	NI	NA	H	N	N	N	NA	NA	L	NI	PN	PN	SC	H

\*High risk for Short-Form 36 (SF-36) due to domain 5, Some concerns for all the other outcomes.

H: high risk of bias; L: low risk of bias; N: no; NA: not applicable; NI: no information; SC: some concerns; Y: yes; PY: possibly yes; PN: possibly no.

**Table IV.** Summary of findings of primary outcomes and quality assessment

Study	Number of participants	Intervention	Control intervention	Primary outcomes	Summary statistics Effect between group difference for primary outcomes (95% CI)	Level of certainty (15)	Reasons for down-rating
Cohen et al. 2014, (90)	169	Conservative treatment (CTT)	Epidural steroid injection (ESI) Combination therapy (CTY)	Arm pain intensity (NRS)	CTT-ESI At 1 month 0.2/100 (-0.7 to 1.1) At 3 months -0.43/100 (-1.0 to 0.2) ESI-CTY At 1 month -1.1/100 (-2.2 to 0), $p=0.045$ At 3 months -0.86/100 (-1.4 to -0.3) ¥ CTT-CTY At 1 month -1.2/100 (-2.3 to -0.1), $p=0.027$ At 3 months -1.29/100 (-1.9 to -0.7) ¥	Low	Risk of bias Imprecision
				Neck pain intensity (NRS)	CTT-ESI At 1 month -0.1/100 (-1.0 to 0.8) At 3 months -0.84/100 (-1.5 to 0.2) ESI-CTY At 1 month -1.1/100 (-2.2 to 0.0), $p=0.054$ At 3 months -0.01/100 (-0.8 to 0.7) CTT-CTY At 1 month -1.1/100 (-2.2 to 0.0), $p=0.056$ At 3 months -0.85/100 (-1.5 to -0.1)	Low	Risk of bias Imprecision
				Disability (NDI)	CTT-ESI At 1 month -1.2/100 (-6.1 to 3.6) ESI-CTY At 1 month -5.5/100 (-11.0 to 0.1), $p=0.055$ CTT-CTY At 1 month -3.6/100 (-8.3 to 1.1), $p=0.130$	Low	Risk of bias Imprecision
Cui et al. 2017 (91)	360	Shi-style cervical manipulation	Mechanical cervical traction	Disability (NDI)	At 2 weeks NDI: 1.51/50 (0.7 to 2.3) At 4 weeks NDI: 1.59/50 (0.8 to 2.4) At 12 weeks NDI: 1.67/50 (0.9 to 2.4) At 24 weeks NDI: 1.37/50 (0.6 to 2.1)	Low	Risk of bias Imprecision
Dederding et al. 2018 (92)	144	Neck-specific training + Cognitive behavioural approach	Prescribed physical activity + Cognitive behavioural approach	Mean arm pain intensity (VAS 100 mm)	At 3 months 9/100 (2.8 to 15.2) At 6 months 12/100 (5.9 to 18.1) At 12 months 7/100 (0.9 to 13.1) At 24 months 11/100 (5.1 to 16.9)	Low	Risk of bias Imprecision
				Mean neck pain intensity (VAS 100 mm)	At 3 months 4/100 (-1.6 to 9.6) At 6 months 7/100 (1.3 to 12.6) At 12 months 6/100 (0.4 to 11.6) At 24 months 4/100 (-1.4 to 9.4)	Low	Risk of bias Imprecision
Enquist et al. 2013 (93)	68	Surgical group	Non-surgical group: Physiotherapy alone.	Disability (NDI 0–100)	At 6 months 4.4/100 (-4.4 to 13.2) At 12 months 6.8/100 (-3.8 to 17.4) At 24 months 2.7/100 (-9.6 to 15.0)	Low	Risk of bias Imprecision
				Arm pain intensity (VAS scale 0–100)	At 6 months 5.1/100 (-15.0 to 25.2) At 12 months 4.8/100 (-16.7 to 26.3) At 24 months -2.4/100 (-27.6 to 22.8)	Low	Risk of bias Imprecision
				Neck pain intensity (VAS scale 0–100)	At 6 months 15.6/100 (-3.4 to 34.6) At 12 months 18.3/100 (-2.0 to 38.6) At 24 months 14.6/100 (-7.5 to 36.7)	Low	Risk of bias Imprecision

VAS: visual analogue scale; NRS: numerical rating scale; NDI: Neck Disability Index; ¥: calculated by current review authors.

it was found that the 4 studies had “some concerns” (90–93), but they were nevertheless considered to be of acceptable quality. Therefore, our overall evidence synthesis did not change.

