

Does the efficacy of neurodynamic treatments depend on the presence and type of criteria used to define neural mechanosensitivity in spinally-referred leg pain? A systematic review and meta-analysis



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Background: It remains unclear whether definite neural mechanosensitivity (NM) is required for neural mobilisations to be beneficial in people with spinally referred leg pain.

Objective: To determine whether the efficacy of neural mobilisations in patients with spinally referred leg pain depends on the presence and type of criteria used to define NM.

Method: PubMed, CINAHL, Cochrane Central Register of Controlled Trials, PEDro and Science Direct were searched from 1980 to March 2020. Randomised controlled trials evaluating the efficacy of neural mobilisations on pain and disability in spinally referred leg pain were included. Studies were grouped according to the certainty of NM into NM_{definite}, NM_{unclear}, NM_{untested} and NM_{absent}. Effects on pain and disability and subgroup differences were examined.

Results: We identified 21 studies in 914 patients (3 NM_{definite}, 16 NM_{unclear}, 2 NM_{untested}, 0 NM_{absent}). Meta-analysis revealed medium to large effect sizes on pain for neurodynamic compared to control interventions in NM_{definite} and NM_{unclear} groups. For disability, neurodynamic interventions had medium to large effects in NM_{unclear} but not NM_{definite} groups. NM_{untested} studies could not be pooled.

Conclusion: The nonexistence of studies in patients with negative neurodynamic tests prevents inferences whether neural mobilisations are effective in the absence of NM. The criteria used to define NM may not impact substantially on the efficacy of neural mobilisations. The mostly high risk of bias and heterogeneity prevents firm conclusions.

Clinical implications: Neural mobilisations seem beneficial to reduce pain and disability in spinally referred leg pain independent of the criteria used to interpret neurodynamic tests.

Keywords: spinally referred leg pain; sciatica; neurodynamics; neural mobilisation; straight leg raise; slump; nerve-related pain.

Introduction

Spinally referred leg pain is a common variation of lower back pain with a prevalence of up to 43% (Konstantinou & Dunn 2008). Recent systematic reviews have demonstrated that neural mobilisations are effective in reducing the pain and disability for people with spinally referred leg pain (Basson et al. 2017; Neto et al. 2017). Neural mobilisations use active and passive movements designed to facilitate movement or tensioning of neural tissue in relation to their surrounding structures (the interface). In early publications, neural mobilisations were recommended to specifically address patient presentations involving neural mechanosensitivity (NM) (Elvey 1979, 1997). Neural mechanosensitivity is clinically identified through heightened sensitivity of peripheral nerve trunks to pressure or tension (Butler 2000). Neurodynamic tests such as the straight leg raise (SLR) and slump test have been developed to elongate the nerve bed, consequently increasing strain on neural structures (Butler 2000). Currently recommended criteria for a positive neurodynamic test and thus heightened NM include at least partial reproduction of patients' symptoms plus their modification with structural differentiation using movement at a site remote to the painful area to further load or unload the nervous system (Nee et al. 2012).

Despite these early recommendations, it remains unclear whether neural mobilisations are indeed only beneficial for patients with confirmed NM or also for patients with spinally referred

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Note: Additional supporting information may be found in the online version of this article as Online Appendix 1 and Online Appendix 2.

pain without clear signs of NM. Undeniably, spinally referred leg pain comprises a heterogeneous group of patients (Schmid & Tamin 2018), including those with NM, but also those with predominant somatic referred pain, radicular pain or radiculopathy. The absence of a diagnostic gold standard and agreed-upon taxonomy means that inconsistent diagnostic and eligibility criteria are used in studies (Lin et al. 1994). Whereas tests for NM are often used to include patients in trials of conservative care for spinally referred leg pain, other selection criteria such as pain distribution, neurological testing and imaging are also common (Lin et al. 2014). This divergence of diagnostic criteria is likely to result in the inclusion of distinct patient populations under the same terminology of spinally referred leg pain. Preclinical literature suggests that neurodynamic treatment may have beneficial effects beyond reducing NM, including increased nerve regeneration, increased muscle strength or decreased neuroinflammation (Da Silva et al. 2015; Giardini et al. 2017; Santos et al. 2014). Knowing whether neural mobilisations are only beneficial in patients with NM or also in those without NM would help clinicians guide their management. The objective of our systematic review was therefore to determine the extent to which the criteria used to define mechanosensitivity, influence the treatment outcomes of neural mobilisation interventions on pain and disability in patients with spinally referred leg pain.

Methods

Our review is reported according to the updated guidance for the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (Page et al. 2021). The protocol of the study was not prospectively registered, but can be downloaded from <https://doi.org/10.5287/bodleian:dm74JX0Bm>.

Literature search

We built our search on a systematic review previously published by Basson et al. (2017) and included the randomised controlled trials evaluating the efficacy of neural mobilisations in populations with spinally referred leg pain identified in that review (search performed in January 2016). We also performed a new search from 01 January 2016 to 26 March 2020 to identify newly published randomised controlled trials of neural mobilisation in this patient population. The databases searched were PubMed (Medline), CINAHL, Cochrane Central Register of Controlled Trials, PEDro and Science Direct. The main search terms related to randomised controlled trials, spinally referred leg pain and neural mobilisation (see Online Appendix 1 for details of the searches). Electronic searches were supplemented by hand-searching of reference lists of relevant articles and previous systematic reviews. The search was limited to studies written in English and those which included human participants.

Selection process and eligibility criteria

Study selection of the new search was completed by a single reviewer in two stages. Firstly, study titles and abstracts were

screened for eligibility. Secondly, the full paper was obtained of those papers passing the title and abstract screen, and a comprehensive assessment for eligibility was performed. The following eligibility criteria were used: randomised controlled trials, published in English, which evaluated the effect of neural mobilisation in participants with spinally referred leg pain over the age of 18 compared to a control intervention which did not include neural mobilisation (e.g., sham neural mobilisation, other intervention or no intervention). Neural mobilisation could be achieved through exercises or manual techniques aimed at the mobilisation of neural tissue or the neural interface. Studies had to report outcome measures related to pain severity (e.g., numerical pain rating scale or visual analogue scale [VAS]) and/or disability (e.g., Oswestry Disability Index [ODI]). Case reports, case-control and cohort studies as well as studies on animals or healthy participants were excluded.

Risk of bias assessment

Papers which met the inclusion criteria were assessed for risk of bias by two independent reviewers (T.M., T.A.) using the Cochrane risk-of-bias tool (Higgins et al. 2011). Agreement rates are reported, and discrepancies were resolved through discussion with a third reviewer (A.B.).

Data extraction

Data were extracted by a single reviewer (T.M.) from eligible studies and double-checked by a second investigator (A.S.). For all studies, we extracted data on the number of patients in each group, patient demographics, type of neural mobilisation and control interventions, timing of assessment, type of outcome measures and results (e.g., mean and standard deviations). In the case of unclear study information, authors were contacted to obtain the required information.

