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Research

Some conservative interventions are more effective than others for people with chronic non-specific neck pain: a systematic review and network meta-analysis

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KEYWORDS

Chronic neck pain
Conservative interventions
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ABSTRACT

Question: Which is the most effective conservative intervention for patients with non-specific chronic neck pain (CNSNP)? **Design**: A systematic review and network meta-analysis of randomised clinical trials. **Participants**: Adults with CNSNP of at least 3 months duration. **Interventions**: All available pharmacological and non-pharmacological interventions. **Outcome measures**: The primary outcomes were pain intensity and disability. The secondary outcome was adverse events. **Results**: Overall, 119 RCTs (12,496 patients; 32 interventions) were included. Risk of bias was low in 50.4% of trials, unclear in 22.7% and high in 26.9%. Compared with inert treatment, a combination of active and/or passive multimodal non-pharmacological inventions (eg, exercise and manual therapy) were effective for pain on a 0-to-10 scale at 1 month (MD range 0.84 to 3.74) and at 3 to 6 months (MD range 1.06 to 1.49), and effective on disability on a 0-to-100 scale at 1 month (MD range 10.26 to 14.09) and 3 to 6 months (MD range 5.60 to 16.46). These effects ranged from possible to definite clinical relevance. Compared with inert treatment, anti-inflammatory drugs alone or in combination with another non-pharmacological treatment did not reduce pain at 1 month or 3 to 6 months. At 12 months, no superiority was found over inert treatment on both outcomes. Most mild adverse events were experienced following acupuncture/dry needling intervention. On average, the evidence varied from low to very low certainty. **Conclusions**: While multimodal non-pharmacological interventions may reduce pain and disability for up to 3 to 6 months of follow-up when compared with inert treatment, the evidence was very uncertain about their effects. Better quality and larger trials are needed to improve the certainty of evidence. **Registration**: PROSPERO CRD42019124501 **[Castellini G, Pillastrini P, Vanti C, Bargeri S, Giagio S, Bordignon E, Fasciani F, Marzioni F, Innocenti T, Chiarotto A, Gianola S, Bertozzi L (2022) Some conservative interventions are more effective than others for people with chronic non-specific neck pain: a systematic review and network meta-analysis. *Journal of Physiotherapy* ■:■–■]**

Introduction

Neck pain is a prevalent cause of pain and disability worldwide.[1] It is a serious public health issue[2] causing a heavy burden, with a prevalence of 223 million people (95% uncertainty interval 179 to 281) and 22 million (95% uncertainty interval 15 to 32) years lived with disability globally.[3] In the latest Global Burden of Disease Study, neck pain ranked 19th as measured by disability-adjusted life years (DALYs) for ages 25 to 49 years.[2]

Neck pain has a multifactorial aetiology; it might be related and modulated to ergonomic or individual factors such as age, behavioural attitude or psychosocial distress such as anxiety or job satisfaction.[4] Since most episodes of neck pain are of unknown origin, this is usually labelled as non-specific neck pain.[5,6] In the United States, together with low back pain, it is the leading cause of healthcare spending.[7] The burden and costs of neck pain are arguably driven by patients with chronic non-specific neck pain (CNSNP). According to symptom duration, CNSNP is usually classified as pain lasting or recurring for > 3 months.[8] Quality of life, mood, ability to cope, social participation, employment rates and job income are reduced and influenced by CNSNP, both for those who are affected by it and their spouses.[9] Nevertheless, neck pain has received very little attention in terms of research efforts compared to burden: 0.12

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trials per million DALYs.[10] Few large and powered randomised clinical trials have focused only on neck pain[11,12] and recommendations for its management are sometimes extrapolated from evidence on general musculoskeletal pain.[13]

Several conservative interventions for patients with CNSNP are commonly used in clinical practice: education, manual therapy, therapeutic exercise, electrotherapy, acupuncture, medication such as non-steroidal anti-inflammatory drugs (NSAIDs), and a combination of these.[14–20] However, heterogeneity among current guideline recommendations[21,22] does not facilitate the clinician's decision-making because it leaves uncertainty about which treatment options are likely to be the most effective.

Furthermore, published systematic reviews have focused only on the pairwise comparison of different treatments,[14–20] and it is believed that none have investigated pain, disability and adverse events involving all comprehensive evidence on conservative interventions in CNSNP. The goal of this study was to compare the available choices for patients with CNSNP in terms of benefits and harms, via a systematic review with network meta-analysis (NMA).

Therefore, the research question for this systematic review and network meta-analysis of randomised clinical trials was:

> Which is the most effective conservative intervention for patients with chronic non-specific neck pain?

Methods

Protocol and registration

The systematic review protocol was registered in the PROSPERO database and published.[23] The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension for NMA was followed for reporting.[24] Additional sections specific to NMA have been considered according to Chaimani et al[25] (see Appendix 1 on the eAddenda).

Data sources and searches

The following electronic databases were searched from their inception up to 8 February 2019 and updated on 3 May 2021: PubMed, Cochrane Controlled Trials Register (CENTRAL), CINAHL, Scopus, ISI Web of Science and PEDro, using the appropriate thesaurus and free-text terms (Appendix 2 on the eAddenda). No restriction regarding year of publication and language was applied. References lists of all eligible studies and any systematic reviews retrieved with the search strategy were also checked for eligibility. In case of non-English studies for which a translation could not be obtained, studies were classified awaiting assessment as potentially eligible but not considered in the full analyses. Their contribution was considered irrelevant when $< 5\%$ of the whole included sample; otherwise their finding was discussed.

Eligibility criteria

Participants

This review included only randomised controlled trials assessing adults ($>$ 18 years old) with CNSNP with no known cause,[26] defined as pain lasting for ≥ 3 months at the time of intervention.[27] Strategies to ensure inclusion of CNSNP patients are reported in Appendix 2 on the eAddenda. We excluded studies involving patients with a specific diagnosis (eg, radicular pain, fracture, tumour, inflammatory disease), whiplash-associated disorders or fibromyalgia, and studies involving mixed populations where data for patients with CNSNP were not presented separately.

Interventions and comparisons

We included trials that allocated participants to any of the conservative therapies (non-pharmacological and pharmacological) listed in Box 1, irrespective of modality, frequency, intensity, and length of treatment. Surgical treatments were excluded.