#### Assessment of evidence

The certainty of the evidence was rated as “low” regarding primary outcomes (neck and arm pain; disability)

with downgrading due to issues with risk of bias in the studies and imprecision (Table IV).

#### Summary of evidence

*Recent-onset cervical radiculopathy: Multimodal rehabilitation interventions that include Shi-style cervical manipulations.* Evidence from 1 RCT (91) suggests that a multimodal rehabilitation programme



that includes Shi-style cervical manipulations leads to similar outcomes to that of mechanical cervical traction in reducing neck pain intensity in adults with recent cervical radiculopathy. The trial compared a combination of soothing tendon step, osteopathic step, and dredging collateral step, performed by trained physiotherapists or physicians, with traction alone. Both groups received 6 sessions over 2 weeks. A trivial and clinically non-important between-group differences in neck pain intensity (measured using VAS) favouring multimodal rehabilitation interventions at 2 weeks (MD 4.9/100, 95% CI 3.1 to 6.7); 4 weeks (MD 4.9/100, 95% CI 3.1 to 6.7); 12 weeks (MD 4.4/100, 95% CI 2.5 to 6.3) and 24 weeks (MD 3.7/100, 95% CI 1.8 to 5.5) was identified. However, there were no clinically important between-group differences in disability at any follow-up point.

*Cervical radiculopathy of mixed duration: Multimodal rehabilitation interventions combining exercises, education, and cognitive behavioural programme.* Evidence from 1 RCT (92) suggests that multimodal rehabilitation that combines neck-specific exercises, education, and a cognitive behavioural programme (treatment group) is superior to combined prescribed physical activity with brief cognitive behavioural approach (comparison group) in improving pain, disability, anxiety, and depression in adults with cervical radiculopathy of any duration (Table V). 91% of participants had chronic ( $\geq 3$  months duration) neck pain in the treatment group and 89% in the comparison group.

In this trial, participants were randomized to: (i) neck-specific training (neck isometric movement, muscle activation, low-load endurance training) and cognitive behavioural approach (3 sessions per week over 3 months); or (ii) prescribed physical activity (aerobic and/or muscular physical activity, at least 30 min, 3 days per week over 3 months) and 1 session of a cognitive behavioural approach. Compared with the comparison group, those in the treatment group reported trivial and non-clinically important improvements in neck pain (VAS) at the 6-month (MD 7.0/100, 95% CI 1.3 to 12.6) and 24-month follow-up (MD 4.0/100, 95% CI -1.4 to 9.4). Moreover, the treatment group reported small reductions in arm pain intensity at 6-month (MD 12.0/100, 95% CI 5.9 to 18.1) and 24-month follow-up (MD 11.0/100, 95% CI 5.1 to 16.9). Participants in the treatment group also reported clinically important improvement in disability at 24-months follow-up (MD 8.0/100, 95% CI 3.1 to 12.9). Finally, those allocated to the treatment group reported small and clinically important changes in anxiety (HADS) (MD 2.0/21, 95% CI 1.0 to 3.0) and depression (HADS) (MD 2.0/21, 95% CI 0.9 to 3.1) at the 24-month follow-up. There were no statistically

clinically important between-group differences in quality of life or fear avoidance at the 3, 6, 12 and 24 month follow-ups.

*Cervical radiculopathy of mixed duration: Multimodal rehabilitation interventions combining exercises and education.* Evidence from 1 RCT (93) suggests that multimodal rehabilitation care that combines exercises and education lead to similar outcomes as a combination of surgery and postoperative multimodal rehabilitation interventions in adults with cervical radiculopathy of any duration (Table V). These multimodal rehabilitation interventions include a 3-step programme: (i) neck-specific exercises and pain relief procedures, (ii) general exercises, (iii) pain coping, self-efficacy, and stress management. The mean duration of neck and arm pain is respectively 15 (SD 12) and 13 (SD 10) months for the surgical group; 21 (SD 19), and 17 (SD 16) months for the non-surgical group.

In this RCT, surgery consisted of anterior cervical decompression and fusion and combined with post-operative education, exercises, procedures for pain relief, pain coping and stress management strategies. The authors reported that the surgical group may have experienced clinically important reduction in neck pain (VAS) at the 6 (MD 15.6/100, 95% CI -3.4 to 34.6), 12 (MD 18.3/100, 95% CI -2.0 to 38.6), and 24-month follow-up (MD 14.6/100, 95% CI -7.5 to 36.7). However, these mean differences are imprecise with the inclusion of the null value within the confidence intervals. There were no clinically important differences between groups in disability or arm pain intensity at any follow-up.

