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A systematic review and meta-analysis of pain neuroscience education for chronic low back pain: short- and long-term outcomes of pain and disability.

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Abstract:	<p>Abstract: Background and Objective: Pain neuroscience education (PNE) has shown promising ability in previous reviews to improve pain and disability in chronic low back pain (CLBP). This review aimed to evaluate randomised controlled trials comparing the effectiveness of PNE on pain and disability in CLBP.</p> <p>Databases and Data Treatment: A systematic search was performed using the databases of EBSCO, Medline, Cochrane and Web of Science. Meta-analysis was performed using the RevMan 5.1 software to pool outcomes using the random effects model, weighted mean differences (WMD), standard deviation, 95% confidence intervals and sample size. GRADEpro software was utilised to calculate overall strength of evidence.</p> <p>Results: 6767 papers were found, 8 were included (n=615). Meta-analysis for short-term pain (n=428) demonstrated a WMD of 0.73 (95%CI -0.14; 1.61) on a ten-point scale of PNE against no PNE (GRADE analysis low evidence). When PNE alongside physiotherapy interventions was grouped for pain (n=212), a WMD of 1.32 was demonstrated (95% CI 1.08; 1.56, p<0.00001) (GRADE analysis moderate evidence). Short-term disability (RMDQ) meta-analysis demonstrated a WMD of 0.42 (95%CI 0.28; 0.56) (p<0.00001) (n=362) (GRADE analysis moderate evidence); whereas the addition of PNE to physiotherapy interventions demonstrated a WMD of 3.94 (95% CI 3.37; 4.52) (p<0.00001) (GRADE analysis moderate evidence).</p> <p>Conclusion: This review presents moderate evidence that the addition of PNE to usual physiotherapy intervention in patients with CLBP improves disability in the short-term. However, this meta-analysis failed to show evidence of long-term improvement on pain or disability when adding PNE to usual physiotherapy.</p>
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special interest in this field

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Luis Garcia-Larrea
Editor-in-Chief
European Journal of Pain

Dear Mr Garcia-Larrea,

Many thanks for considering the included manuscript for publication in the European Journal of Pain. The paper is entitled:

“A systematic review and meta-analysis of pain neuroscience education for chronic low back pain: short- and long-term outcomes of pain and disability” by Lianne Wood and Paul Hendrick.

Pain neuroscience education is a novel tool to assist patients with reconceptualising nociplastic or chronic pain. This review demonstrates a moderate level of evidence that the inclusion of pain neuroscience education alongside physiotherapy interventions probably improves pain and disability in the short-term in chronic low back pain.

I hereby certify that this paper consists of original, unpublished work which is not under consideration for publication elsewhere. Both authors read and confirmed that specified above requirements for co-authorship is fulfilled, each author believes that the submitted text is a reliable work of all mentioned authors.

Yours sincerely,

Lianne Wood

Dear reviewers,

Thank you very much for your valuable comments. We have now amended the manuscript to address all the comments from the reviewers in order to improve the clarity and accuracy of the manuscript for the reader.

Please see the below table for how your concerns have been amended, with extracts from the text to support the changes.

	Reviewers Comment	Changes made with page number and quotation
1	Ad 1 and 7) „Traditional" pain education is not teaching only an anatomical and biomedical model, but a biopsychosocial approach including self-management strategies. Please explain how PNE differs from „traditional pain education", e.g, as outlined in (see Syst Rev. 2015 Oct 1;4:132)	Please see pg. 1 for definition of PNE and how it differs. “PNE differs from traditional pain education by aiming to desensitise the neural system by focusing on the neurophysiology, neurobiology, representation of pain and meaning of pain, in place of using a traditional anatomical and biomedical model (e.g. what is broken and how do we fix it) (Louw et al. 2015).” Further it aims to shift one’s concept of pain as a portrayal of harm, to one of pain as a form of an alarm system for protection of bodily tissue (Moseley & Butler 2015). (Geneen et al. 2015) describe education as a means for self-empowerment and self-management (Wong et al., 2017), but until recently, most traditional educational models have focussed on anatomical and biomedical models of pain as a representation of damage (Moseley et al. 2004) or traditional biopsychosocial approaches (Engel 1980).
4	Ad 4) PICO is still not correct: Please specify your comparators (e.g. treatment as usual, waiting list...) and your study population (e.g. all age groups or only adults?)	<p>Many thanks for this comment. The PICO is outlined below</p> <p>P – adults with CLBP</p> <p>I – PNE in isolation and or combined with another conservative therapy</p> <p>C – All comparator interventions were considered provided they did not include PNE. This may have included waitlist controls, physiotherapy, other educational methods or no treatment.</p> <p>O – Pain and disability</p> <p>This statement (within the manuscript) addresses the identified PICO: “The purpose of this systematic review was to evaluate the evidence for the effectiveness of PNE in isolation and in combination therapy in comparison to</p>