Studies that compared the same class of treatment (eg, low-intensity versus high-intensity exercise) are less informative for this question and were excluded. Studies involving comparisons with multiple arms (eg, three-arm trials) with two arms investigating the same intervention at different dosage/intensity compared with a control group were included following Cochrane guidance for analyses, splitting the sample size of the shared group into two or more groups with equal sample size.[28]

Outcomes and time points

The primary outcomes were pain intensity (eg, measured with a numeric rating scale or a visual analogue scale) and disability (eg, measured with the Neck Disability Index or the Neck Pain and Disability Scale). The secondary outcome was any adverse event reported. According to the Methodological Expectations of Cochrane Intervention Reviews, information was gathered at the following time points: short-term (closest to 1 month assessment), intermediate-term (closest to 3 to 6 months), and long-term follow-up (closest to 12 months).[29] Comparisons with immediate-term follow-ups (eg, 60 seconds after intervention) were excluded.

Study selection

Two independent authors screened the title and abstract list obtained with the search strategy and assessed full-text copies of potential papers for eligibility. Disagreements were resolved through discussion or consulting a third author. We used Endnote[a] for removing duplicates and Rayyan QCRI to manage the screening phase.[30,31] Further details about selection criteria are provided in the published protocol.[23]

Data extraction and risk of bias assessment

A pre-defined standardised data extraction in an Excel spreadsheet was used to collect the data from the included studies. Two authors independently extracted data about general characteristics and outcomes of interest from the included studies and assessed the risk of bias using the Cochrane Collaboration's Risk of Bias tool (version modified by the Cochrane Back and Neck Group).[32] For the clinical context, since blinding is implausible for most of the interventions that were considered, we judged the importance of potential bias using a proxy of the overall assessment for 'low', 'high' or 'unclear' risk of bias with the following domains: 'selection bias', 'detection bias' and 'outcome reporting bias'. Disagreements were resolved via discussion with another member of the reviewing team. The following characteristics were extracted from each study: name of first author, country, year of publication, setting, number of centres, population characteristics (eg, age, sex, pain duration), number of participants, percentage of dropouts at each follow-up, type of experimental/control interventions with details (eg, length of treatment, frequency), and primary and secondary outcomes. The outcome measures of interest were collected at post-treatment assessments. Corresponding authors were contacted in cases of missing data. In cases of no response, missing standard deviations were imputed using their baseline value for a small proportion of studies.[33] Data from intention-to-treat analysis were used. When outcome data were available only in graphs, they were extracted as numerical data using WebPlotDigitiser.[34] Further details about outcome and missing data are provided in Appendix 2 on the eAddenda.

Data synthesis and analysis

Systematic review expressed as qualitative synthesis

Overall, the main study and patients' characteristics were summarised using descriptive synthesis and risk of bias assessment. Studies with unavailable outcome data to allow the NMA (eg, data expressed in median due to skewed distribution, p-value, time points not reported) were narratively summarised.

Box 1. Eligibility criteria.

Population
- Adults
- Chronic non-specific neck pain (> 3 months)

Interventions
- Any conservative therapies (non-pharmacological and pharmacological) irrespective of modality, frequency or intensity, and length of treatment, alone or combined (maximum two treatments):
  - Acupuncture/dry needling: acupuncture; electroacupuncture; needling on trigger points without medication
  - Cognitive: cognitive behavioural therapy
  - Education: advice; neck pain educational program; pain education; self-care group
  - Exercise: active therapeutic exercise (eg, deep cranio-cervical muscle training; exercise with balance devices; free exercise; motor control; postural control; proprioceptive training; supervised exercise); muscle stretching; strength and endurance training
  - Mind-body practices: Pilates; Qi Gong; Tai-Chi; Yoga; other types of common gymnastics, Alexander technique
  - Manual therapy: high-velocity low-amplitude/thrust manipulation (applied to any cervical, thoracic or spinal level); mobilisation (eg, passive mobilisation, mobilisation-with-movement); soft tissue techniques (massage; myofascial techniques; trigger point manual treatment; tuina); manual traction
  - Usual care: any type of common treatment used in primary care by general practitioner as minimal intervention (advice to stay active and/or to take drugs as needed)
  - Non-steroidal anti-inflammatory drugs (NSAIDs): any kind of NSAIDs drug, including COX-2 inhibitors (eg, ibuprofen, naproxen, sulindac, ketoprofen, tolmetin, etodolac, fenoprofen, diclofenac, flurbiprofen, piroxicam, ketorolac, indomethacin, meloxicam, nabumetone, oxaprozin, mefenamic acid, diflunisal)
  - Paracetamol: any dose of paracetamol
  - Physical agents: cryotherapy; electrotherapy; electromagnetic therapy; electro neuro adaptive regulator therapy device (ENAR); heat therapy; infrared radiation; laser therapy; phonophoresis; transcutaneous electrical nerve stimulation (TENS); ultrasound
  - Relaxation: guided imagery; relaxation training; stress management
  - Taping: any type of taping, both elastic (kinesio taping) and non-elastic
  - Traction: any type of neck or spinal traction (eg, gravitational; mechanical; underwater traction) performed alone without any other manual intervention.

Comparators
- Inert treatment: any type of intervention described as no intervention; placebo; sham; waiting list.
- All against all

Outcomes
- Pain intensity (eg, Numeric Rating Scale or a Visual Analogue Scale)
- Disability (eg, Neck Disability Index or the Neck Pain and Disability Scale)
- Adverse events

Time points
- Short term (closest to 1 month)
- Intermediate term (closest to 3 to 6 months)
- Long term (closest to 12 months)

Study design
- Randomised controlled trials

Pairwise meta-analysis (direct evidence)

We performed conventional pairwise meta-analysis for each outcome using a random effects model for each treatment comparison with at least two studies.[35] We assessed statistical heterogeneity using the I^2 statistic. When the I^2 value was > 90% (ie, high degree of heterogeneity), we did not perform meta-analysis.[36,37]

Summary of the network

According to the PRISMA-NMA guideline,[24] the process leading to node grouping[38] and rationale for node adopted are displayed in Appendix 3 on the eAddenda.