*Cervical radiculopathy of mixed duration: Multimodal rehabilitation interventions that combine pharmacological and non-pharmacological treatments.* Evidence from 1 RCT (90) suggests that multimodal rehabilitation combining pharmacological and non-pharmacological treatments (with or without epidural steroid injection) leads to similar outcomes as epidural steroid injection alone in adults with cervical radiculopathy of any duration (Table V). The mean duration of pain is 1 year in the multimodal rehabilitation intervention group, 0.8 years in the epidural steroid injection group, and 0.7 years in the combination therapy group.

In this RCT, multimodal rehabilitation included education, electrical stimulation, ultrasound, massage, exercise, and pharmacotherapy (as indicated according to standard practice). Participants in the multimodal rehabilitation group could also receive 1 or more inter-laminar epidural steroid injection. The authors reported no clinically important between-group differences in neck pain intensity, arm pain intensity and disability at the 1, 3 and 6-month follow-ups. Moreover, medication reduction and positive global perceived effect of the treatment were similar between groups.

**Table V.** Evidence table for acceptable randomized controlled trials assessing the effectiveness of multimodal interventions for the management of grade III neck pain and associated disorders in adults

Author(s), Year, Country	Subjects and setting Number (n) enrolled	Interventions; number (n) of subject	Comparisons; number (n) of subjects	Follow-up	Outcomes	Key findings
Cohen et al. 2014, USA (90)	Adults (≥18 years old) recruited from academic civilian teaching facilities, military treatment facilities and a veterans' administration hospital. Case definition: Patients with cervical radicular pain (1 month to 4 years duration) extending into the arm(s) based on history and physical; numerical rating scale arm pain score ≥4/10 or equivalent in intensity to neck pain; magnetic resonance imaging correlation of symptoms with pathology. (n = 169)	Conservative treatment (CTT): Patients (mean duration of pain: 1 year) received either pharmacotherapy with gabapentin and/or nortriptyline and PT. Treatments could include education, electrical stimulation, ultrasound, massage, and exercise (n = 59)	1. Epidural steroid injection (ESI) Patients (mean duration of pain: 0.8 year) received at least one interlaminar ESI performed under the supervision of a pain management specialist. Repeat injections could be performed after 1- and 3-month follow-ups at the physician's discretion. (n = 55) 2. Combination therapy (CTY) Patients (mean duration of pain: 0.7 year) received both ESI and pharmacotherapy with gabapentin and/or nortriptyline plus PT (education, electrical stimulation, ultrasound, massage, exercise). (n = 55)	1, 3, 6 months follow-up from baseline	Primary outcomes: Arm and neck pain score over the past week (NRS 0-100) and Disability (NDI 0-100) Secondary outcomes: Medication reduction (%), positive global perceived effect (%), positive categorical outcome (%), number of patients proceeded to surgery (%). Adverse events	Group difference in mean change from baseline (CTT-ESI) Between-group difference at 1 month (95%CI), p value: NRS arm: MD 0.2/100 (95% CI -0.7 to 1.1); p = 0.722 NRS neck: MD -0.1/100 (95% CI -1.0 to 0.8), p = 0.890 NDI: MD -1.2/100 (95% CI -6.1 to 3.6); p = 0.610 Medication reduction: OR 1.0 (95% CI 0.4 to 2.7); p = 0.97 Positive global perceived effect: OR 1.0 (95% CI 0.4 to 2.2); p = 0.98 Positive categorical outcome: OR 1.0 (95% CI 0.5 to 2.1); p = 0.94 Proceeded to surgery: OR 2.1 (95% CI 0.4 to 12.8); p = 0.41  At 3 months NRS arm MD -0.43/100 (95% CI -1.0 to 0.2) ¥ NRS neck MD -0.84/100 (95% CI -1.5 to 0.2) ¥  At 6 months NRS arm MD 1.12/100 (95% CI 0.5 to 1.7) ¥ NRS neck MD 1.62/100 (95% CI 1.0 to 2.3) ¥  Group difference in mean change from baseline (ESI-CTY) Between-group difference at 1 month (95%CI), p value: NRS arm: MD -1.1/100 (95% CI -2.2 to 0.0), p = 0.045 NRS neck: MD -1.1/100 (95% CI -2.2 to 0.0), p = 0.054 NDI: MD -5.5/100 (95% CI -11.0 to 0.1), p = 0.055 Medication reduction: OR 2.3 (95% CI 0.9 to 5.8); p = 0.08 Positive global perceived effect: OR 1.8 (95% CI 0.7 to 4.5); p = 0.19 Positive categorical outcome: OR 1.6 (95% CI 0.7 to 3.6); p = 0.29 Proceeded to surgery: OR 0.8 (95% CI 0.1 to -6.6); p = 0.82  Between-group difference at 3 months NRS arm MD -0.86/100 (95% CI -1.4 to -0.3) ¥ NRS neck MD -0.01/100 (95% CI -0.8 to 0.7) ¥  Between-group difference at 6 months NRS arm MD -0.56/100 (95% CI -1.1 to 0.0) ¥ NRS neck MD -0.29/100 (95% CI -1.0 to 0.5) ¥  Group difference in mean change from baseline (CTT-CTY) Between-group difference at 1 month (95%CI), p value: NRS arm: MD -1.2/100 (95% CI -2.3 to -0.1), p = 0.027 NRS neck: MD -1.1/100 (95% CI -2.2 to 0.0), p = 0.056 NDI: -3.6/100 (-8.3 to 1.1), p = 0.130 Medication reduction: OR 1.9 (95% CI 0.7 to 4.9); p = 0.18 Positive global perceived effect: OR 1.8 (95% CI 0.7 to 4.3); p = 0.21 Positive categorical outcome: OR 1.7 (95% CI 0.7 to 3.9); p = 0.20 Proceeded to surgery: OR 0.4 (95% CI 0.1 to 2.5); p = 0.33  Between-group difference at 3 months NRS arm MD -1.29/100 (95% CI -1.9 to -0.7) ¥ NRS neck MD -0.85/100 (95% CI -1.5 to -0.1) ¥