In addition, we extracted the criteria used to define the patient population and in particular whether studies included patients with established NM or not. Studies were grouped according to the certainty of the presence of NM as follows. The NM_{definite} subgroup consisted of studies which used tests for NM as an essential inclusion criterion and adhered to recommended principles of (1) at least a partial symptom reproduction plus (2) modulation of symptoms upon structural differentiation (sensitising movements at a site distant to the symptoms) (Nee et al. 2012). The NM_{unclear} subgroup consisted of studies which used tests for NM as an essential inclusion criterion but did either not specify which principles were used to deem a test positive or the principles used did not conform with current recommendations (e.g., range of motion deficit upon SLR, symptom reproduction without mention of structural differentiation). The NM_{untested} subgroup consisted of studies which did not include tests for NM as part of their inclusion criteria. If studies performed neurodynamic tests as part of their inclusion criteria, but only included patients with negative neurodynamic tests, these studies were allocated to the NM_{absent} subgroup.

Data synthesis and meta-analysis

Data are reported separately for studies that included patients in the NM_{definite}, NM_{unclear}, NM_{untested} and NM_{absent} subgroups. Where more than two studies reported the same outcome measures, data from the final follow-up time point were pooled in a statistical meta-analysis and presented as forest plots using the computer software Cochrane Review Manager (The Cochrane Collaboration 2020). Means, standard deviations and sample sizes from studies reporting continuous data were used to calculate standardised mean differences (SMD) and 95% confidence intervals (CI). Separate random effects models and inverse variance weighting methods were used to compare effects on pain and disability between neural mobilisation and control groups. Subgroup differences were compared using Chi-square tests for heterogeneity (Cochran's Q test). Heterogeneity was defined with I² statistics and interpreted as 'might not be important' (0%–40%), 'moderate' (30%–60%), 'substantial' (50%–90%), and 'considerable' (75%–100%) (Higgins et al. 2011).

Ethical considerations

Our review followed all ethical standards for research without direct contact with human or animal subjects.

Results

Study selection

Our previous search from January 1980 to January 2016 identified 13 studies to be included (Basson et al. 2017). The new search from 2016 onwards identified a total of 291 studies, of which eight were deemed eligible. This resulted in a total of 21 studies included in our systematic review (Figure 1).

Quality assessment

Risk-of-bias assessment revealed that 18 out of 21 studies were classified as high risk of bias (Figure 2). In addition to the lack of blinding of participants and personnel (52.4% of studies), blinding of outcome assessment (19%) and incomplete outcome data (33.3%) were the most frequently identified high-risk biases. Investigator agreement for the Cochrane risk-of-bias tool was 86.4%.

Characteristics of included studies

Characteristics of the 21 studies are summarised in Online Appendix 2, Table-A2, which also displays to which mechanosensitivity subgroup each study belongs. In total, $n = 914$ participants were included. The smallest sample size was $n = 22$ (Lee & Kim 2017) and the largest $n = 108$ (Dwornik et al. 2009).

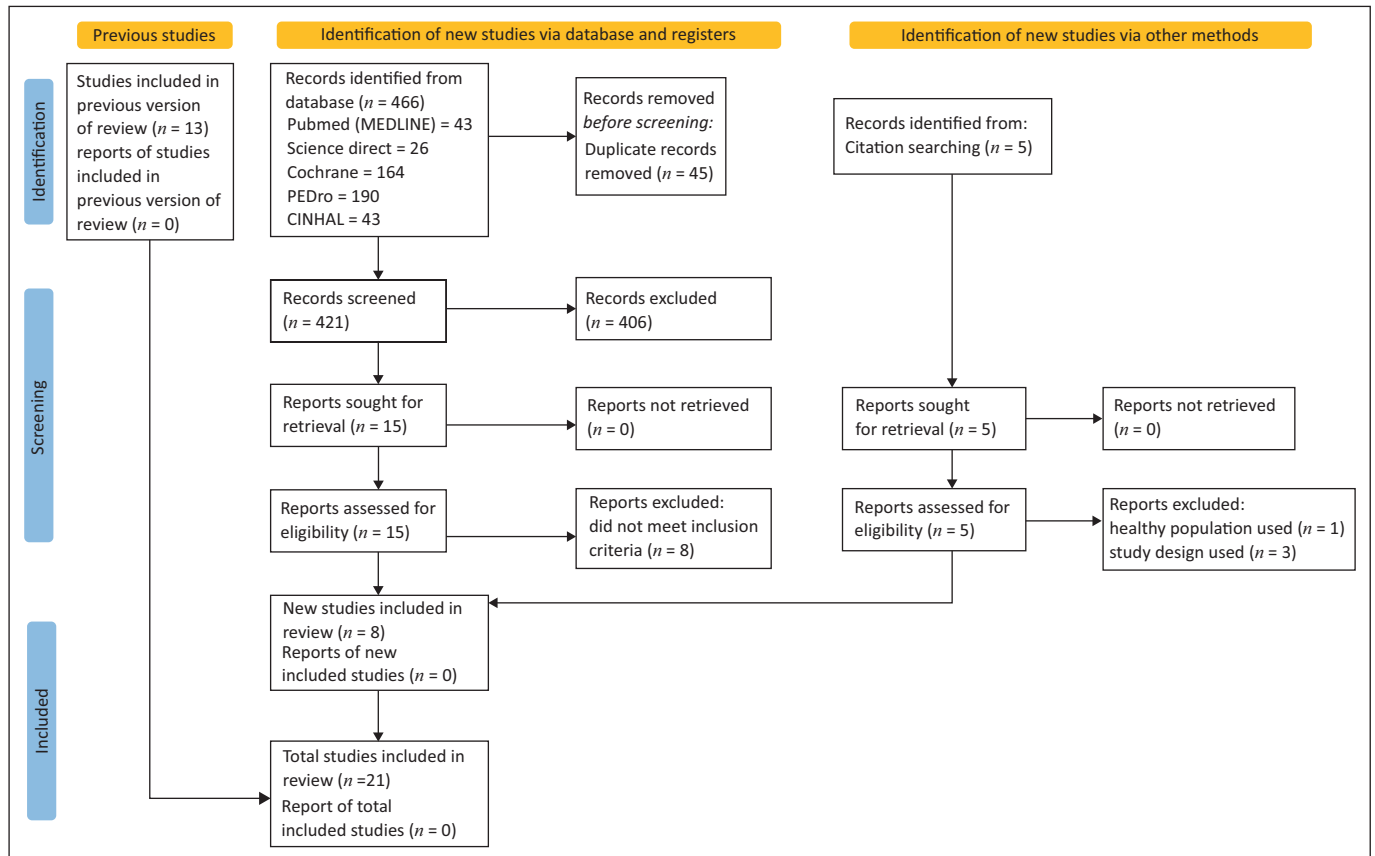
All studies monitored pain and/or disability either as primary or secondary outcome measures. The VAS and numeric pain rating scale (NPRS) were the most commonly used outcome measures to monitor pain. To quantify disability, most studies used a version of the Oswestry Disability Index (MODI or ODI).

The type of neural mobilisation technique and dosage varied amongst groups. The techniques used included slump (Ali et al. 2015; Cleland et al. 2006; Jain et al. 2012; Jeong et al. 2016; Karthikeyan, Jothikaran & Kiran 2014; Kirthika et al. 2016; Malik, Kataria & Sachdev 2012; Nagrale et al. 2012; Patel 2014; Rezk-Allah, Shehata & Gharib 2011; Tambekar et al. 2015; Waleed 2015), SLR (Adel 2011; Ahmed et al. 2013; Kaur & Sharma 2011; Malik et al. 2012; Rezk-Allah et al. 2011; Waleed 2015), bent leg raise mobilisation (Dwornik et al. 2009; Patel 2014; Tambekar et al. 2015) and neural mobilisations in side lying (Colakovic & Avdic 2013; Ferreira et al. 2016; Lee & Kim 2017). One study reported a neural slider technique of the sciatic nerve involving the hip, knee and foot (Plaza-Manzano et al. 2020). Another study did not describe their neural mobilisation intervention (Sharma & Sheth 2017). More detailed information on the techniques and dosages used can be found in Online Appendix 2, Table 1-A2.