Assumption of transitivity and geometry of the network

We first evaluated the transitivity assumption,[39-41] defined as the balance between the distribution of potential effect modifiers (age, sex, mean pain duration, presence of widespread pain, presence of somatisation, length of treatment, number of randomised participants, and baseline pain intensity)[42] across pairwise comparisons. Transitivity was judged exploring these variables by trials, interventions, pairwise comparisons and single networks (eg, outcome and follow-up). Then, the connection of treatments was evaluated graphically by a network plot for each primary outcome at follow-ups: 1 month, 3 to 6 months, and 12 months.[43]

Assumption of inconsistency (heterogeneity and coherence)

The assessment of statistical heterogeneity in the entire network was based on the magnitude of the heterogeneity variance parameter (τ^2) estimated by using network meta-analysis models. Heterogeneity was calculated across all treatment comparisons, accounting for correlations induced by multi-arm studies.[44-46]

The design-by-treatment interaction model was used in the whole network (global χ^2 test) and the node splitting function for each pairwise comparison was used to evaluate the global and local consistency (ie, statistical manifestation of transitivity), respectively.[39-41] If the data were consistent with the possibility that both global and local inconsistency parameters were equal to zero, we fit a consistency model. When substantial global inconsistency was found,[39,40] multiple strategies were explored, such as checking data, splitting nodes to possibly remove sources of the problem, inspecting the influence of effect modifiers using the meta-regression random effects within a frequentist framework (metareg command in Stata).[47,48] If these strategies did not resolve the inconsistency, we presented only pairwise comparisons.[40]

Network meta-analysis (mixed and indirect evidence)

Pain and disability estimates were calculated using the standardised mean differences (SMDs) alongside 95% confidence intervals (CIs). The SMDs were back-translated to a typical scale (ie, 0 to 10 for pain and 0 to 100 for disability) by multiplying the SMD by the average standard deviation of the sample,[49,50] as reported in Appendices 4 and 5 on the eAddenda.

The outcome data were first carefully checked to detect unusually large effect estimates. We defined a 'large effect size', visually inspecting pairwise meta-analysis, when SMDs were > 1.5.[51] Further details are provided in Appendix 6 on the eAddenda.

After checking the shared nodes in the compared interventions and covariates for any effect modifiers, it was assumed that people

with CNSNP meeting the inclusion criteria were, in principle, equally likely to be randomised to any of the eligible interventions.

We assessed direct (ie, pairwise comparisons) and indirect evidence by network forest plots (mixed evidence) for each primary outcome using a random-effects model within a frequentist framework.[35,52,53] We presented effect sizes of all interventions against a reference standard (ie, inert treatment, including sham therapy, placebo drugs, waiting list control, no intervention) in each outcome network at all follow-ups according to the certainty of evidence (ie, from high to low) and the clinical relevance in ad hoc tables. The clinical relevance for both pain and disability was achieved considering 25% relative improvement based on baseline values of the dataset, which meant 1.3 points for pain (0-to-10 scale) and 7.4 for disability (0-to-100 scale) (Appendices 4 and 5 on the eAddenda).[54-56] Then, clinical relevance was interpreted considering the categories proposed by Man-Son-Hing et al[57] (ie, definite, probable, possible, definitely not). All details for interpretation are shown in Appendix 7 on the eAddenda. Then, we reported the effect size of all available interventions against each other intervention for each outcome at each follow-up in a league table. In order to identify the superiority of each intervention we estimated: the relative ranking probabilities of being the best, the mean rank and the surface under cumulative ranking (SUCRAs), which expresses the percentage of effectiveness of an intervention ranked first without uncertainty.[58] Stata 16 software[b] was used in the analyses.[48,59,60]

Sensitivity analyses

The sensitivity analysis was conducted excluding studies with high risk of bias and missing information (eg, imputed SD). The robustness of evidence (ie, same direction of results and global inconsistency) was evaluated to assess any change from primary analyses.

Certainty of evidence

For all consistent networks, using the Grading of Recommendation, Assessment, Development and Evaluation (GRADE) approach, we evaluated four levels of certainty of evidence from very low (ie, the true effect is probably markedly different from the estimated effect) to high (ie, a lot of confidence that the true effect is similar to the estimated effect).[61,62,63] Study limitations, reporting bias, indirectness, inconsistency (ie, heterogeneity and incoherence), imprecision and publication bias domains were evaluated using CINeMA (Confidence in Network Meta-Analysis) to interpret all the findings.[64] Imprecision, heterogeneity and incoherence of network were assessed in relation to the clinical relevance.[65] The frameworks for pain and disability are reported in Appendices 4 and 5 on the eAddenda, respectively.

Results

Deviations from the study protocol

Deviations from the protocol are reported in Appendix 8 on the eAddenda.

Study selection

After removing duplicates, the whole search strategy retrieved 6,468 records. Screening of titles and abstracts led to 6,170 irrelevant hits. The remaining 337 full-text articles were assessed, of which 119 studies met the inclusion criteria (Appendix 9 on the eAddenda). Of these, 18 were not included in the quantitative synthesis (16 had outcome reporting bias/unusable data and two had interventions with unclear eligibility). One study provided unusable data for the pain outcome but was included in quantitative analysis for disability. For a more detailed description of the screening process, see the PRISMA flow diagram in Figure 1 and full reasons for exclusion at OSF https://osf.io/ac653/.

General characteristics

A total of 12,496 participants were included in 119 trials (277 arms, 32 different interventions) published between 1986 and 2021. Most of studies were conducted in Europe (42.0%) and Asia (37.8%). The sample size per arm ranged from 5 to 1,886 participants, with a median of 24 participants. Overall, 108 (90.8%) trials were monocentric. The median of the arms' mean ages was 44.3 years (IQR 38.6 to 48.1), whereas the median percentage of males was 26.5 (IQR