**Table V (Continues).** Evidence table for acceptable randomized controlled trials assessing the effectiveness of multimodal interventions for the management of grade III neck pain and associated disorders in adults

Author(s), Year, Country	Subjects and setting Number (n) enrolled	Interventions; number of subject	Comparisons; number (n) of subjects	Follow-up	Outcomes	Key findings
Cui et al. 2017 China (91)	Adults (18–65 years old) recruited from 5 different traditional Chinese hospitals. Case definition: Patients with acute ( $\geq 2$ weeks duration) cervical radiculopathy (VAS $\geq 30$ mm for neck pain), diagnosed by a senior neurologist based on clinical manifestations (pain or stiffness in the neck, pain along the cutaneous distribution of 1 or more cervical roots, physical examination (neck symptoms reproducible during physical examination, at least 1 positive test among: provocation of neck and arm pain by neck movements, brachial traction test, foraminal compression test, sensory changes, or muscles weakness) and imaging. (n = 360)	Shi-style cervical manipulation (SCM) for 6 sessions over 2 weeks: soothing tendon step, osteopathic step (including cervical manipulation), dredging collateral step, performed by physiotherapists or physicians trained ( $\geq 3$ years of experience, training sessions) (n = 180). Mean duration of neck pain: 96 days (+/-184)	Mechanical cervical traction (Traction) for 6 sessions over 2 weeks: 20 min traction in a sitting position with the head forward at 10°-15° of flexion, traction performed by physiotherapists or physicians trained ( $\geq 3$ years of experience, training sessions) (n = 180). Mean duration of neck pain: 97 days (+/-154).	2, 4, 12 and 24 weeks follow-up after randomization	Primary outcome: Disability (NDI 0–50) Secondary outcomes: neck pain (100mm line VAS), health related quality of life (HRQoL, short form of SF36 0–100) Adverse events	Between-group difference at 6 months NRS arm MD 0.56/100 (95% CI -0.1 to 1.2) ✕ NRS neck MD 1.33/100 (95% CI 0.6 to 2.0) ✕  Adverse events Notriptyline only (n = 48) None 20.8%, Sleepiness, fatigue 29.2%, Cognitive 12.5%, Weight gain 4.2%, Dry mouth 18.8%, Gastrointestinal 2.1%, Bowel/bladder 4.2%, Other* 10.4%, Multiple 16.7% Gabapentin only (n = 37) None 70.3%, Sleepiness, fatigue 21.6%, Cognitive 13.5%, Gastrointestinal 5.4%, Other* 10.8%, Multiple 18.9% Notriptyline + Gabapentin (n = 29) None 41.4%, Sleepiness, fatigue 31 %, Cognitive 13.8%, Dry mouth 17.2%, Gastrointestinal 6.9%, Bowel/bladder 3.5%, Other* 17.2%, Multiple 27.6%. * Includes nightmares, hair loss, tremors, rash, headache, visual changes, wheezing, paresthesias, cramping, and decreased libido.  Group difference in mean change from baseline (SCM-Traction) Between-group difference at 2 weeks Neck pain: MD 4.89/100 (95% CI 3.1 to 6.7) ✕ NDI: MD 1.51/50 (95% CI 0.7 to 2.3) ✕ SF-36: MD -2.92/100 (95% CI -5.0 to -0.8) ✕ Between-group difference at 4 weeks Neck pain: MD 4.88/100 (95% CI 3.1 to 6.7) ✕ NDI: MD 1.59/50 (95% CI 0.8 to 2.4) ✕ Between-group difference at 12 weeks Neck pain: MD 4.39/100 (95% CI 2.5 to 6.3) ✕ NDI: MD 1.67/50 (95% CI 0.9 to 2.4) ✕ Between-group difference at 24 weeks Neck pain: MD 3.66/100 (95% CI 1.8 to 5.5) ✕ NDI: MD 1.37/50 (95% CI 0.6 to 2.1) ✕  Adverse events: No serious adverse events reported. Only one patient (SCM group) reported dizziness and nausea.