		<p>control groups on pain and disability outcomes in a population of non-specific CLBP adult patients.” Pg. 2</p> <ul style="list-style-type: none"> • Type of Comparator: <p>All comparator interventions were considered provided they did not include PNE.</p> <p>This may have included waitlist controls, physiotherapy, other educational methods or no treatment. Added to Pg4.</p>
5	I Ad 5) Please add the lack of a protocol in DISCUSSION as a limitation of the review	<p>This statement has been added to the limitations of the review paragraph to address this comment.</p> <p>The lack of a registered protocol for this review is also recognised as a methodological shortcoming.</p> <p>Pg 18</p>
6	Non-PNE" is not an adequate term (e.g. Abstract; METHODS/Objectives; figures 8-10). Substitute by „controls" in the whole manuscript and please define your control groups precisely in METHODS	<p>Thank you for highlighting this. This term has been replaced with control group(s) wherever possible:</p> <p>-No PNE replaced with control groups page 10, Methods/ Objectives updated (pg 3). Figures 4, 8-10 updated Abstract updated. (background and results)</p>

Abstract:**Background and Objective:**

Pain neuroscience education (PNE) has shown promising ability in previous reviews to improve pain and disability in chronic low back pain (CLBP). This review aimed to evaluate randomised controlled trials comparing the effectiveness of PNE on pain and disability in CLBP.

Databases and Data Treatment: A systematic search was performed using the databases of EBSCO, Medline, Cochrane and Web of Science. Meta-analysis was performed using the RevMan 5.1 software to pool outcomes using the random effects model, weighted mean differences (WMD), standard deviation, 95% confidence intervals and sample size. GRADEpro software was utilised to calculate overall strength of evidence.

Results: 6767 papers were found, 8 were included (n=615). Meta-analysis for short-term pain (n=428) demonstrated a WMD of 0.73 (95%CI -0.14; 1.61) on a ten-point scale of PNE against no PNE (GRADE analysis low evidence). When PNE alongside physiotherapy interventions was grouped for pain (n=212), a WMD of 1.32 was demonstrated (95% CI 1.08; 1.56, p<0.00001) (GRADE analysis moderate evidence). Short-term disability (RMDQ) meta-analysis demonstrated a WMD of 0.42 (95%CI 0.28; 0.56) (p<0.00001) (n=362) (GRADE analysis moderate evidence); whereas the addition of PNE to physiotherapy interventions demonstrated a WMD of 3.94 (95% CI 3.37; 4.52) (p<0.00001) (GRADE analysis moderate evidence).

Conclusion: This review presents moderate evidence that the addition of PNE to usual physiotherapy intervention in patients with CLBP improves disability in the short-term. **However, this meta-analysis failed to show evidence of long-term improvement on pain or disability when adding PNE to usual physiotherapy.**

A systematic review and meta-analysis of pain neuroscience education for chronic low back pain: short- and long-term outcomes of pain and disability.

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Category for submission: Reviews

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Conflicts of interest: There are no conflicts of interest declared

Significance: What's already known about this topic? Pain neuroscience education has shown promise for reducing pain and disability previously for chronic low back pain. However, meta-analysis has not been possible to date.

“What does this study add?” This review demonstrates moderate level evidence that the use of pain neuroscience education alongside physiotherapy interventions probably improves disability and pain in the short-term in chronic low back pain. These results provide greater support for the addition of pain neuroscience education in routine physiotherapy practice in chronic low back pain.

Introduction:

Low back pain (LBP) is one of the most common musculoskeletal conditions worldwide (Hoy et al., 2014), and it is estimated that most people will at some point in their lifetime experience LBP. Recent guidelines for LBP advocate the use of education as a key component of LBP management (National Guideline Centre 2016; Wong et al. 2017). Education typically aims to reduce the risk for further symptoms by enhancing and improving the participant's knowledge to create a change in the participant's behaviour (Linton & van Tulder, 2001; Haines et al., 2009). Strong evidence has demonstrated the effectiveness of individual education in subacute LBP on short-term and long-term return to work in comparison to no intervention. Further, it is as effective as non-educational interventions on long term pain and global improvement in subacute LBP. However, in chronic low back pain (CLBP), the effectiveness of individual education remains unclear (Engers et al. 2011).