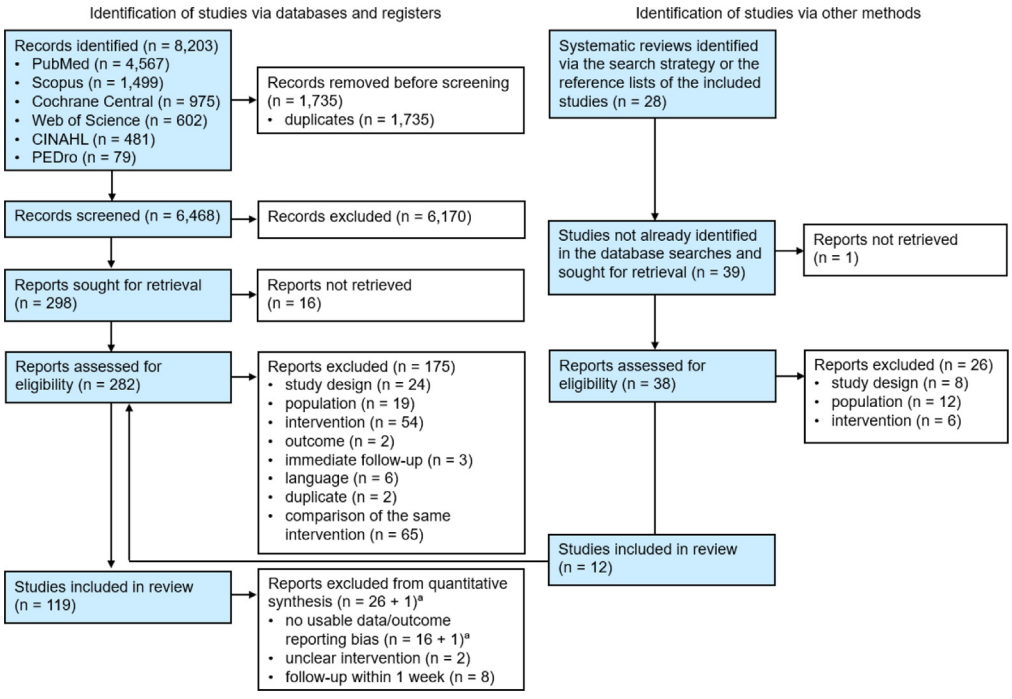

Figure 1. Flow of studies through the review.
[a] One study was assessed in the qualitative synthesis only for pain outcome due to not usable data, whereas disability was assessed in the quantitative synthesis.

14.4 to 37.0). The median pain duration was 73.7 months (IQR 40.8 to 95.8) and the median length of treatments was 4 weeks (IQR 3 to 8). Baseline mean pain was 53.8 on a 0-to-100 scale; baseline mean disability was 29.6 on the 0-to-100 NDI scale. The most studied interventions were exercise (n = 60 arms) and manual therapy (n = 38 arms) (Table 1). Characteristics of all included studies are reported in Appendix 10 on the eAddenda.

Risk of bias assessment

The risk of bias assessments are summarised in Appendix 11 on the eAddenda. Regarding the overall risk of bias across studies (n = 119), 50.4% trials were at low risk of bias (n = 60), 22.7% trials at unclear risk of bias (n = 27) and 26.9% at high risk of bias (n = 32).

Quantitative synthesis

Transitivity assumption

Studies and participants' characteristics stratified by network (eg, outcome and follow-up), intervention nodes, trial and pairwise comparison are summarised in Appendix 12 on the eAddenda. No important concerns were raised regarding the violation of the transitivity assumption when the potential effect modifiers were evaluated. The transitivity assumption was guaranteed in terms of clinical and methodological features, except for eight trials that were dissimilar in terms of length of treatment (ie, intervention performed within 1 week); thus, these trials were excluded from the quantitative analyses at the short term (Appendix 4 on the eAddenda). The inconsistency assessment is reported globally and locally in Appendix 13 on the eAddenda.

Table 1
General characteristics of the included studies.

Characteristic	N (%)
Country[a]	
Africa	2 (1.68)
Asia	45 (37.82)
Europe	50 (42.02)
America	15 (12.60)
Oceania	7 (5.88)
Year of publication[a]	
1980 to 1989	2 (1.68)
1990 to 1999	4 (3.36)
2000 to 2009	23 (19.33)
2010 to 2019	72 (60.50)
2020 to 2021	18 (15.13)
Study setting[a]	
monocentre	107 (90.76)
multicentre	10 (8.40)
not stated	1 (0.84)
Interventions[b]	
acupuncture/dry needling	23 (8.30)
acupuncture/dry needling + exercise	4 (1.44)
acupuncture/dry needling + manual therapy	1 (0.36)
acupuncture/dry needling + NSAIDs	1 (0.36)
acupuncture/dry needling + physical therapy	1 (0.36)
acupuncture/dry needling + usual care	1 (0.36)
cognitive	2 (0.72)
cognitive + exercise	3 (1.08)
cognitive + manual therapy	2 (0.72)
education	8 (2.89)
education + exercise	9 (3.25)
education + manual therapy	2 (0.72)
exercise	60 (21.66)
exercise + kinesio taping	2 (0.72)
exercise + manual therapy	19 (6.86)
exercise + physical agents	11 (3.97)
exercise + relaxation	1 (0.36)
inert treatment	44 (15.88)
kinesio taping	3 (1.08)
kinesio taping + manual therapy	1 (0.36)
manual therapy	38 (13.72)
manual therapy + physical agents	3 (1.08)
mind-body practices	8 (2.89)
mind-body practices + paracetamol	1 (0.36)
mind-body practices + usual care	1 (0.36)
NSAIDs	3 (1.08)
paracetamol	1 (0.36)
physical agents	14 (5.05)
relaxation	4 (1.44)
traction	1 (0.36)
usual care	2 (0.72)
unclear	3 (1.08)

NSAIDs = non-steroidal anti-inflammatory drugs.
[a] Out of 119 studies
[b] Out of 277 arms

Outcome: Pain intensity

Pain intensity was investigated by 73 studies at 1 month, 43 studies at 3 to 6 months, and seven studies at 12 months. Table 2 reports the overall summary of the estimates back-translated to a typical scale (ie, 0-to-10 scale) along with the clinical relevance interpretation.

Short term: After checking data and connection of the network, the network meta-analysis of pain at 1 month (55 studies; 4,206 participants) (Figure 2 and Appendix 14 on the eAddenda) provided data on 40 direct comparisons and 236 indirect comparisons between 24 different treatment nodes. No local inconsistency was found. Under global consistency, the network meta-analysis showed that manual therapy was effective compared with inert treatment, with low certainty of evidence (SMD –0.42, 95% CI –0.82 to –0.01), followed by six other conservative treatments (SMD range 0.77 to 1.87) with very low certainty of evidence (Appendix 15 on the eAddenda). The forest plot of the network meta-analysis is presented in Appendix 16 on the eAddenda. The ranking of treatments based on cumulative probability plots and SUCRAs is presented in Appendix 17 on the eAddenda. The most effective treatment to reduce pain at 1 month was exercise with kinesio taping (93.2%), followed by acupuncture/dry needling with manual therapy (92.6%). All NMA estimates of all interventions compared with each other intervention are shown in Appendix 18 on the eAddenda.

Intermediate term: After checking data and connection of network, the NMA on pain at 3 to 6 months (38 studies, 3,782 participants) provided data on 28 direct and 125 indirect comparisons between 18 different treatment nodes (Appendix 14 on the eAddenda**)**. No local inconsistency was found but global inconsistency was found; thus, different strategies were followed to explore it (Appendix 13 on the eAddenda). Pairwise meta-analyses and NMA are presented in Appendix 6 on the eAddenda**.** The forest plot of the pairwise meta-analysis showed that three conservative treatments (education with exercise, mind body practices and physical agents) are effective compared with inert treatment (SMD range 0.53 to 0.75).