The neural mobilisation interventions were a standalone treatment in six studies (Dwornik et al. 2009; Kaur & Sharma 2011; Lee & Kim 2017; Patel 2014; Tambekar et al. 2015; Waleed 2015) and were combined with exercise programmes in 15 studies (Adel 2011; Ahmed et al. 2013; Ali et al. 2015; Cleland et al. 2006; Colakovic & Avdic 2013; Ferreira et al. 2016; Jain et al. 2012; Jeong et al. 2016; Karthikeyan et al. 2014; Kirthika et al. 2016; Malik et al. 2012; Nagrale et al. 2012; Plaza-Manzano et al. 2020; Rezk-Allah et al. 2011; Sharma & Sheth 2017). The control groups were diverse, including lumbar stabilisation, lumbar mobility exercises, hamstring stretching, advice, physical modalities or a combination treatment.

Mechanosensitivity subgroups

Three studies (Ferreira et al. 2016; Kaur & Sharma 2011; Sharma & Sheth 2017) were categorised to the NM_{definite} subgroup. Sixteen studies (Adel 2011; Ahmed et al. 2013; Ali et al. 2015; Cleland et al. 2006; Colakovic & Avdic 2013; Dwornik et al. 2009; Jain et al. 2012; Jeong et al. 2016; Karthikeyan et al. 2014; Kirthika et al. 2016; Lee & Kim 2017; Malik et al. 2012; Nagrale et al. 2012; Patel 2014; Plaza-Manzano et al. 2020; Tambekar et al. 2015) were attributed to the NM_{unclear} subgroup. Of those, eight studies (Ahmed et al. 2013; Colakovic & Avdic 2013; Jeong et al. 2016; Karthikeyan et al. 2014; Malik et al. 2012; Patel 2014; Plaza-Manzano et al. 2020; Tambekar et al. 2015) used pain provocation within a certain range of motion (15–75 degrees hip flexion) as a criterion for NM. Three studies (Adel 2011; Cleland et al. 2006; Nagrale et al. 2012) used pain provocation as a criterion without reporting whether structural differentiation was applied. One study (Jain et al. 2012) used either symptom reproduction during slump testing or symptom decrease during cervical extension. Three studies (Dwornik et al. 2009; Kirthika et al. 2016; Lee & Kim 2017) did not specify the criteria used during neurodynamic testing. Two studies (Rezk-Allah et al. 2011; Waleed 2015) were attributed to the NM_{untested} subgroup. Their inclusion criteria did not evaluate NM, but instead used abnormal electromyography and prolonged latency of H-reflex >30 ms (no further specification of which nerve or test criteria) (Rezk-Allah et al. 2011) magnetic resonance imaging



CINHAL, Cumulative Index to Nursing and Allied Health Literature; PEDro, Physiotherapy Evidence Database; MEDLINE, Medical Literature Analysis and Retrieval System Online.

FIGURE 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart of study selection.

confirming lumbar disc herniation at L5-S1 disc level (Waleed 2015). No study was identified for the NM_{absent} subgroup.

NM_{definite} subgroup

Participants from three studies were identified as NM^{definite} (total sample size = 111) (Ferreira et al. 2016; Kaur & Sharma 2011; Sharma & Sheth 2017). Ferreira et al. (2016) investigated a nerve slider technique with advice to remain active compared to a control group which only received advice to remain active. At the 2-week follow-up, no significant between-group difference was present, whilst the neural mobilisation group had significantly improved leg pain compared to the control group at the 4-week follow-up. Disability did not differ significantly between groups at any time point. Kaur and Sharma (2011) investigated neural mobilisation using passive SLR mobilisation in comparison to an exercise programme consisting of back mobilisation exercises (e.g., pelvic tilting, prone back extension). The results showed a greater improvement in pain and reduction in disability in the neural mobilisation group than in the exercise group at 10 days follow-up. Sharma and Sheth (2017) used a remote or local slider and tensioner neural mobilisation technique which was adjusted based on the location of symptoms and compared it to 'conventional' treatment consisting of hot packs, stabilisation and core exercises. Following a 7-day period, there was a significant between-group difference favouring neural mobilisation for disability and pain during activity. Pain at rest was not different between groups.

Meta-analysis for pain (NM_{definite}): All three studies could be included in the meta-analysis for pain (VAS) in the NM_{definite} subgroup (total sample size = 105) (Ferreira et al. 2016; Kaur & Sharma 2011; Sharma & Sheth 2017). Pooling showed a significant effect favouring neural mobilisation over control interventions (standardised mean difference [SMD] -0.90 [95% CI -1.30– -0.49], $p < 0.0001$, Figure 3). Heterogeneity was considered not important ($I^2 = 0\%$).

Meta-analysis for disability (NM_{definite}): Two studies were included in the meta-analysis for disability (MODI) in the NM_{definite} subgroup (total sample size = 78) (Ferreira et al. 2016; Sharma & Sheth 2017). Pooling did not identify between-group differences (SMD -0.30 [95% CI -0.75–0.15], $p = 0.19$, Figure 4). Heterogeneity between studies was considered not important ($I^2 = 0\%$)