In response to a growing body of research, a model of education called pain neuroscience education (PNE) has been developed (Butler & Moseley, 2003; Nijs, et al., 2011a; Nijs et al., 2013; Zimney et al., 2013; Louw, et al., 2015; Moseley & Butler, 2015). PNE originates from educational psychology and aims to reconceptualise pain as “a marker of tissue damage” to being a representation of the threat or need to protect the body from harm (Moseley 2003a; Moseley & Butler 2015). PNE differs from traditional pain education by aiming to desensitise the neural system by focusing on the neurophysiology, neurobiology, representation of pain and meaning of pain, in place of using a traditional anatomical and biomedical model (e.g. what is broken and how do we fix it) (Louw et al. 2015). Further it aims to shift one's concept of pain as a portrayal of harm, to one of pain as a form of alarm system for protection of bodily tissue (Moseley & Butler 2015). Geneen et al. (2015) describe education as a means for self-empowerment and self-management (Wong et al., 2017), but until recently, most traditional educational models have focussed on anatomical and biomedical models of pain as a representation of damage (Moseley et al. 2004) or traditional biopsychosocial approaches (Engel 1980). Recent reviews have reported strong evidence for PNE to change pain intensity, knowledge of pain, disability, psychological function and pain behaviours (meta-analysis was not performed) in patients with musculoskeletal pain (Louw et al., 2011; Louw et al.,

2016), however they highlight that PNE alone was not sufficient to have an impact on reducing pain scores. Clarke et al. (2011), similarly found a statistically but not clinically significant improvement for pain reduction in the short-term (5mm on the 100mm VAS [95% CI 0,10.0]), when PNE was added to a pain management program and a clinically and statistically significant improvement at one –year compared to the control group (27-point difference, 68% improvement). However, Clarke et al. (2011) were unable to pool the disability scores due to lack of homogeneity in outcome measures, but did not report statistically or clinically significant improvements in this outcome. Although Clarke et al. (2011) found promising results to support the use of PNE on pain, physical-, social- and psychological function in CLBP, they highlight that this was very low quality evidence due to a high level of publication bias (both included studies were authored by a prominent author of PNE) and both included studies had small sample sizes (n=122) increasing the risk of inadequate power to demonstrate a significant difference.

Since this review (Clarke et al. 2011) a number of studies on the use of PNE in the management of CLBP have been published (Télez-García et al., 2014; Pires et al., 2015; Wälti et al., 2015) which warrants an updated review. Given the increasing popularity and clinical utility of PNE for CLBP it is imperative to systematically evaluate the evidence for its effectiveness on pain and disability in CLBP.

Study Objectives:

This purpose of this systematic review was to evaluate the evidence for the effectiveness of PNE in isolation and in combination therapy in comparison to the absence of PNE control groups on pain and disability outcomes in non-specific CLBP adult patients. This study also aims to summarize the results of included studies in a meta-analysis (where possible according to heterogeneity) for statistical significance and weighted mean differences of grouped outcomes to be derived.

Methods:

- i) Inclusion and exclusion criteria:
 - Type of Study:

RCTs published in English were searched from 2011(01) to 2017 (12). The search was limited at 2011 given the most recent review on CLBP was performed at this

point (Clarke et al., 2011). Secondary searching from before this time point were sourced from secondary searching of relevant reviews (Clarke et al., 2011; Louw et al., 2011).

- Type of Participants:

Trials involving adult populations (>18 years) were included. All participants were required to have chronic non-specific LBP of at least 3-month duration, with or without leg pain but excluding specific pathology such as spinal stenosis, lumbar instability, post-surgical pain, pregnancy-related low back pain etc. Trials of participants with specific diagnoses of serious pathologies (cauda equina, spinal tumours, spinal fractures, spondyloarthropathies etc.) and patients with widespread chronic pain or systemic pain conditions such as fibromyalgia, chronic fatigue, rheumatoid arthritis, polymyalgia rheumatic were also excluded.

- Type of Intervention:

Pain neuroscience education (PNE) (Nijs et al., 2011), or therapeutic neuroscience education (Louw & Puentedura 2013), or “explain pain” (Moseley & Butler, 2015) was required to be a component of the experimental group ~~in comparison to the absence of PNE~~. The PNE could be delivered in isolation or in combination with other forms of physiotherapy treatment: including exercise, manual therapy, acupuncture or dry needling. Since there is no standardisation for the delivery of PNE, all forms of delivery will be considered: such as group instruction, individual explanation, the use of presentations, books or leaflets to supplement the explanations.

- Type of Comparator:

All control groups were considered provided they did not include PNE. This may have included waitlist controls, physiotherapy, other educational methods or no treatment.

- Type of Outcome:

The outcome measures of pain and disability were included for this review. The principal summary method was mean difference between-groups assessed at short-

term (<12 weeks) and long (>1 year) term follow-up. Adverse events were also captured where mentioned.

ii) Search Strategy

The databases of CINAHL, Medline, Cochrane and Web of Science were searched from 2011 (01) to 2017 (12). The search terms were developed using the PICO format (Population, Intervention, Comparator and Outcome) which is advocated by the York Centre for Reviews and Dissemination team (Centre for Reviews and Dissemination & University of York 2008) and the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement (Liberati et al. 2009). Search terms utilised were: (("low* back" OR lumbar OR sciatic* OR "low back pain" OR "back pain" OR "back ache" OR backache OR spinal OR spine) AND (education OR "pain education" OR "neuroscience education" OR "pain biology education" OR "pain physiology education" OR "neurophysiology education")). Key authors in this field were also contacted to ensure no papers had been missed (G.L. Moseley, J. Nijs, A Louw). Secondary searching of systematic reviews of PNE in musculoskeletal pain occurred to ensure no papers were missed (Louw et al. 2016; Moseley and Butler 2015; Clarke et al. 2011; Louw et al. 2011).