Long term: After checking data and connection of network, the network meta-analysis on pain at 12 months (7 studies, 1,417 participants) provided data on 11 direct and 25 indirect comparisons between nine different treatment nodes (Appendix 14 on the eAddenda). No local inconsistency was found. Under consistency, the network meta-analysis showed that no intervention was substantially better than inert treatment (Appendix 15 on the eAddenda). The certainty of the evidence ranged from very low to low. The forest plot of network meta-analysis is presented in Appendix 16 on the eAddenda. The ranking of treatments based on cumulative probabilities plots and SUCRAs is presented in Appendix 17 on the eAddenda. In terms of efficacy, the most effective treatments to reduce pain at 12 months were acupuncture/dry needling (79.7%) and exercise (73.1%). All network meta-analysis estimates of all interventions against each other intervention are shown in Appendix 18 on the eAddenda.

Outcome: Disability

Disability was investigated by 61 studies at 1-month follow-up, 33 studies at 3 to 6 months, and eight studies at 12 months. Table 2 reports the overall summary of the estimates back-translated to a typical scale (ie, 0-to-100 scale) along with the clinical relevance interpretation.

Table 2
Summary of all estimates (back-translated).

Treatments vs inert treatment	Pain 1 month	Pain 3 to 6 months[a]	Pain 12 months	Disability 1 month[a]	Disability 3 to 6 months	Disability 12 months
	MD (95% CI)	MD (95% CI)	MD (95% CI)	MD (95% CI)	MD (95% CI)	MD (95% CI)
Acu/dn	0.60 (−0.02 to 1.22)	0.63 (−0.22 to 1.47)	0.26 (−0.42 to 0.94)	0.77 (−1.44 to 2.99)	**6.94 (2.02 to 11.87)**	2.58 (−1.23 to 6.38)
Acu/dn + exercise	1.24 (−0.36 to 2.84)				**16.46 (4.93 to 28.00)**	
Acu/dn + manual therapy	**3.24 (1.12 to 5.36)**					
Acu/dn + NSAIDs	0.60 (−1.76 to 2.96)					
Acu/dn + usual care						**−6.50 (−12.66 to −0.34)**
Cognitive	1.62 (−0.52 to 3.74)		0.04 (−0.86 to 0.94)		11.42 (−0.45 to 23.30)	1.46 (−3.70 to 6.50)
Cognitive + exercise	1.46 (−0.76 to 3.68)				13.44 (−2.13 to 28.90)	
Cognitive + manual therapy	2.26 (−0.16 to 4.68)				12.54 (−1.68 to 26.88)	
Education	−0.52 (−1.98 to 0.92)					
Education + exercise	0.40 (−0.64 to 1.44)	**1.31 (0.13 to 2.48)**	−0.32 (−1.04 to 0.42)		0.11 (−7.17 to 7.39)	−3.25 (−7.28 to 0.90)
Exercise	0.80 (−0.04 to 1.64)		0.08 (−0.40 to 0.56)		3.36 (−1.12 to 7.84)	−1.57 (−4.26 to 1.12)
Exercise + kinesio taping	**3.74 (1.36 to 6.12)**					
Exercise + manual therapy	**1.62 (0.60 to 2.62)**		−0.10 (−0.70 to 0.52)		**8.18 (2.35 to 14.11)**	−2.02 (−5.38 to 1.46)
Exercise + physical agents	**1.60 (0.48 to 2.72)**					
Exercise + relaxation	1.06 (−1.12 to 3.22)					
Kinesio taping	1.28 (−0.22 to 2.80)			0.29 (−4.85 to 5.42)		
Manual therapy + physical agents	**1.72 (0.18 to 3.26)**				9.07 (−2.13 to 20.27)	
Manual therapy	**0.84 (0.02 to 1.64)**		−0.54 (−1.20 to 0.14)		4.70 (−1.79 to 11.20)	**−5.60 (−9.41 to −1.79)**
Mind-body	1.16 (−0.16 to 2.46)	**1.06 (0.22 to 1.90)**			**5.60 (0.22 to 10.98)**	
Mind-body + usual care						**−6.72 (−12.99 to −0.56)**
NSAIDs	0.10 (−2.24 to 2.46)	−1.34 (−2.78 to 0.10)				
Physical agents	**1.54 (0.64 to 2.44)**	**1.49 (0.66 to 2.33)**		**10.26 (5.40 to 15.12)**	**7.28 (0.34 to 14.22)**	
Relaxation	0.98 (−0.28 to 2.24)	−0.07 (−0.56 to 0.42)	−0.08 (−0.56 to 0.40)	**14.09 (7.80 to 20.38)**	1.34 (−7.62 to 10.19)	−1.57 (−4.26 to 1.23)
Traction	1.44 (−0.72 to 3.60)				5.82 (−6.94 to 18.70)	
Usual care	0.28 (−1.92 to 2.46)		−0.68 (−1.68 to 0.34)			**−9.74 (−15.46 to −4.03)**
Definite	Probable	Possible	Not probable	Not possible	Definitely not	

Abbreviations: Acu/dn = acupuncture or dry needling, Mind-body = mind body practices, NSAIDs = non-steroidal anti-inflammatory drugs.
SMDs were back-translated to a typical scale (ie, 0 to 10 for pain and 0 to 100 for disability) by multiplying the SMD by the average standard deviation of the sample as reported in Appendices 17 and 18. The clinical relevance for both pain and disability was achieved considering 25% relative improvement based on baseline values of the dataset, which means 1.3 points for pain (0-to-10 scale) and 7.4 for disability (0-to-100 scale). Positive MDs favour the row treatments. Interpretation of clinical relevance was graded in the categories reported in the coloured bar (Appendix 7). Darker green indicates that the intervention listed in the row is more likely to be clinically relevant, whereas darker orange indicates that the intervention is not likely to be clinically relevant. Estimates with confidence intervals that do not include zero are bolded.
[a] Pairwise meta-analysis (network meta-analysis inconsistent).

Short term: After checking data and connection of network, the network meta-analysis on disability at 1 month (54 studies, 3,979 participants) (Appendix 14 on the eAddenda) provided data on 40 direct comparisons between 24 different treatment nodes. No local inconsistency was identified but global inconsistency was found; thus, different strategies were followed to explore inconsistency (Appendix 13 on the eAddenda). Pairwise meta-analyses are presented in Appendix 6 on the eAddenda. The forest plot of the pairwise meta-analysis showed that two conservative treatments (physical agents, relaxation) are effective compared with inert treatment (SMD range 0.92 to 1.26).