NM_{unclear} subgroup

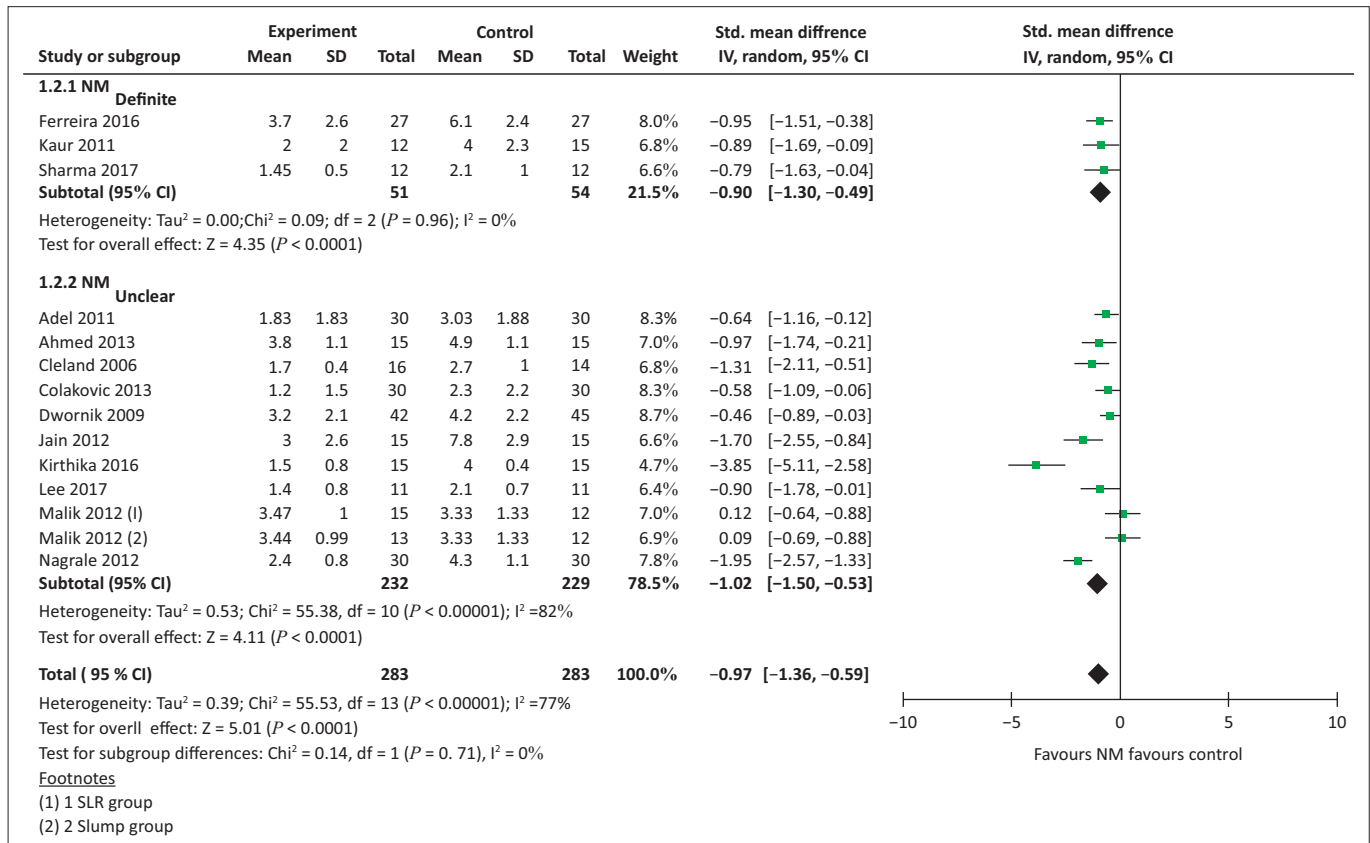
In 16 studies, the presence of NM remained unclear (total sample size = 693) (Adel 2011; Ahmed et al. 2013; Ali et al. 2015; Cleland et al. 2006; Colakovic & Avdic 2013; Dwornik et al. 2009; Jain et al. 2012; Jeong et al. 2016; Karthikeyan et al. 2014; Kirthika et al. 2016; Lee & Kim 2017; Malik et al. 2012; Nagrale et al. 2012; Patel 2014; Plaza-Manzano et al. 2020; Tambekar et al. 2015). Of these, seven studies (Ali et al. 2015; Cleland et al. 2006; Dwornik et al. 2009; Jain et al. 2012; Jeong et al. 2016; Kirthika et al. 2016; Nagrale et al. 2012) provided

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias	Overall risk of bias
Adel 2011	?	?	—	?	+	+	+	high
Ahmed 2013	+	+	—	—	+	+	+	high
Ali 2015	+	—	—	?	+	+	+	high
Cleland 2006	+	+	—	+	+	+	+	high
Colakovic 2013	+	?	?	?	+	+	+	some concerns
Dwornik 2009	+	—	—	?	?	+	+	high
Ferreira 2016	+	+	—	—	+	+	+	high
Jain 2012	+	?	—	?	—	+	—	high
Jeong 2016	+	?	?	—	—	+	+	high
Karthikeyan 2014	?	—	?	?	—	+	+	high
Kaur 2011	+	?	?	?	?	+	+	high
Kirthika 2016	+	?	?	?	+	+	+	some concerns
Lee 2017	+	?	?	?	—	+	+	high
Malik 2012	+	+	—	?	—	?	+	high
Nagrle 2012	+	+	—	+	+	+	+	high
Patel 2014	+	?	—	?	?	+	+	high
Plaza-Manzano 2019	+	+	?	—	—	+	+	high
Rezk-Allah 2011	+	—	—	?	?	+	+	high
Sharma 2017	+	+	+	+	+	+	+	low
Tambekar 2015	+	?	?	+	—	+	+	high
Waleed Salah El-din 2015	+	—	—	—	+	—	+	high

FIGURE 2: Risk of bias of included studies.

neural mobilisation in a slump position and reported greater improvements in pain and disability for neural mobilisation compared to control interventions. Of the remaining studies, Ahmed et al. (2013) compared an SLR neural mobilisation plus conventional physiotherapy (spinal flexion or extension exercises and transcutaneous electrical nerve stimulation) to conventional physiotherapy alone. The findings revealed a significant between-group difference for pain and disability favouring the SLR neural mobilisation plus conventional physiotherapy group. Colakovic and Avdic (2013) compared lumbar stabilisation exercises plus oscillating neural mobilisation in side-lying to lumbar stabilisation exercises and active range of movement exercises for back and distal extremities. The findings revealed a significant between-group difference for pain and SLR range of motion favouring neural mobilisation. Lee and Kim (2017) compared a neural slider technique and physiotherapy (including superficial thermal treatment and interference wave) to hamstring stretching and physiotherapy. Pain alleviation was more pronounced with neural mobilisation. Plaza-Manzano et al.

(2020) compared neural slider techniques and motor control exercises (consisting of bridging and four-point kneeling) to motor control exercises alone. There was no significant between-group difference for pain and disability. Tambekar et al. (2015) compared two neural mobilisation techniques, Mulligan's bent leg raise to Butler's neural tissue mobilisation. Both reduced the pain immediately post-treatment, but this was not sustained at the 24-h follow-up and no between-group differences were apparent. Patel (2014) compared slump stretch to Mulligan's bent leg raise and reported no significant between-group differences for pain. Adel (2011) compared a SLR stretch plus lumbar stabilisation exercises and a standardised exercise programme to lumbar stabilisation exercises and standardised exercise programme (Adel 2011). The findings revealed a significant between-group difference post intervention for pain and disability favouring the SLR stretch. Malik et al. (2012) compared lumbar stabilisation alone to SLR mobilisation plus lumbar stabilisation exercises alongside slump neural mobilisation plus lumbar



SD, standard deviation; CI, confidence interval; NM, neural mechanosensitivity; df, degrees of freedom; SLR, straight leg raise.

FIGURE 3: Meta-analysis for pain in people with spinally referred leg pain.

stabilisation exercises. The findings revealed that SLR and slump mobilisations are equally effective in reducing pain. Karthikeyan et al. (2014) compared joint mobilisation plus static spinal exercise to slump mobilisation. The study concluded both interventions to be beneficial for pain and disability but no significant between-group differences were reported.

Meta-analysis for pain (NM_{unclear}): Ten studies (Adel 2011; Ahmed et al. 2013; Cleland et al. 2006; Colakovic & Avdic 2013; Dwornik et al. 2009; Jain et al. 2012; Kirthika et al. 2016; Lee & Kim 2017; Malik et al. 2012; Nagrle et al. 2012) were included in the meta-analysis for pain in the NM_{unclear} subgroup (total sample size = 461). As Malik et al. (2012) compared both a SLR and slump mobilisation group to control intervention, these data are reported separately. Pooling showed a significant effect favouring neural mobilisation compared to control interventions consisting of either exercise or lumbar mobilisation and exercises (SMD -1.02 [95% CI -1.50–-0.53], $p < 0.0001$, Figure 3). Heterogeneity was substantial to considerable ($I^2 = 82\%$).