iii) Study Selection

Search results were imported into Refworks for screening. All study titles and abstracts of search results were screened by the lead author for preliminary elimination. Screened titles and abstracts, and full-text studies were then reviewed independently by both authors. Disagreements were resolved with discussion. At this point any articles which did not fulfil the inclusion criteria above were discarded, with reasons documented, and the remaining articles comprised the review and meta-analysis.

iv) Data Collection

Data was collected from included studies by means of a data extraction spreadsheet in Microsoft Excel which included the headings: author, year, setting, population, intervention, comparator, follow-up periods, outcome measures, and numerical values for each reported outcome **measure by the lead author**. This form was piloted in a literature review on the topic before being utilized for this study.

v) Methodological Quality Assessment:

Studies were rated using the Cochrane Risk of Bias tool (Ottawa Methods Centre, Clinical Epidemiology Program 2015) to evaluate the risk of bias in each RCT by the lead author. These results were reviewed independently by the second author (PH) to ensure accuracy and agreement. Guidance to interpretation of the bias levels was scored in accordance with the Cochrane Back Review Group (CBRG), whereby RCT studies with a score greater than 6 out of 12 are considered to have a low risk of bias (Furlan et al., 2009). Liddle, Gracey, & Baxter (2007) further assessed the quality scores into low, medium and high, risk of bias. This review is reported according to the PRISMA statement for reporting systematic reviews that evaluate health care interventions (Liberati et al. 2009).

vi) Unit of analysis issues

Pain scores, where reported on a 0-100 scale were converted to a 0-10 score where necessary for ease of meta-analysis. The NRS has been shown to be highly correlated with the VAS in patients with chronic pain of more than six months ($r=0.86$ to 0.95), with test-retest reliability observed in both literate and illiterate patients ($r=0.96$ and 0.95 respectively) (Hawker et al. 2011). Disability scores were grouped according to outcome measure used, and pooled where 2 or more trials utilized the same score for comparison with minimally clinically important change scores reported in the literature. Disability scores were not grouped across outcome measures due to poor correlation found between scores (Morris et al., 2015). Grouped scores were entered into the Review Manager (RevMan 5.1) software for analysis. Where scores were unable to be grouped, narrative review occurred.

vii) Dealing with missing data

Authors were contacted for unpublished missing data for the purposes of meta-analysis.

viii) Data Analysis

Reported outcomes were pooled where possible for meta-analysis using the RevMan 5.1 software. Statistical pooling of the overall effect (random effects model)

compared to a comparison treatment with a 95% confidence interval was used in accordance with previously reported reviews (Clarke et al. 2011) and the CBRG (Furlan et al. 2009). Results for each of the primary outcome measures (pain and disability) were pooled according to outcome measure utilised. Mean difference for outcomes from baseline outcomes, standard deviation, 95% confidence intervals and total participants, were input into RevMan 5.1, where possible, for meta-analyses. Weighted mean difference was then interpreted in relation to minimal detectable clinical change scores recommended in the literature for pain (NRS), Roland Morris Disability Questionnaire (RMDQ), Oswestry Disability Index (ODI) and Patient specific functional scale (PSFS). The minimal clinically important change for the RMDQ was 2 points or 8-12% (Furlan et al. 2009). The MCID for the ODI has been reported as eight, and the PSFS needs a change of more than two points to be considered clinically significant (Maughan & Lewis 2010). The QBPDS has a minimal detectable change of 20 points or 30% (Smeets et al. 2011), whilst the PDI-DV requires a clinically important change in score to decrease by 8.5 to 9.5 points (Soukup et al. 2001). The recommended minimal detection of clinical change for the NRS is 2 points or 30%, in a low back pain subgroup over a short-term (duration of one-month) follow-up (Hawker et al. 2011). In accordance with the CBRG, statistical pooling of the overall effect (random effects model) was compared to a comparison treatment with a 95% confidence interval (Furlan et al. 2009).

GRADE Assessment

The evidence for each outcome was further assessed in accordance with the GRADE system recommended by the CBRG guidelines (Furlan et al. 2009), namely: study design limitations, consistency between studies, directness (ability to generalize), precision (sufficient or precise data) of results and publication bias. Five levels of evidence may then be generated for each pooled outcome from this information: high, moderate, low, very low quality of evidence and no evidence. Please see table s5 for details on the criteria used for assessment (Ryan & Hill 2016).