Intermediate term: After checking data and connection of network, the network meta-analysis on disability at 3 to 6 months (27 studies, 6,636 participants) provided data on 23 direct comparisons and 82 indirect comparisons between 15 different treatment nodes (Appendix 14 on the eAddenda). No local inconsistency was found. Under consistency, the network meta-analysis showed that five conservative treatments were statistically significant compared with inert treatment, with certainty of the evidence ranging from very low to low (SMD range 0.50 to 1.47) (Appendix 15 on the eAddenda). The forest plot of network meta-analysis is presented in Appendix 16 on the eAddenda. The ranking of treatments based on cumulative probabilities plots and SUCRAs is presented in Appendix 17 on the eAddenda. In terms of efficacy, the most effective treatment to reduce disability at 3 to 6 months was acupuncture/dry needling with exercise (88.2%) followed by cognitive behavioural treatment with exercise (77.3%). All network meta-analysis estimates of all interventions against each other intervention are shown in Appendix 18 on the eAddenda.

Long term: After checking data and connection of network, the network meta-analysis on disability at 12 months (eight studies, 1,934 participants) provided data on 14 direct comparisons and 41 indirect comparisons between 11 intervention nodes (Appendix 14 on the eAddenda). No local inconsistency was found. Under consistency, the NMA showed that inert treatment was statistically significant compared with four conservative treatments (Appendix 15 on the eAddenda) with low certainty of evidence. The forest plot of network meta-analysis is presented in Appendix 16 on the eAddenda. The ranking of treatments based on cumulative probabilities plots and SUCRAs is presented in Appendix 17 on the eAddenda. In terms of efficacy, the most effective treatments to reduce disability at 12 months were acupuncture/dry needling (94.1%) and cognitive behavioural treatment (86.6%). All NMA estimates of all interventions against each other intervention are shown in Appendix 18 on the eAddenda.

Outcome: Adverse events

Overall, 54 of 119 studies collected adverse events. Since reporting of adverse events was heterogeneous for number of people and number of events, these data could not be quantitated. The majority of mild events that were reported were experienced by the acupuncture/dry needling arm (1,288 events in 10 studies on 2,353 randomised participants). No serious event was reported. Further details about adverse events are provided in Table 3 and Appendix 10 on the eAddenda.

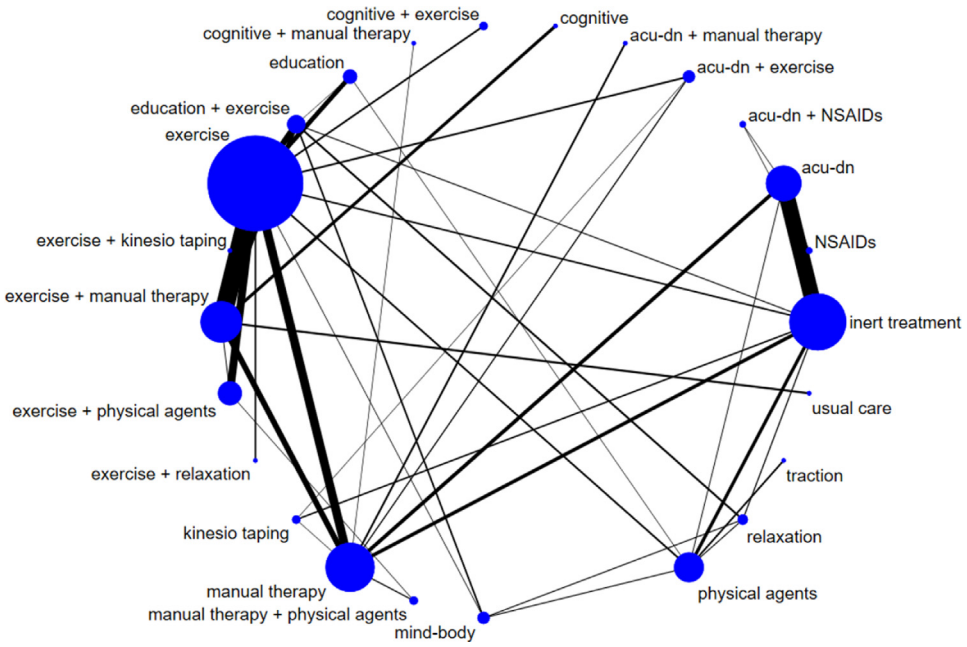

Figure 2. Network graph for pain at 1-month follow-up.
Acu-dn = acupuncture/dry needling, NSAIDs = non-steroidal anti-inflammatory drugs, Mind-body = mind-body practices
The size of the nodes is proportional to the number of studies evaluating each intervention, and the thickness of the edges is proportional to the precision (the inverse of the variance) of each direct comparison.

Sensitivity analysis

Sensitivity analysis was conducted on all outcome networks at 1 month and 3 to 6 months follow-ups (Appendix 19 on the eAddenda). Overall, exclusion of missing information (eg, imputed SD) and high-risk of bias studies did not affect the robustness of evidence.

Certainty of evidence

The GRADE judgments are reported in Appendix 4 for the pain network meta-analysis and Appendix 5 for the disability network meta-analysis on the eAddenda. In the analysis of pain at 1 month (n = 276 comparisons), the evidence was mainly downgraded with major concerns for incoherence (due to disagreement about the range of clinical relevance) (n = 250) and imprecision (due to wide confidence intervals) (n = 122), and with some concerns for within-study bias (due to selection, detection and outcome reporting bias) (n = 185) and indirectness (due to the majority of evidence coming from indirect comparisons) (n = 218). In the analysis of pain at 12 months (n = 36 comparisons), the evidence was mainly with some concerns for indirectness (n = 25). In the analysis of disability at 3 to 6 months (n = 105), there were major concerns for imprecision (n = 72) and some concerns for within-study bias (n = 74). In the analysis of disability at 12 months (n = 55), there were some concerns for within-study bias (n = 23) and indirectness (n = 41). No publication bias was evident assessing small-study effects in both pain and disability outcome at each follow-up (Appendix 20 on the eAddenda). Additional references are presented in Appendix 21 on the eAddenda.