Meta-analysis for disability (NM_{unclear}): Six studies (Adel 2011; Cleland et al. 2006; Jain et al. 2012; Kirthika et al. 2016; Lee & Kim 2017; Nagrle et al. 2012) were included in the meta-analysis for disability in the NM_{unclear} subgroup (total sample size = 232). Pooling revealed a significant difference favouring neural mobilisation over control interventions consisting of lumbar stabilisation (Jain et al. 2012; Nagrle et al. 2012),

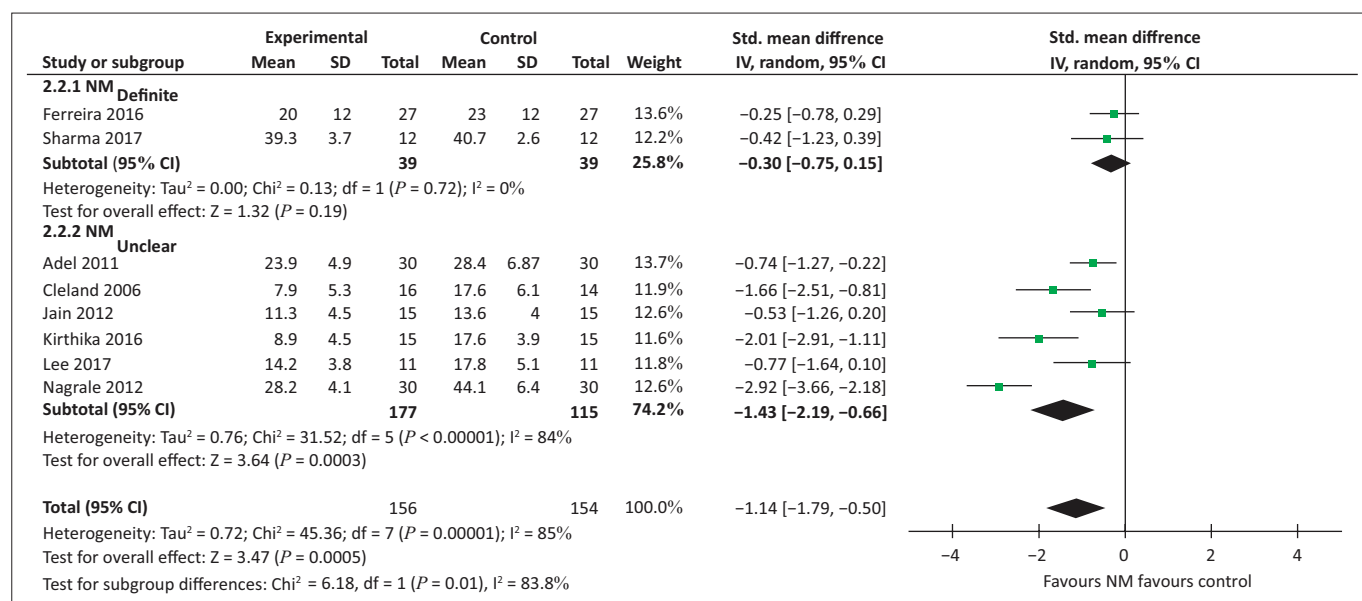
standardised exercise programme (including squats, pelvic tilts and bridging) (Cleland et al. 2006; Kaur & Sharma 2011; Kirthika et al. 2016) and hamstring stretching (Lee & Kim 2017) (SMD -1.43 [95% CI -2.19–-0.66], $p = 0.0003$, Figure 4). Heterogeneity was substantial to considerable ($I^2 = 84\%$).

NM_{untested} subgroup

In two studies, the presence of neural mechanosensitivity remained untested (Rezk-Allah et al. 2011; Waleed 2015). A meta-analysis could not be performed because the authors compared two different neural mobilisation exercises without including a non-neural mobilisation control group. Rezk-Allah et al. (2011) applied a slump mobilisation in comparison to a SLR mobilisation; a significant reduction in pain in both groups was reported with no significant between-group differences. Waleed (2015) applied slump mobilisation plus SLR in comparison to lumbar manipulation plus rotation with SLR. A more pronounced decrease of pain and disability was reported in the group which received the lumbar manipulation.

Subgroup comparison

Tests for subgroup differences (NM_{definite} vs. NM_{unclear}) revealed comparable benefits on pain independent of the criteria used to define NM ($\chi^2 = 0.14$, $p = 0.71$, $I^2 = 0\%$). For disability, effects were larger for the NM_{unclear} than the NM_{definite} subgroup; however, heterogeneity was substantial to considerable ($\chi^2 = 6.18$, $p = 0.01$, $I^2 = 83.8\%$).



SD, standard deviation; CI, confidence interval; NM, neural mechanosensitivity; df, degrees of freedom.

FIGURE 4: Meta-analysis for disability in people with spinally referred leg pain.

Discussion

Our review identified 21 studies evaluating neural mobilisation interventions in $n = 914$ people with spinally referred leg pain. No study included patients with negative neurodynamic tests in their study population, which prevents any inferences on whether neural mobilisations are effective even in the absence of NM. Only three studies described the criteria used to define a neurodynamic test as positive in sufficient detail such that their patients could be classified as displaying definite NM. Two studies did not use neurodynamic tests as an inclusion criterion, and in 16 studies, it remained unclear whether patients had definite NM because of either insufficient information provided or criteria that did not allow firm conclusions. The meta-analysis suggested medium to large effect sizes of neural mobilisation interventions compared to control treatment on measures of pain, irrespective of the criteria used to determine nerve mechanosensitivity. For disability, meta-analysis demonstrated medium to large effects of neural mobilisation compared to control treatments for patients with NM_{unclear} but not NM_{definite}. The mostly high risk of bias of included studies, small numbers of studies in the NM_{definite} subgroup and high heterogeneity of studies in the NM_{unclear} subgroup limit firm conclusions. Nevertheless, our findings currently do not support the view that the criteria used to define NM of the lower extremity may impact substantially on the clinical efficacy of neural mobilisations.

Our review clearly highlights the challenges associated with the lack of a diagnostic reference standard for spinally referred leg pain. Similar to previous reports, a wide range of inclusion criteria and their combination were used amongst studies (e.g., symptom localisation, magnetic resonance imaging findings, NM) (Lin et al. 2014). Most studies identified in our review (19 out of 21) included mechanosensitivity testing as part of their inclusion criteria.

However, only three (Ferreira et al. 2016; Kaur & Sharma 2011; Sharma & Sheth 2017) adhered to the recommended criteria to determine the outcome of nerve mechanosensitivity tests (partial symptom reproduction plus structural differentiation) (Nee et al. 2012). These recommendations were originally based on data from upper limb neurodynamic tests rather than SLR or slump, which were used in our studies. Nevertheless, structural differentiation and confirmatory manoeuvres have been part of the early publications of the Lasègue sign (Forst 1969) as well as slump test (Maitland 1985). The face validity of structural differentiation is strongly backed up in the upper extremity with biomechanical (Coppieters & Butler 2008; Coppieters, Hough & Dilley 2009) as well as experimental pain studies (Coppieters, Alshami & Hodges 2006). In the lower extremity, most studies similarly show altered peripheral nerve movement during neurodynamic testing, including differentiation at distant sites (Sierra-Silvestre et al. 2018) whilst one study did not (Ellis et al. 2017).