**Table V (Continues).** Evidence table for acceptable randomized controlled trials assessing the effectiveness of multimodal interventions for the management of grade III neck pain and associated disorders in adults

Author(s), Year, Country	Subjects and setting Number (n) enrolled	Interventions; number (n) of subject	Comparisons; number (n) of subjects	Follow-up	Outcomes	Key findings
Dedering et al. 2018 Sweden (92)	Adults (NST mean age 46.8 (SD 9.6) years; PPA mean age 49.7 (SD 9.5) years) recruited from a neurosurgical department. Case definition: magnetic resonance imaging verified cervical disc disease showing cervical nerve root compression; and neck and/or arm pain, verified with a neck extension test or a neurodynamic provocation test. (n = 144)	Neck-specific training (NST) and a cognitive behavioral approach at each session by experienced physiotherapists. Patients were requested to train 3 sessions per week over 3 months and included gentle isometric neck movement, activation of deep cervical muscles, and progression to low-load endurance training. (n = 72). Neck pain duration: 9% subacute (n = 4); 91% chronic (n = 38). Arm pain duration: 10% subacute (n = 4); 90% chronic (n = 38)	Prescribed physical activity (PPA) (aerobic and/or muscular physical activity, at least 30 minutes of physical activity at least 3 days per week over 3 months) and a cognitive behavioral approach at first session by experienced physiotherapists. Patients were requested to exercise after a one patient-centered counseling session (n = 72). Neck pain duration: 11% subacute (n = 6); 89% chronic (n = 50). Arm pain duration: 11% subacute (n = 6); 89% chronic (n = 47)	3, 6, 12 and 24 months follow-up from baseline	Primary outcomes: neck and arm pain intensity (VAS 100 mm). Secondary outcomes: headache intensity (VAS 100 mm), disability (NDI 0–100), quality of life (EuroQol 5D 0–100), fear avoidance belief (FABQ 0–96), anxiety and depression (HADS 0–21).	Group difference in mean change (NST–PPA): Between-group difference at 3 months (95%CI) Pain intensity of present neck-pain: MD 7/100 (95%CI 1.2 to 12.8) ¥ Pain intensity of mean neck-pain: MD 4/100 (95 % CI -1.6 to 9.6) ¥ Pain intensity of mean arm pain: MD 9/100 (95 % CI 2.8 to 15.2) ¥ Mean headache intensity: MD 7/100 (95% CI 0.8 to 13.2) ¥ NDI: MD 3/100 (95% CI -1.8 to 7.8) ¥ EQ-5D index: MD -0.06/100 (95% CI -0.1 to 0.0) ¥ EQ-5D VAS: MD 0/100 (95%CI -5.4 to 5.4) ¥ FABQ: MD 1/96 (95%CI -2.5 to 4.5) ¥ HADS anxiety: MD 0/21 (95%CI -1.1 to 1.1) ¥ HADS depression: MD -1/21 (95% CI -2.0 to 0.0) ¥ Between-group difference at 6 months (95%CI) Pain intensity of present neck-pain: MD 11/100 (95 % CI 5.2 to 16.8) ¥ Pain intensity of mean neck-pain: MD 7/100 (95 % CI 1.3 to 12.7) ¥ Pain intensity of mean arm pain: MD 12/100 (95 % CI 5.9 to 18.1) ¥ Mean headache intensity:MD 12/100 (95% CI 5.9 to 18.1) ¥ NDI: MD 5/100 (95% CI 0.1 to 9.9) ¥; EQ-5D index: MD -0.08/100 (95% CI -0.1 to 0.0) ¥ EQ-5D VAS: MD -2/100 (95%CI -7.7 to 3.7) ¥ FABQ: MD 6/96 (95%CI 2.2 to 9.8) ¥ HADS anxiety: MD 1/21 (95%CI -0.1 to 2.1) ¥ HADS depression: MD 1/21 (95% CI -0.0 to 2.0) ¥ Between-group difference at 12 months (95%CI) Pain intensity of present neck-pain: MD 7/100 (95 % CI 1.6 to 12.4) ¥ Pain intensity of mean neck-pain: MD 6/100 (95 % CI 0.4 to 11.6) ¥ Pain intensity of mean arm pain: MD 7/100 (95 % CI 0.9 to 13.1) ¥ Mean headache: MD 9/100 (95% CI 3.0 to 15.0) ¥ NDI: MD 7/100 (95% CI 2.0 to 12.0) ¥ EQ-5D index: MD -0.11/100 (95% CI -0.2 to 0.0) ¥ EQ-5D VAS: MD -1/100 (95%CI -6.2 to 4.2) ¥ FABQ: MD 6/96 (95%CI 2.1 to 9.9) ¥ HADS anxiety: MD 1/21 (95%CI -0.1 to 2.1) ¥ HADS depression: MD 2/21 (95% CI 0.9 to 3.1) ¥ Between-group difference at 24 months (95%CI) Pain intensity of present neck-pain: MD 11/100 (95 % CI 5.3 to 16.7) ¥ Pain intensity of mean neck-pain: MD 4/100 (95 % CI -1.4 to 9.4) ¥ Pain intensity of mean arm pain: MD 11/100 (95 % CI 5.1 to 16.9) ¥ Mean headache: MD 15/100 (95% CI 9.1 to 20.9) ¥ NDI: MD 8/100 (95% CI 3.1 to 12.9) ¥ EQ-5D index: MD -0.1/100 (95% CI -0.2 to 0.0) ¥ EQ-5D VAS: MD -7/100 (95%CI -12.4 to -1.6) ¥ FABQ: MD 5/96 (95%CI 0.8 to 9.2) ¥ HADS anxiety: MD 2/21 (95%CI 1.0 to 3.0) ¥ HADS depression: MD 2/21 (95% CI 0.9 to 3.1) ¥