Results:

- i) Included studies:

6761 papers were found through the computer aided search strategy with 2110 duplicates removed. Title and abstract screening resulted in removal of 4631 results with 26 full-text articles reviewed, of which four trials were included. Six full text papers were reviewed following secondary literature searching, of which three were included (Louw et al., 2016; Moseley, 2002; Moseley et al., 2004). One paper was included further to correspondence with the authors (J.N) (Malfliet et al. 2017). The details of trial selection are visually depicted in figure 1. In total eight RCTs were included (n=615) and the study characteristics are detailed in table 1.

Figure 1: PRISMA flow chart demonstrating study search results.

ii) Excluded studies:

Following full-text review, two records were excluded as they were poster presentations of the original RCTs (Luomajoki et al., 2016; Pires et al., 2016), pain mechanism education was given to both groups in Aasa et al. (2015) and (Moseley, 2003a). One study was excluded due to being unpublished and sourced from secondary referencing (Moseley, 2009), and another study was excluded as it had no control group (Demoulin et al., 2016). One study did not include the outcomes of pain and disability (Lochting et al., 2017). The other twelve papers did not use pain education (PNE) as described by Butler & Moseley (2003)(Chaleat-Valayer et al., 2016; Chan et al., 2016; Childs et al., 2014; George et al., 2011; Luomajoki et al., 2016; Murphy et al., 2014; O’Keeffe et al., 2016; Pieber et al., 2014; D. Pires et al., 2016; Rantonen et al., 2014; Roche-Leboucher et al., 2011; Saper et al., 2014; Tousignant-Laflamme et al., 2013; Vibe Fersum et al., 2013).

iii) Description of Studies:

Details of the included studies can be seen in the table below (Table 1). Five of the eight studies delivered PNE alongside physiotherapeutic treatment (Louw et al., 2016; Moseley, 2002; Pires et al., 2015; Téllez-García et al., 2015; Wälti et al., 2015), whilst two studies compared PNE in isolation against biomedical education (Malfliet et al. 2017; Moseley et al., 2004) and a third compared PNE to guideline recommended care (Werner et al., 2016);

Delivery and dosage

Please see table s2 for details regarding PNE dosage and delivery methods amongst included trials.

Outcomes

Five of the studies measured short-term pain (within the first 6 weeks), whereas Wälti et al. (2015) reported results at 12 weeks. Five studies utilised the Numeric Pain Rating Scale (NRS)(0-10) (Louw et al., 2016; Moseley, 2002; Tellez-Garcia et al., 2015; Wälti et al., 2015; Werner et al., 2016), whilst Pires et al. (2015) utilised a 100mm visual analogue scale (VAS). Six of the eight studies reported back-specific disability outcomes in the short-term. Five studies used the Roland Morris Disability Questionnaire (RMDQ) (0-24) (Moseley, 2002; Moseley et al., 2004; Tellez-Garcia et al., 2015; Wälti et al., 2015; Werner et al., 2016). Pires et al., (2015) utilised the Quebec Back Pain and Disability Scale (QBPDS) (0-20 points), Tellez-Garcia et al. (2015) also utilised the Oswestry Disability Index. Wälti et al. (2015) used the Patient Specific Functional Scale, whilst Malfliet et al. (2017) utilized the Pain Disability Index (PDI-DV). Moseley (2002) and Werner et al., (2016) were the only trials to perform long-term follow-ups of participants at twelve months.

Table 1: Included Trials Characteristics

iv) Risk of Bias in Included Studies

Figure 2 demonstrates the results of the risks of bias assessment. Using the GRADE classification, one trial was of high quality (Malfliet et al. 2017) (10/12), with the other seven studies of moderate quality (>6/12)(Werner et al. 2016; Wälti et al. 2015; Louw, Farrell, et al. 2016; Moseley et al. 2004; Moseley 2002; Tellez-Garcia et al. 2015; Pires et al. 2015). All studies apart from Moseley et al. (2004) utilized random sequence generation. Adequate description of the allocation concealment was performed in Pires et al. (2015) and Werner et al. (2016). Blinding of care providers was not performed in all studies apart from Moseley et al. (2004). All trials were considered to have a low risk of bias, suggesting that although a degree of bias was present, the criteria that are unfulfilled are unlikely to change the results or conclusion of the study (Furlan et al. 2009). For detailed risk of bias assessment, please see table s3.

Figure 2: Risk of Bias Summary

- v) Effects of interventions
- a) Pain

Six studies comprised of 428 participants provided data on short-term pain outcomes. Meta-analysis of the results demonstrated a weighted mean difference of 0.73 (95% CI -0.14; 1.61) on a 10-point scale of PNE in comparison to **control groups** at a mean of 31.8 days. This is not statistically significant ($p=0.10$). There was significant heterogeneity with I^2 statistic of 95% and $\chi^2=109.57$ ($p<0.000001$) (see figure 3). There is low quality evidence that the use of PNE in isolation/ combination with other treatment may improve pain relief in the short-term.