Nevertheless, and as highlighted in our review, different authors used a wide range of criteria for lower limb neurodynamic tests, including symptom provocation (Ali et al. 2015; Cleland et al. 2006; Nagrle et al. 2012) and range of motion (Jeong et al. 2016; Patel 2014; Plaza-Manzano et al. 2020; Tambekar et al. 2015). Unfamiliar symptoms are provoked during a SLR even in the healthy population (mean 39.6 ± 13.7 degrees hip flexion) and can be altered with sensitising movements (Boyd et al. 2009). Hence, reliance on range-of-motion cut-offs in isolation to interpret neurodynamic tests would require lower hip angles than used in the included studies, e.g., <45 degrees (Colakovic & Avdic 2013), $30\text{--}70$ degrees (Jeong et al. 2016), $35\text{--}70$ degrees (Tambekar et al. 2015) or $40\text{--}70$ degrees (Plaza-Manzano et al. 2020). Overall, our findings do not support the view that the criteria used to determine the outcome of neurodynamic tests

have a major impact on the efficacy of neurodynamic interventions for people with spinally referred leg pain. Indeed, our meta-analyses confirmed that outcomes for pain improved comparably in both NM_{definite} and NM_{unclear} subgroups. For disability, neural mobilisation interventions were superior to control interventions in the NM_{unclear} but not the NM_{definite} subgroup. The subgroup comparison indicated that the NM_{unclear} group may outperform the NM_{definite} subgroup. Whereas these findings are intriguing, they must be interpreted in the light of high risk of bias, the small number of studies and participants included in the NM_{definite} subgroup and considerable heterogeneity.

Our findings suggest that neural mobilisation interventions are mostly performed in patients where neurodynamic tests are thought to be positive (independent of criteria used). We only identified two studies in which neurodynamic tests were not used to define the study sample (Rezk-Allah et al. 2011; Waleed 2015). Unfortunately, both studies did not include a non-neural mobilisation control group, thereby preventing conclusions on the efficacy of neural mobilisations on patients with untested NM. However, even in a study population defined by neurological loss of function (electromyography, H-reflex) (Rezk-Allah et al. 2011), the neural mobilisation groups improved from baseline, suggesting that neurodynamic treatments are unlikely to make patients worse.

Neurodynamic tests can be negative in patients with clear nerve injury (Baselgia et al. 2017). Indeed, about a third of patients with 'sciatica' have negative SLR (Konstantinou et al. 2015; Mathieson et al. 2017). Despite this relatively large subgroup, we did not identify a single study that performed neural mobilisation interventions in patients with negative neurodynamic tests. Preclinical studies suggest that neurodynamic treatments may not only decrease neuropathic pain behaviour (Santos et al. 2012; Zhu et al. 2018), but also improve regeneration and remyelination (Da Silva et al. 2015; Martins et al. 2011), modulate biomarkers of inflammation (Giardini et al. 2017; Martins et al. 2011; Santos et al. 2012; Zhu et al. 2018) and opioid pathways (Martins et al. 2012; Santos et al. 2014). As such, preclinical benefits of neurodynamic interventions extend well beyond improving NM. Future studies will have to determine whether neurodynamic interventions are also beneficial in patients with nerve injury but without heightened nerve mechanosensitivity.

Limitations

Whereas the study selection in the original search was undertaken by two investigators, the new search and article selection were performed by a single investigator. Most studies showed high risk of bias in one or more domains. In addition, most studies included relatively small sample sizes (range $n = 11$ to $n = 56$ in each group) and short duration of follow-up (maximum 2 months). The overall number of included studies was small, particularly in the NM_{definite} subgroup, and high heterogeneity was present, particularly

in the NM_{unclear} group. This heterogeneity may, amongst other causes, be attributed to the varying neural mobilisation techniques and dosages used in different studies. Furthermore, the limited or unclear reporting of the criteria used to interpret the outcome of neurodynamic tests challenged a clear allocation of several studies in our systematic review. Of the 16 studies allocated to the NM_{unclear} subgroup, three did not specify the criteria used during neurodynamic testing (Dwornik et al. 2009; Kirthika et al. 2016; Lee & Kim 2017). Thus, some studies may have been wrongly attributed to the NM_{unclear} group. It is however unlikely that this has influenced our conclusions, because we found efficacy of neural mobilisation interventions independent of test criteria. Our findings might have additionally been influenced by other variations in diagnostic criteria used for spinally referred leg pain (e.g., use of neurological examination, MRI; see Online Appendix 1, Table 1). Critically, our findings highlight the importance of more careful reporting of criteria used for neurodynamic testing in future studies and the need for uniformly accepted criteria for neurodynamic testing and spinally related leg pain.

Conclusion

Our review was unable to answer the question whether neural mobilisations are effective in patients with spinally referred leg pain and negative neurodynamic tests. However, we have shown a benefit of neural mobilisation for pain and disability in patients with NM independent of the criteria used during neurodynamic testing. Whereas firm conclusions are prevented by high risk of bias, small sample sizes and high heterogeneity across studies, our results currently do not support the view that the type of criteria used to define NM may majorly impact on the efficacy of neural mobilisation interventions.

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Competing interests

The authors declare that there is no conflict of interest.

Authors' contributions

All authors were involved in the conceptualisation of the review. T.A. and A.B.S. were in charge of overall direction and planning. T.M. and T.A. were responsible for data analyses. A.B. acted as third reviewer. T.M. and A.B.S. wrote the manuscript with contributions by T.A. and A.B.

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Data availability

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

Disclaimer

The views expressed are those of the authors and not necessarily those of the National Health Service, the NIHR or the Department of Health.