**Table V (Continues).** Evidence table for acceptable randomized controlled trials assessing the effectiveness of multimodal interventions for the management of grade III neck pain and associated disorders in adults

Author(s), Year, Country	Subjects and setting Number (n) enrolled	Interventions; number (n) of subject	Comparisons; number (n) of subjects	Follow-up	Outcomes	Key findings
Engquist et al. 2013, Sweden (93)	Adults (SG mean age 49 (SD 8); NSG mean age 44 years (SD 9), referred to and elected for surgery in a spine centre, Case definition: Patients with cervical radiculopathy with 1) pain (with or without sensory and motor deficit) (symptoms duration 8 weeks to 5 years) in 1 or both arms indicating nerve-root affection, caused by disc herniation with or without osteophytes, or a stenosis caused by osteophytes, confirmed by MRI (n = 68)	Surgical group (SG) Disc and osteophytes removal and cervical fusion. Physiotherapy programme three months after surgical intervention for a minimum of three months. Physiotherapy treatment performed daily by the patient at home and twice a week at the clinic and continued for a minimum of three months. This treatment included a 3-step programme: 1) neck specific exercises and pain relief procedures, 2) general exercises, 3) pain coping, self-efficacy and stress management strategies (n = 33)	Non-surgical group (NSG) Physiotherapy treatment performed daily by the patient at home and twice a week at the clinic and continued for a minimum of three months. This treatment included a 3-step programme: 1) neck specific exercises and pain relief procedures, 2) general exercises, 3) pain coping, self-efficacy and stress management strategies (n = 33)	6, 12 and 24 months follow-up from baseline	Primary outcomes: neck disability (NDI 0–100), neck pain intensity (VAS scale 0–100), arm pain intensity (VAS scale 0–100), patient's global assessment. Surgical complications	SG-NSG Between-group difference at 6 months NDI MD 4.4/100 (95% CI -4.4 to 13.2)¥ Neck pain VAS MD 15.6/100 (95% CI -3.4 to 34.6) ¥ Arm pain VAS MD 5.1/100 (95%CI -15.0 to 25.2)¥ Patient's global assessment RR 1.22 (95% CI 0.9 to 1.4) (p=0.180) Between-group difference at 12 months NDI MD 6.8/100 (95% CI -3.8 to 17.4) ¥ Neck pain VAS MD 18.3/100 (95% CI -2.0 to 38.6) ¥ Arm pain VAS MD 4.8/100 (95% CI -16.7 to 26.3) ¥ Patient's global assessment RR 1.39 (95% CI 1.0 to 1.9) (p=0.031) Between-group difference at 24 months NDI MD 2.7/100 (95% CI -9.6 to 15.0) ¥ Neck pain VAS MD 14.6/100 (95%CI -7.5 to 36.7) ¥ Arm pain VAS MD -2.4/100 (95% CI -27.6 to 22.8) ¥ Patient's global assessment RR 1.17 (95% CI 0.9 to 1.6) (=0.281) Surgical complications: No complications related to the surgical procedures.