Discussion

It is believed that this is the largest systematic review with network meta-analysis regarding comparative effectiveness of 32 different conservative interventions in 12,496 patients with CNSNP. Overall, it was found that multimodal non-pharmacological interventions were more efficacious than inert treatment for reducing both pain and disability outcomes, with possible to definite clinical importance. At 1 month of follow-up, exercise with kinesio taping, exercise with manual therapy, exercise with physical agents, manual therapy, manual therapy with acupuncture/dry needling, manual therapy with physical agents, and physical agents may reduce pain (mixed and indirect evidence), whereas physical agents and relaxation may reduce disability (direct evidence). At 3 to 6 months, education with exercise, physical agents and mind-body practices may reduce pain (direct evidence), whereas acupuncture/dry needling, acupuncture/dry needling with exercise, exercise with manual therapy, physical agents and mind-body practices may reduce disability (mixed and indirect evidence). At 12 months, no superiority was found between interventions and inert treatment on pain (mixed and indirect evidence), whereas a few conservative interventions may have a less helpful effect on disability than inert treatment (indirect evidence).

These interventions can generally be safely provided by clinicians; however, acupuncture/dry needling may elicit some mild adverse events.

Generally, network meta-analysis findings (mixed and indirect evidence) were also confirmed in the probability of being the best treatment. However, readers and stakeholders developing or updating guidelines should take caution in the interpretation of the results, given the low and very low certainty evidence, mainly due to mostly indirect evidence, imprecision in the estimates (ie, small nodes and large confidence intervals), outcome non-reporting bias and unclear reporting of effect modifiers. Further research may have a considerable impact on the results.

Short-term follow-up can be considered the most reliable follow-up as a proxy of the treatment effects because it is the closest measurement to the length of the majority of treatments (median 4 weeks). Consequently, intermediate term is the first follow-up that evaluates persistence of effects, whereas the long-term follow-up is the latest. This could be the reason why treatment effects at the long-term follow-up seem to be equal; previous Cochrane systematic reviews displayed similar results for long-term outcomes.[16,18]

Clinical implications

The main findings support the current recommended interventions reported in the latest published guidelines, in which multimodal interventions (ie, rehabilitative programs including two interventions) are recommended for patients with CNSNP.[21,66]

Table 3
Adverse events.

Node	Events[a] (n)	Participants (n)	Studies (n)	Description of events
Acu/dn	1,288	2,353	10	Muscle soreness; pain at acupoint, dizziness, local bleeding, numbness; haematoma; fainting; bruise at the site; chest discomfort; neck pain, headache; swelling of the hand, pain and ulcer of the ear; vegetative symptoms; euphoria
Acu/dn + exercise	0	28	2	–
Acu/dn + manual therapy	0	47	1	–
Acu/dn + NSAIDs	1	15	1	Flushing, skin rash
Acu/dn + usual care	10	173	1	Bruising, swelling, or numbness; muscle spasms; pain; and respiratory problems
Cognitive + exercise	1	130	2	Increased pain
Cognitive + manual therapy	0	16	1	–
Education	0	48	1	–
Education + exercise	30	193	4	Muscle soreness, upper extremity symptoms, headache, back pain, jaw pain, nausea, and dizziness
Education + manual therapy	9	32	1	Discomfort or pain, soreness, nausea
Exercise	127	758	22	Muscle soreness; muscle tension, aching muscles; transient limb pain, worsening of neck pain; increase radicular pain; migraine; vertigo; nausea and vomiting; dizziness, fainting; headache, back pain, jaw pain; knee pain and myogelosis, worsening of tinnitus
Exercise + kinesio taping	0	48	2	–
Exercise + manual therapy	99	405	10	Dizziness, fainting, nausea and vomiting; muscle soreness, increases in neck or headache pain; upper extremity symptoms, back pain, jaw pain.
Exercise + physical agents	0	78	3	–
Exercise + relaxation	0	35	1	–
Inert treatment	57.	688	16	Increased pain; headache; nausea; tingling; 'spaced-out' feeling; sleepiness; tiredness; skin sensitivity; jaw pain; stiffness; depression; numbness; aching; fainting; swelling of the hand; muscle soreness; myogelosis; vertigo; other pain; thirst; engorged hands; twinge in the neck; urinary urgency; bursitis; cephalea; euphoria, dizziness, itching palm, warm feeling
Kinesio taping	2	76	2	Cutaneous irritations
Manual therapy	49	453	13	Muscle fatigue; headache, local soreness; increases in neck pain, thoracic pain; aching muscles; tensions, dizziness; sleepiness; mood swings; painful point; nausea; 'head not movable'
Mind-body	49	205	6	Aching muscles, muscle tension; worsening of neck pain; muscle soreness after practice; transient limb pain, migraine, nausea; vertigo; other musculoskeletal, pain; Achilles tendon pain; meniscal tear; low back pain; myogelosis; headache; thirst; engorged hands; twinge in the neck, urinary urgency; bursitis.
Mind-body + paracetamol	0	32	1	–
Mind-body + usual care	3	172	1	Pain and incapacity, knee injury, and muscle spasms
NSAIDs	3	21	1	Gastric symptoms
Physical agents	21.9 [b]	107	4	Increased pain; headache; nausea; light-headed/dizzy; tingling in extremity 'spaced-out' feeling; sleepiness; tiredness; skin sensitivity; stiffness depression; worsening symptoms
Relaxation	3	70	2	Dizziness; headache; tinnitus
Usual care	2	172	1	Pain and incapacity
Total	1,754.9	–	–	–

Acu/dn = acupuncture or dry needling, Mind-body = mind body practices, NSAIDs = non-steroidal anti-inflammatory drugs,
[a] Number of adverse events or number of patients experiencing adverse events. More than one event may occur in the same patient.
[b] For one study (Chow 2006) adverse events were collected calculating the mean of overall events reported.

Nevertheless, this review provides some guidance on which a combination of interventions may be the most effective. While guidelines focus more on active interventions (eg, education and exercise), this review shows that a combination of active and passive treatment (eg, exercise and manual therapy), or a combination of two passive modalities (eg, acupuncture and manual therapy) may also be among the most effective intervention options. Neck pain guidelines also recommend, with weak evidence, the use of some painkillers.[66] Our network meta-analysis highlights negligible differences between NSAIDs with or without another conservative treatment and inert treatment for pain at 1 month. However, only a minority of pharmacological interventions were included in this systematic review (six arms) and we cannot exclude the presence of co-interventions (eg, drug as needed).