References

- Adel, S.M., 2011, 'Efficacy of neural mobilization in treatment of low back dysfunctions', *Journal of American Science* 7(4).
- Ahmed, N., Tufel, S., Khan, M.H. & Khan, P.B., 2013, 'Effectiveness of neural mobilization in the management of Sciatica', *Journal of Musculoskeletal Research* 16(3), 1350012–7. <https://doi.org/10.1142/S0218957713500127>
- Ali, M., Rehman, S.S., Ahmad, S. & Farooq, M.N., 2015, 'Effectiveness of slump neural mobilization technique for the management of chronic radicular low back pain', *Rawal Medical Journal* 40, 41–43.
- Baselgia, L.T., Bennett, D.L., Silbiger, R.M. & Schmid, A.B., 2017, 'Negative neurodynamic tests do not exclude neural dysfunction in patients with entrapment neuropathies', *Archives of Physical Medicine and Rehabilitation* 98(3), 480–486. <https://doi.org/10.1016/j.apmr.2016.06.019>
- Basson, A., Olivier, B., Ellis, R., Coppieters, M., Stewart, A. & Mudzi, W., 2017, 'The effectiveness of neural mobilization for neuromusculoskeletal conditions: A systematic review and meta-analysis', *Journal of Orthopaedic and Sports Physical Therapy* 47(9), 593–615. <https://doi.org/10.2519/jospt.2017.7117>
- Boyd, B.S., Wanek, L., Gray, A.T. & Topp, K.S., 2009, 'Mechanosensitivity of the lower extremity nervous system during straight-leg raise neurodynamic testing in healthy individuals', *Journal of Orthopaedic and Sports Physical Therapy* 39(11), 780–790. <https://doi.org/10.2519/jospt.2009.3002>
- Butler, D., 2000, *The sensitive nervous system*, Noigroup Publications, Adelaide.
- Cleland, J.A., Childs, J.D., Palmer, J.A. & Eberhart, S., 2006, 'Slump stretching in the management of non-radicular low back pain: A pilot clinical trial', *Manual Therapy* 11(4), 279–286. <https://doi.org/10.1016/j.math.2005.07.002>
- Colakovic, H. & Avdic, D., 2013, 'Effects of neural mobilization on pain, straight leg raise test and disability in patients with radicular low back pain', *Journal of Health Sciences* 3(2), 109–112. <https://doi.org/10.17532/jhsci.2013.73>
- Coppieters, M.W., Alshami, A.M. & Hodges, P.W., 2006, 'An experimental pain model to investigate the specificity of the neurodynamic test for the median nerve in the differential diagnosis of hand symptoms', *Archives of Physical Medicine and Rehabilitation* 87(10), 1412–1417. <https://doi.org/10.1016/j.apmr.2006.06.012>
- Coppieters, M.W. & Butler, D.S., 2008, 'Do "sliders" slide and "tensioners" tension? An analysis of neurodynamic techniques and considerations regarding their application', *Manual Therapy* 13(3), 213–221. <https://doi.org/10.1016/j.math.2006.12.008>
- Coppieters, M.W., Hough, A.D. & Dille, A., 2009, 'Different nerve-gliding exercises induce different magnitudes of median nerve longitudinal excursion: An in vivo study using dynamic ultrasound imaging', *Journal of Orthopaedic and Sports Physical Therapy* 39(3), 164–171. <https://doi.org/10.2519/jospt.2009.2913>
- Da Silva, J.T., Dos Santos, F.M., Giardini, A.C., De Oliveira Martins, D., De Oliveira, M.E., Ciena, A.P. et al., 2015, 'Neural mobilization promotes nerve regeneration by nerve growth factor and myelin protein zero increased after sciatic nerve injury', *Growth Factors* 33(1), 8–13. <https://doi.org/10.3109/08977194.2014.953630>
- Dwornik, M., Kujawa, J., Bialoszewski, D., Slupik, A. & Kiezbak, W., 2009, 'Electromyographic and clinical evaluation of the efficacy of neuromobilization in patients with low back pain', *Ortopedia Traumatologia Rehabilitacja* 11, 164–176. <https://doi.org/10.1097/00004356-200908001-00116>
- Ellis, R., Osborne, S., Whitfield, J., Parmar, P. & Hing, W., 2017, 'The effect of spinal position on sciatic nerve excursion during seated neural mobilisation exercises: An in vivo study using ultrasound imaging', *Journal of Manual and Manipulative Therapy* 25(2), 98–105. <https://doi.org/10.1179/2042618615Y0000000020>
- Elvey, R.L., 1979, 'Brachial plexus tension tests and the pathoanatomical origin of arm pain', in D. Dewhurst, E.F. Glasgow, P. Tehan & A.R. Ward, *Aspects of Manipulative Therapy*, pp. 105–110, Lincoln Institute of Health Sciences, Melbourne.
- Elvey, R.L., 1997, 'Physical evaluation of the peripheral nervous system in disorders of pain and dysfunction', *Journal of Hand Therapy* 10(2), 122–129. [https://doi.org/10.1016/S0894-1130\(97\)80066-X](https://doi.org/10.1016/S0894-1130(97)80066-X)
- Ferreira, G., Stieven, F., Araujo, F., Wiebusch, M., Rosa, C., Plentz, R. et al., 2016, 'Neurodynamic treatment did not improve pain and disability at two weeks in patients with chronic nerve-related leg pain: A randomised trial', *Journal of Physiotherapy* 62(4), 197–202. <https://doi.org/10.1016/j.jphys.2016.08.007>
- Forst, J.J., 1969, 'Contribution to the clinical study of Sciatica', *Archives of Neurology* 21(2), 220–221. <https://doi.org/10.1001/archneur.1969.00480140120016>
- Giardini, A.C., Santos, F.M. dos, Da Silva, J.T., De Oliveira, M.E., Martins, D.O. & Chacur, M., 2017, 'Neural mobilization treatment decreases glial cells and brain-derived neurotrophic factor expression in the central nervous system in rats with neuropathic pain induced by CCI in rats', *Pain Research and Management* 2017, 7429761. <https://doi.org/10.1155/2017/7429761>
- Higgins, J.P.T., Altman, D.G., Gotzsche, P.C., Juni, P., Moher, D., Oxman, A.D. et al., 2011, 'The Cochrane collaboration's tool for assessing risk of bias in randomised trials', *BMJ* 343(18), d5928. <https://doi.org/10.1136/bmj.d5928>
- Jain, R., Hameed, U.A., Tuteja, R., Musculoskeletal, M.P.T. & Th, M.P., 2012, 'Effectiveness of slump stretching in comparison to conventional physiotherapy in treatment of subacute non-radicular low back pain', *Indian Journal of Physiotherapy and Occupational Therapy* 6(1), 123–126.
- Jeong, U.C., Kim, C.Y., Park, Y.H., Hwang-Bo, G. & Nam, C.W., 2016, 'The effects of self-mobilization techniques for the sciatic nerves on physical functions and health of low back pain patients with lower limb radiating pain', *Journal of Physical Therapy Science* 28(1), 46–50. <https://doi.org/10.1589/jpts.28.46>
- Karthikeyan, T., Jothikaran, J. & Kiran, P., 2014, 'Effect of slump stretching with static spinal exercise for the management of non radicular low back pain among non active sports persons', *Indian Journal of Physiotherapy and Occupational Therapy – An International Journal* 8(4), 175. <https://doi.org/10.5958/0973-5674.2014.00033.1>
- Kaur, G. & Sharma, S., 2011, 'Effect of passive straight leg raise sciatic nerve mobilization on low back Pain of neurogenic origin', *Indian Journal of Physiotherapy and Occupational Therapy* 5, 179–184.
- Kirthika, V., Rajalaxmi, V., Sudhakar, S., Bhuvaneshwaran, T. & Fousiya Thaslim, K., 2016, 'Effect of combining slump stretching with conventional physiotherapy in the treatment of subacute non-radicular low back pain', *International Journal of Physiotherapy & Occupational Therapy* 2, 9–16.
- Konstantinou, K. & Dunn, K.M., 2008, 'Sciatica: Review of epidemiological studies and prevalence estimates', *Spine* 33(22), 2464–2472. <https://doi.org/10.1097/BRS.0b013e318183a4a2>
- Konstantinou, K., Dunn, K.M., Ogollah, R., Vogel, S. & Hay, E.M., 2015, 'Characteristics of patients with low back and leg pain seeking treatment in primary care: Baseline results from the ATLAS cohort study epidemiology of musculoskeletal disorders', *BMC Musculoskeletal Disorders* 16(1), 332. <https://doi.org/10.1186/s12891-015-0787-8>
- Lee, J.H. & Kim, T.H., 2017, 'The treatment effect of hamstring stretching and nerve mobilization for patients with radicular lower back pain', *Journal of Physical Therapy Science* 29(9), 1578–1582. <https://doi.org/10.1589/jpts.29.1578>
- Lin C.W., Verwoerd A.J., Maher C.G., et al. How is radiating leg pain defined in randomized controlled trials of conservative treatments in primary care? A systematic review. *European Journal of Pain* 18, 455–464.
- Maitland, G.D., 1985, 'The slump test: Examination and treatment', *Australian Journal of Physiotherapy* 31(6), 215–219. [https://doi.org/10.1016/S0004-9514\(14\)60634-6](https://doi.org/10.1016/S0004-9514(14)60634-6)
- Malik, N., Kataria, C. & Sachdev, N.B., 2012, 'Straight leg raise and slump stretching in treatment of low back pain comparative effectiveness of straight leg raise and slump stretching in subjects with low back pain with adverse neural tension', *International Journal of Health and Rehabilitation Sciences* 1(1), 2–10. <https://doi.org/10.5455/ijhrs.000002>
- Martins, D.F., Bobinski, F., Mazzardo-Martins, L., Cidral-Filho, F.J., Nascimento, F.P., Gadotti, V.M. et al., 2012, 'Ankle joint mobilization decreases hypersensitivity by activation of peripheral opioid receptors in a mouse model of postoperative pain', *Pain Medicine* 13(8), 1049–1058. <https://doi.org/10.1111/j.1526-4637.2012.01438.x>
- Martins, D.F., Mazzardo-Martins, L., Gadotti, V.M., Nascimento, F.P., Lima, D.A.N., Speckhann, B. et al., 2011, 'Ankle joint mobilization reduces axonotmesis-induced neuropathic pain and glial activation in the spinal cord and enhances nerve regeneration in rats', *Pain* 152(11), 2653–2661. <https://doi.org/10.1016/j.pain.2011.08.014>
- Mathieson, S., Maher, C., McLachlan, A., Latimer, J., Koes, B., Hancock, M. et al., 2017, 'Trial of Pregabalin for Acute and Chronic Sciatica', *The New England Journal of Medicine* 376(12), 1111–1131. <https://doi.org/10.1056/NEJMoa1614292>
- Nagrale, A.V., Patil, S.P., Gandhi, R.A. & Learman, K., 2012, 'Effect of slump stretching versus lumbar mobilization with exercise in subjects with non-radicular low back pain: A randomized clinical trial', *Journal of Manual and Manipulative Therapy* 20(1), 35–42. <https://doi.org/10.1179/2042618611Y0000000015>
- Nee, R., Jull, G., Vicenzino, B. & Coppieters, M., 2012, 'The validity of upper-limb neurodynamic tests for detecting peripheral neuropathic pain', *Journal of Orthopaedic and Sports Physical Therapy* 42(5), 413–424. <https://doi.org/10.2519/jospt.2012.3988>
- Neto, T., Freitas, S.R., Marques, M., Gomes, L., Andrade, R. & Oliveira, R., 2017, 'Effects of lower body quadrant neural mobilization in healthy and low back pain populations: A systematic review and meta-analysis', *Musculoskeletal Science and Practice* 27, 14–22. <https://doi.org/10.1016/j.msksp.2016.11.014>
- Page, M., McKenzie, J., Bossuyt, P. & Boutron, I., Hoffmann, T.C. & Mulrow, C.D., 2021, 'Updating guidance for reporting systematic reviews: Development of the PRISMA 2020 statement', *Journal of Clinical Epidemiology* 134, 103–112. <https://doi.org/10.1016/j.jclinepi.2021.02.003>
- Patel, G., 2014, 'To compare the effectiveness of Mulligan Bent leg raising and slump stretching in patient with low back pain', *Indian Journal of Physiotherapy and Occupational Therapy – An International Journal* 8(3), 24. <https://doi.org/10.5958/0973-5674.2014.00350.5>
- Plaza-Manzano, G., Cancela-Cilleruelo, I., Fernández-De-Las-Penás, C., Cleland, J.A., Arias-Buriá, J.L., Thoomes-De-Graaf, M. et al., 2020, 'Effects of adding a neurodynamic mobilization to motor control training in patients with lumbar radiculopathy due to disc herniation: A randomized clinical trial', *American Journal of Physical Medicine and Rehabilitation* 99(2), 124–132. <https://doi.org/10.1097/PHM.0000000000001295>