SD: standard deviation; PPA: prescribed physical activity; VAS: Visual Analogue Scale; NDI: Neck Disability Index; FABQ: Fear Avoidance Beliefs Questionnaire; EuroQol 5 D: EuroQol 5 Dimension; HADS: Hospital Anxiety and Depression Scale; FCR: Flexor Carpi Radialis; H-Reflex: Hoffmann Reflex; NST: neck-specific training; PPA: prescribed physical activity; PT: physiotherapy; ESI: epidural steroid injection; WAD: whiplash-associated disorder; SCM: Shi-style cervical manipulation; CTY: combination therapy; CTT: conservative treatment; CT: computed tomography; MRI: magnetic resonance imaging; ULTI: Upper Limb Tension Test; GA: Group A; GB: Group B; GC: Group C; OR: odds ratio; SES: Self-Efficacy Scale; SG: surgical group; NSG: non-surgical group; ¥: calculated by current review authors



### Adverse events

Three of the 4 acceptable studies reported adverse events (Table V) (90, 91, 93). No severe adverse events were reported in any of these studies. In the trial by Cui et al. dizziness and nausea occurred in 1 patient who received multimodal rehabilitation that included manual therapy (91). Cohen et al. reported minor adverse events for patients who received medication (90). Seventy-five percent of individuals experienced an adverse effect with nortriptyline, 45.4% with gabapentin, and 64.3% with combination medical management (90). The most frequently reported minor events secondary to medication were fatigue (27.3%), dry mouth (18%) and cognitive symptoms (13.3%) (90). Engquist et al., reported no complications related to surgery (93).

## DISCUSSION

The evidence on multimodal rehabilitation for adults with cervical radiculopathy has progressed slowly since the publication of the OPTIMA clinical practice guideline in 2016 (103). This current update identified 4 recent acceptable RCTs published since 2013. Overall, these new trials provide much needed evidence to inform the management of patients with cervical radiculopathy. One of these RCTs investigated the effectiveness of multimodal rehabilitation for the management of patients with recent-onset cervical radiculopathy and three included patients with varying duration of symptoms. However, we still lack clear knowledge to inform the evidence-based rehabilitation of persistent cervical radiculopathy.

### Update of the findings from the OPTIMA Collaboration

In 2016, the OPTIMA Collaboration recommended that clinicians may consider treating patients with recent onset (<3 months) with supervised graded strengthening exercise in combination with structured patient education (103). Moreover, OPTIMA recommended that cervical collars, traction, and low-level laser therapies should not be used to manage recent-onset cervical radiculopathy. The new evidence identified in our systematic review advances our knowledge on the effectiveness of multimodal rehabilitation care for the management of cervical radiculopathy. This systematic review identified 4 RCTs of multimodal interventions that may offer small benefits to patients with cervical radiculopathy. These multimodal interventions are heterogeneous and included combinations of: (i) cervical manipulation or mobilization, and soft-tissue therapy; or (ii) neck-specific exercises, education, and a cognitive behavioural approach. Based on our

systematic review findings, specific multimodal rehabilitation programmes may offer small, but clinically meaningful, benefits to patients.

We also identified 3 RCTs that investigated participants with heterogeneous durations of symptoms. These studies suggest that patients with cervical radiculopathy may benefit from a rehabilitation programme that combines neck-specific exercises, education, and a cognitive behavioural programme (91, 92). However, we found no convincing evidence that cervical fusion and post-operative rehabilitation was superior to a stepped multimodal rehabilitation programme that includes neck-specific exercises and pain relief procedures, general exercises, and pain coping, self-efficacy and stress management strategies (93). Finally, we found no evidence that a multimodal rehabilitation included education, electrical stimulation, ultrasound, massage, exercise, and pharmacotherapy and an epidural injection (if indicated) was superior to an epidural injection alone (90).

Considering evidence on the effectiveness and safety of these multimodal rehabilitation programmes, clinicians and patients are left with few evidence-based treatments for cervical radiculopathy. Therefore, shared decision-making should occur between the clinician and patient that considers the patient's preferences and values towards each multimodal rehabilitation intervention.