Figure 3: Forest plot of PNE versus alternative intervention in short-term

Subgroup analysis of physiotherapy interventions combined with PNE (Wälti et al. 2015; Louw, Farrell, et al. 2016; Pires et al. 2015; Tellez-Garcia et al. 2015; Moseley 2002) demonstrates a statistically significant difference in favour of the addition of PNE ($p<0.00001$), with a weighted mean difference of 1.32 (95% CI 1.08, 1.56) for 212 participants, which is clinically insignificant (Hawker et al. 2011). The heterogeneity was low $I^2= 0\%$ and $\chi^2=3.55$ ($p=0.47$) (please see figure 4). There is moderate quality evidence that the addition of PNE to a physiotherapy intervention has a short-term improvement on pain.

Figure 4: Forest plot of PNE with physiotherapy intervention versus PNE

Two studies captured data at a 12 month follow-up period (Moseley, 2002; Werner et al., 2016). The weighted mean difference for long-term effects of PNE on pain was 0.44 (95% CI -1.03, 1.91) for 254 participants which was not statistically significant ($p=0.56$). Considerable heterogeneity was demonstrated between these two studies with $I^2= 99\%$ and $\chi^2=80.40$ ($p<0.00001$) (please see figure 5). We are uncertain whether the use of PNE is effective in reducing pain in the long-term, due to the domains of imprecision and indirectness not being met, as well as publication bias

due to the small number of papers included (n=2) and one of these being authored by a prominent PNE author (Moseley, 2002).

Figure 5: Forest plot to depict PNE versus alternative intervention at 12 months

b) Disability

Meta-analysis was performed with all five studies which used the RMDQ (n=362) at a mean of 32.8 days (Moseley, 2002; Moseley et al., 2004; Tellez-Garcia et al., 2015; Wälti et al., 2015; Werner et al., 2016). The overall mean difference was 2.28 (95% CI 0.20,4.25; p=0.02) which is both clinically and statistically significant when compared to the minimal clinically important change of 2 points or 8-12% (Furlan et al. 2009), however due to the wide confidence interval, this should be interpreted with caution. Between study variability demonstrated considerable heterogeneity ($I^2 = 98\%$, $\text{Chi}^2 = 215.51$, $p < 0.00001$) (please see figure 6). There is moderate quality evidence that the use of PNE either as stand-alone intervention or in combination with physiotherapy probably improves disability in the short-term.

Figure 6: Forest Plot to depict combined RMDQ scores for PNE compared to alternative intervention in short-term

Subgroup analysis of PNE in addition to a physiotherapy intervention utilizing the RMDQ for disability, demonstrates a weighted mean difference of 3.94 (95% CI 3.37,4.52) for 88 participants (Moseley 2002; Tellez-Garcia et al. 2015; Wälti et al. 2015) which is both clinically and statistically significant ($p < 0.00001$). Between study variability was low $I^2 = 0\%$, $\text{Chi}^2 = 0.86$ ($p = 0.65$) (please see figure 7). There is moderate quality evidence that the addition of PNE to physiotherapy improves disability in the short-term.

Figure 7: Forest plot to depict combined RMDQ scores for PNE in addition to physiotherapy intervention compared to physiotherapy interventions alone

Subgroup analysis of the long-term effect of PNE on RMDQ disability demonstrated a weighted mean difference of 2.18 (95% CI -0.67, 5.02) ($p=0.13$) for 254 participants (Werner et al. 2016; Moseley 2002) which was **not statistically significant**. This demonstrated significant between study variability with $I^2=95\%$ and $\text{Chi}^2=21.80$ ($p<0.00001$) (please see figure 8). We are uncertain whether the intervention of PNE influences disability in the long term due to the very low quality of evidence.

Werner et al. (2016) reported a between group difference of 0.70 (-0.32, 1.72) in favour of PNE which was **not statistically significant** ($p=0.18$) at 1-year. However, there was a statistically significant difference in favour of physiotherapist delivered education in comparison to GP delivery (1.41 points, 95% CI 1.12,1.70) ($p<0.00001$) at twelve-month follow-up.