- Rezk-Allah, S.S., Shehata, L.A. & Gharib, N.M., 2011, 'Slump stretching versus straight leg raising in the management of lumbar disc herniation', *The Egyptian Journal of Neurology, Psychiatry and Neurosurgery* 48(4), 345–349.
- Santos, F.M., Grecco, L.H., Pereira, M.G., Oliveira, M.E., Rocha, P.A., Silva, J.T. et al., 2014, 'The neural mobilization technique modulates the expression of endogenous opioids in the periaqueductal gray and improves muscle strength and mobility in rats with neuropathic pain', *Behavioral and Brain Functions* 10(1), 19. <https://doi.org/10.1186/1744-9081-10-19>
- Santos, F.M., Silva, J.T., Giardini, A.C., Rocha, P.A., Achermann, A.P.P., Alves, A.S. et al., 2012, 'Neural mobilization reverses behavioral and cellular changes that characterize neuropathic pain in rats', *Molecular Pain* 8. <https://doi.org/10.1186/1744-8069-8-57>
- Schmid A.B., Tampin, B. Spinally Referred Back and Leg Pain. In: Spine ISftSotL, eds. Lumbar Spine Online Textbook. <http://www.wheelsonline.com/ISSLS/section-10-chapter-10-spinally-referred-back-and-leg-pain/>: 2018:
- Sharma, S. & Sheth, M., 2017, 'Effect of neurodynamic mobilization on pain and function in subjects with lumbo-sacral radiculopathy', *Medicine Science | International Medical Journal* 1–4. <https://doi.org/10.5455/medscience.2017.06.8664>
- Sierra-Silvestre, E., Bosello, F., Fernández-Carnero, J., Hoozemans, M.J.M. & Coppieters, M.W., 2018, 'Femoral nerve excursion with knee and neck movements in supine, sitting and side-lying slump: An in vivo study using ultrasound imaging', *Musculoskeletal Science and Practice* 37, 58–63. <https://doi.org/10.1016/j.msksp.2018.06.007>
- Tambekar, N., Sabnis, S., Phadke, A. & Bedekar, N., 2015, 'Effect of Butler's neural tissue mobilization and Mulligan's bent leg raise on pain and straight leg raise in patients of low back ache', *Journal of Bodywork and Movement Therapies* 20(2), 280–285. <https://doi.org/10.1016/j.jbmt.2015.08.003>
- The Cochrane Collaboration, 2020, *Review Manager (RevMan)* [Computer program].
- Waleed, S.E.-D.M., 2015, 'Effect of neural mobilization versus spinal manipulation in patients with radicular chronic low back pain', *European Journal of Scientific Research* 131, 122–132.
- Zhu, G.C., Tsai, K.L., Chen, Y.W. & Hung, C.H., 2018, 'Neural mobilization attenuates mechanical allodynia and decreases proinflammatory cytokine concentrations in rats with painful diabetic neuropathy', *Physical Therapy* 98(4), 214–222. <https://doi.org/10.1093/ptj/ptx124>