### Other systematic reviews

The results of this systematic review agree with previous reviews (104–106). In their review, Boyles et al. (104) reported that using manual therapy techniques (including cervical and thoracic manipulation and mobilization, neural dynamic techniques, and soft-tissue therapy) in conjunction with therapeutic exercise is effective in improving pain and disability for cervical radiculopathy. Zronek et al. (105) reported that strength-based exercises when used alone or in combination with another treatment lead to a reduction of pain related to neck pain. Finally, Salt et al. (106) reported that, for cervicobrachial pain: (i) behavioural therapy improved pain in the long-term compared with “usual care”; and (ii) that the combination of manual therapy and exercise seems to be beneficial in reducing pain, but without statistical significance. However, it is important to note that those previous reviews had methodological limitations regarding the inclusion of high risk of bias studies in their summary of evidence section (104–106), some non-suitable study design of the included articles (104) and the absence of using SIGN criteria or RoB 2 for critical appraisal (104–106).

None of the acceptable RCTs identified in this systematic review were captured in these previous

reviews because their literature searches ended in 2013 or earlier.

### *Clinical implications*

This study found that the multimodal rehabilitation interventions associated with statistically significant benefits often included different combinations of exercise, education, and a cognitive-behavioural approach (90, 92, 93). Neck pain is a complex condition associated with physical and psychological symptoms that can impact functioning, including activity limitations and work absenteeism (34–36, 107–109). Conceptually, rehabilitation may include different interventions that aim to improve functioning by using a biopsychosocial approach to the management of cervical radiculopathy. However, evaluating the effectiveness of rehabilitation interventions of care is challenging when conducting a systematic review of the literature, because the interventions often include heterogeneous combinations of different interventions. Nonetheless, clinicians are likely to combine interventions in clinical practice, and studying rehabilitation care offers greater insight to inform evidence-based management of cervical radiculopathy (37–40, 110–113). Future studies examining rehabilitation should consider a biopsychosocial model to inform the selection of intervention components, as well as incorporating interventions that have demonstrated effectiveness on their own.

It is important to note that the included studies had trivial and non-clinically important or clinically important, but small, effect sizes favouring multimodal rehabilitation interventions. It is possible that the placebo effect is higher in multimodal rehabilitation interventions that include a high frequency of treatment visits with healthcare providers. However, in the current systematic review, the mean treatment frequency across treatment arms with superior vs inferior outcomes was the same (i.e. 24 treatments over 7 weeks). More research is needed to assess optimal dose related to multimodal treatment outcomes. In addition, a potential reason for the small reported effects may be poor implementation of a reasonable treatment, such as poor adherence to the treatment by the patient (114). For example, education aims to improve knowledge and behaviour, exercises should be completed regularly by patients, and cognitive behavioural treatment aims to change negative patterns of thought and alter unwanted behaviours. None of the studies included in the current review assessed changes in thought, behaviour, or adherence/performance of exercises as intermediate outcomes. Poor adherence or implementation of these intervention

components of multimodal care may contribute to the reported small effects.

### *Strengths and limitations*

This review has a number of strengths. First, we developed a sensitive and rigorous search strategy that was peer-reviewed by a second librarian using the PRESS Checklist and searched 9 databases (13). Secondly, we defined explicit inclusion and exclusion criteria to identify relevant citations from the searched literature. Thirdly, we used 2 independent reviewers for screening and critical appraisal to minimize error and bias. Fourthly, we used a well-accepted and valid set of criteria for critical appraisal using the SIGN criteria (14). Finally, we tested the validity of the results by conducting a sensitivity analysis to determine whether the findings were dependent on the method used to assess risk of bias.

This review also has a number of limitations. First, critical appraisal requires scientific judgment that may vary among reviewers. This potential bias was minimized by training reviewers to use a standardized critical appraisal tool, and by using a consensus process among reviewers to reach decisions. In addition to using the SIGN checklist in our risk of bias assessment, a sensitivity analysis was conducted in which we appraised the included studies using RoB 2 (7). Using the SIGN criteria and RoB 2, it was deemed that the trial by Ludvigsson et al. (94) had a high risk of bias, and thus it was excluded from the evidence synthesis. Secondly, the study did not assess for potential publication bias. Thirdly, for feasibility reasons, the study did not search grey literature. However, the review used a comprehensive search of 9 databases that were peer-reviewed, using the PRESS Checklist for completeness and accuracy (13). Finally, due to feasibility, the review only included studies published in English and French. However, systematic bias is unlikely when using language restrictions to conduct systematic reviews in conventional medicine (115).

## CONCLUSION

The best available evidence suggests that some multimodal rehabilitation care may provide small and trivial reduction in neck pain or improvement in function to patients with cervical radiculopathy. However, most of these effects are not clinically important. This review cannot identify which specific interventions included in these multimodal programmes of care provide benefits to patients. Further research, using RCTs, are needed to determine the therapeutic modalities that should be included in an effective programme of multimodal rehabilitation for cervical radiculopathy.

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