Figure 8: Forest plot to demonstrate the long-term effect of the addition of PNE compared to no PNE on RMDQ disability scores

In the results of PSFS, although the PNE group improved by a clinically significant 2.55 points (95% CI 1.3,3.8), the between-group difference was not significant at 1.42 points (95%CI -0.25,3.09) ($p=0.09$) in the short-term (12 weeks) (Wälti et al. 2015). Similarly, Malfliet et al. (2017) reported a between group difference on the Pain-Disability Index of 1.84 points (95% CI -2.80; 6.47) which was **not statistically significant**. Comparing PNE and aquatherapy against aquatherapy, both groups demonstrated a **statistically non-significant** improvement in their QBPDS score (3.40 difference; 95% CI -3.34, 10.14)($p=0.32$) (Pires et al. 2015). Tellez-Garcia et al. (2015), in the comparison of dry needling with PNE against dry needling alone, reported a non-significant difference in ODI scores between groups of -4.50 (95% CI-10.62, 1.61; $p=0.15$).

c) Psychological effects

Three studies reported on the short-term outcomes of fear of movement or kinesiophobia (Pires et al., 2015; Tellez-Garcia, de-la-Llave-Rincon, et al., 2015; Malfliet et al., 2017) utilising the Tampa Scale of Kinesiophobia. The weighted mean

group difference was 4.72 (95% CI 2.32, 7.13) in favour of PNE ($p=0.0001$)(please see figure 9), however this was clinically insignificant falling short of the required 5.5 points to demonstrate a minimal clinically important change in CLBP (Monticone et al. 2016).

Figure 9: Forest plot to depict the effect of addition of PNE compared to no PNE on the TSK

Two studies ($n = 178$) utilised the Pain Catastrophizing Scale (PCS), and the weighted mean group difference was 2.54 points (95% CI-4.23, 9.31) in favour of the PNE group ($p=0.46$)(please see figure 10). However, this difference was not statistically significant. However, very high scores of heterogeneity were present with I^2 of 99% and $Chi^2=195.85$.

Figure 10: Forest plot to depict the effect of the addition of PNE compared to no PNE on the PCS

c) Reported harmful effects

There were no adverse effects reported due to PNE. Téllez-García et al. (2015) reported soreness in 83% of their participants after the trigger point dry-needling treatment, but this resolved spontaneously within 32 hours for all participants. There were no adverse effects reported by Moseley (2002), Pires et al. (2014) or Werner et al. (2016). Adverse events were not reported by Louw et al. (2015), Malfliet et al. (2017), Moseley et al. (2004) or Wälti et al. (2015).

vi) GRADE analysis

Please see figure 11 for the detailed GRADE assessment and table s4 for the criterion used for assessment. When PNE is delivered in addition to a physiotherapy intervention, there is moderate quality evidence of benefit on pain scores in the short-term, as the domain of imprecision was not met. However, when PNE is delivered either in isolation or in combination with physiotherapy, there is very low evidence for the effectiveness of PNE in reducing pain in the long-term. In the long-term, this was due to the domains of imprecision and indirectness not being met, as

well as an additional risk of publication bias due to the small number of papers included (n=2) and one of these being authored by a prominent PNE author (Moseley, 2002).

For disability, there is moderate quality evidence that the use of PNE either as a stand-alone intervention or in combination with physiotherapy improves disability as measured with the RMDQ in the short-term (both clinically and statistically significant improvement), as the domain of indirectness was not met. There is moderate quality evidence that the addition of PNE to physiotherapy provides a statistically and clinically significant improvement in disability in the short-term, limited by the domain of imprecision not being met due to the small sample sizes. There was low quality evidence that the use of PNE as a stand-alone intervention improved disability in the long-term due to the domains of indirectness, imprecision and publication bias not being met. This was due in part to the small number of papers included (n=2) and one of these being a prominent PNE author (Moseley, 2002).

Discussion

Summary of main findings:

This study aimed to evaluate the effectiveness of PNE on pain and disability in CLBP. The results of this review show that the use of PNE probably improves disability in the short-term, irrespective of whether it is delivered in conjunction with physiotherapy or not. The minimal clinically detectable change for the RMDQ is 2 points on the 24-point scale and this review demonstrated a change of 2.28 (95% CI 0.20,4.25; p=0.02) and 2.18 (95% CI -0.67, 5.02) for the short-term and long-term effects. However, when PNE was added to a physiotherapy intervention the between group difference for disability was 3.94 (95% CI 3.37; 4.52) suggesting a greater clinical improvement in favour of the addition of PNE to physiotherapy treatment. When PNE in addition to physiotherapy interventions was analysed in a subgroup analysis, heterogeneity was found to be negligible ($I^2=0\%$). Therefore, supporting the results that the addition of PNE to physiotherapy interventions is clinically significant in improving disability.

When PNE was added to usual physiotherapy interventions, there is moderate evidence that it probably slightly improves pain scores (weighted mean difference 1.32 (95% CI 1.08, 1.56) $p < 0.0001$). However, PNE as a stand-alone intervention or in combination with physiotherapy had little or no effect on pain scores in the short-term 0.73 (95% CI -0.14; 1.61) ($p = 0.10$). Similarly, when PNE in addition to physiotherapy interventions was analysed in a subgroup analysis, heterogeneity was found to be negligible ($I^2 = 0\%$). The small but clinically insignificant benefits on pain in the short-term may also be considered robust.