Additionally, discrepancies with recommended interventions are present because this review was based on the most recent evidence that has emerged in the last few years, whereas review teams of clinical guidelines did not take this evidence into account; as an example, 18 trials (19.4%) published from 2019 to 2021 were included in the quantitative synthesis in this review. Additional evidence can improve the precision of the estimated effect size.[67]

Another network meta-analysis for CNSNP was recently published, but this review displayed a different goal because the authors investigated only the effectiveness of exercise interventions,[68] confirming the current results and thus the effectiveness of some types of exercise (eg, motor control, strengthening exercises) compared with no treatment, even if no type of exercise was superior to others.

Strength and limitations

Some strengths of this review include a comprehensive systematic review methodology that followed the Cochrane Handbook and PRISMA-NMA reporting guidance.[24,33] It transparently reported the differences between protocol and review, as well as the assessment of transitivity in all networks.

There were several limitations to this study. First, disability at 1 month and pain at 3 to 6 months showed inconsistency, which prevented network meta-analysis from being performed. In fact, a high percentage of sparse nodes (32% at 1 month for disability and 55% at 3 to 6 months for pain) was found (treatment investigated by one

study), leaving analyses poorly informative.[40] To be more conservative, pairwise meta-analysis was reported.

Second, some studies (21.9% of the whole sample) did not contribute to the network meta-analysis because of non-transitive follow-up (within 1 week), missing outcome data, or unusable measurements (eg, skewed distribution, p-value, time points not reported).[69] The last two points reflect a potential for selective non-reporting bias that can distort quantitative analyses because available results differ systematically from missing results.[70] A recent meta-research study found that at least one important outcome was missing for 63% of randomised trials, but this waste was avoidable.[71] This percentage increased when also considering the missing SD and imputations for some outcomes in the included trials. However, the current review did not exclude these studies from the primary analyses because, under some circumstances, it can reduce precision in the estimated treatment effects and produce biased results; we transparently presented the sensitivity analyses instead (excluding imputation of missing data).[72]

Third, we did not separate no treatment/waiting list from sham/placebo interventions because too few studies reported a no-intervention or waiting-list control to allow the analyses. By not separating them, we also avoided a sparse network.[73] A recent meta-analysis showed that placebo interventions are more effective than no intervention on chronic low back pain in the short term.[74] To acknowledge this limitation of our approach, comparisons with a combined inert treatment node (no treatment/waiting list and sham/placebo interventions) were downgraded in the certainty of the evidence.

Fourth, the evaluation of the transitivity assumption was challenging because the majority of the included trials did not report the presence of widespread pain, somatisation and pain catastrophising, even though these may be treatment effect modifiers.[75] Most of the included interventions were combined interventions (eg, exercise with manual therapy) and the usual care node was broadly defined by study authors, increasing the chance of incorporating more heterogeneity within the node and widening the confidence intervals across the whole analysis. However, we carefully appraised the usual care intervention to select only those that met our a priori definition. Further difficulties in the categorisation of treatments were due to poor reporting in the description of interventions. In addition, we did not consider the head-to-head study design configuration comparing different characteristics of delivery (eg, low-intensity versus high-intensity exercise, different drugs dosages) because they were less informative for the review question.

Fifth, very few studies assessed long-term follow-up analysing persistence of effects. We did not select studies based on treatment effect duration. Currently, only one systematic review based on individual patient data has evaluated the persistence of effects.[76]

Research implications

This is the first attempt to make quantitative comparison of interventions in the absence of pairwise comparison trials and to provide ranking of each treatment being the best. Overall, while network meta-analysis is an attractive statistical tool, this review highlights that the limitations of the evidence base (eg, trials with small samples, high risk of bias, poor reporting, risk of bias due to missing evidence) may hamper its applicability. To facilitate future network meta-analyses in the field of CNSNP, higher quality and well-planned larger trials are necessary. For instance, one-third of the sample was at high risk of bias and most studies were monocentric (90.8%) with a median of 24 participants. Randomised trials should be adequately designed using sample size calculation, well-conducted, appropriately reported using checklists like the TIDieR on the reporting of interventions[77] and well-described in all effect modifiers. This could help generate a better configuration of the network nodes, assuring similarity of interventions and also allowing the inspection of different modalities of the same interventions (eg, inclusion of low-intensity versus high-intensity exercise). Since continuous outcome data are challenging and more prone to missing outcome data,[72,78] trials should report all outcome measurements (eg, mean and SD at each follow-up) avoiding missing evidence for quantitative analysis[70,79] (eg, graphs, p-values) following the CONSORT statement to ensure transparency of results.[80] Lastly, future systematic reviews should specify the duration of treatment in the study question because this element can influence the timepoint for the post-treatment therapy effects and persistence of effects. Furthermore, the power of meta-analyses may benefit from the existence of a core outcome set for CNSNP, like those existing for low back pain trials.[81,82] All these considerations may help to improve the certainty of the evidence and, consequently, future network meta-analyses in people with CNSNP.

Conclusion

This network meta-analysis showed that multimodal non-pharmacological interventions may be safe and effective for pain and disability at short-term and intermediate-term follow-up when compared with inert treatment in patients with CNSNP. Overall, given the generally unclear certainty of evidence, all results should be interpreted with caution.

Author contributions: Conceptualisation: PP, SG, AC, CV, LB; data curation: LB, FF, FM, CV, CG, SG, SB; formal analysis: GC, SG, SB; investigation: LB, FF, FM, CV, SG, TI; methodology: GC, SG, AC, LB, SB; resources: CG, SG, SB; software: CG, SG, SB; supervision: LB, PP; writing – original draft: GC, SG, CV, LB, SB; writing – review and editing: GC, PP, CV, SB, SG, EB, FF, FM, TI, AC, SG, LB.

Availability of data and materials: The full dataset is freely available online in OSF (https://osf.io/ac653/), a secure online repository for research data.

What was known on this topic: Chronic non-specific neck pain is common and can affect quality of life, mood, social participation and employment. Clinical practice guidelines focus on active interventions (eg, education and exercise) and recommend with weak evidence the use of analgesic medication.
What this study adds: A combination of active and/or passive multimodal non-pharmacological treatments (eg, exercise and manual therapy) may be the most effective options compared with inert treatment whereas anti-inflammatory drugs with or without another non-pharmacological treatment are not superior to inert treatment to reduce pain in the short term. Mild adverse events were mainly experienced during acupuncture/dry needling treatment. Clinicians should opt for the best intervention balancing benefits and harms according to patients' preferences.

Footnotes: [a]EndNote, Version EndNote X9, Clarivate, Philadelphia, USA.

[b]Stata Statistical Software, v 15. StataCorp LLC, College Station, USA.

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