The use of PNE either in conjunction with physiotherapy or in isolation created a statistically significant improvement in TSK scores (4.72 (95% CI 2.32, 7.13) $p = 0.0001$), in the short-term. However, neither of these changes was clinically significant, and both these analyses demonstrated a high degree of heterogeneity ($I^2 = 99\%$ and 95% respectively): thus these results should be interpreted cautiously.

Considerable heterogeneity was found in a number of factors including age, with mean ages of 38 years (Werner et al. 2016) to 60 years (Louw et al. 2016); duration of pain, with Werner et al. (2016)'s participants having an average of 6 weeks of pain, whereas Louw et al. (2015)'s participants had an average of 9 years of pain (see table 1). Further, the delivery of the PNE was applied in a wide variety of formats, from one-to-one sessions, to webinars, group delivery; with variable prescriptions of reading to perform at home which may assist with improved outcomes. The comparator group also varied between trials, with only one trial utilising a waiting list control (Moseley, 2002) whilst Wälti et al. (2015) compared multi-modal treatment group to a usual physiotherapy group. All other intervention groups compared the same intervention with or without PNE which can reduce the bias of co-interventions,

Limitations of included studies

For the meta-analysis of pain and disability in the short- and long-term, there was a high degree of heterogeneity with I^2 statistics of 95% and 98% respectively. This was possibly due to the variety of interventions assessed and reduces the robustness of the short-term and long-term results for all studies combined. Attempts to reduce the heterogeneity of trials was attempted by subgrouping trials into the intervention of

PNE in addition to physiotherapy and as an educational stand-alone which successfully reduced the I^2 coefficient.

A further limitation was the small sample sizes of some of the included studies (n=12 (Tellez-Garcia et al. 2015), n=28 (Wälti et al. 2015)), which reduces the ability of the trial to detect a significant difference, whilst also reducing the likelihood that any significant results found reflect a true effect (Button et al. 2013).

The trials included within this review all scored above 6/12 on the Cochrane Risk of Bias score, indicating a low level of bias. However, the most common source of bias was blinding of care providers, which was only performed by Moseley et al. (2004); followed by inadequate description of allocation concealment in 75% of trials. 50% of trials had inadequate blinding of participants and personnel, and 25% of included trials did not blind the outcome assessors. Only two studies followed up participants at twelve months (Werner et al., 2016; Moseley et al., 2002), of which Werner et al., (2016) had a higher rate of attrition bias due to an increased rate of drop-out in the GP group (38%) in comparison to the physiotherapist-delivered intervention group (26%).

It is interesting to note the variation in delivery methods by Werner et al. (2016) whereby GPs and physiotherapists were used to deliver the intervention and control, as opposed to Moseley et al. (2004) who utilised physiotherapists only. Both trials found improvements in both groups, with the addition of PNE providing no extra benefit in Werner et al. (2016). However, Moseley et al. (2004) found improvement in physical performance and a normalization of pain attitudes and beliefs which favoured the PNE intervention group. Werner et al. (2016) noted the difficulty in recall across delivery agents of the content in sessions provided and postulated that patients may have received treatments more similar than intended. Further, the training received in the delivery of PNE may require standardization, as we know from previous studies the content and understanding of PNE by those delivering the intervention can potentially effect adequate reconceptualization in others (Mosely 2003b; Moseley and Butler 2015): health professionals may potentially underestimate patients' ability to understand PNE, and without specific training, health professionals themselves were found to be unlikely to demonstrate sufficient

understanding of PNE on the pain neurophysiology knowledge test when compared to trained counterparts (Moseley, 2003b).

Comparison with other reviews

The findings of this study are in keeping with Moseley and Butler's review of Explain Pain (2015) in which they reiterate the clinically intended use of PNE as an adjunct to biopsychosocial rehabilitation. These results are in contrast to the last review of PNE in CLBP whereby Clarke et al. (2011) reported non-significant improvements in favour of the PNE group in physical function but significant improvements in pain scores in the short-term (a mean difference of 5mm (95% CI 0,10.0) on the 100mmVAS) and long-term (27 point (68%) between group difference). However, they had limited study inclusion (n=2), with small sample sizes (n=58; n=64) which increases the risk of false positive results (Button et al. 2013). Similarly, the recent review by (Louw, Zimney, et al. 2016) included 13 studies evaluating PNE, and concluded strong evidence for the use of PNE in reducing pain ratings and disability in all musculoskeletal conditions.

The strength of evidence for the effect of PNE on pain in the short-term is low to moderate, suggesting that further evidence may well alter the results of this review, although we are moderately confident that the results of this review reflect a positive effect of PNE on disability.

Despite the small mean differences shown for pain and disability, it is important to note that in all studies, both groups demonstrated an improvement from baseline, regardless of whether they received an intervention or not. Subgroup analysis provided moderate quality evidence for the support of PNE in addition to physiotherapy interventions on pain and disability in the short-term, which is supported by existing literature (Moseley and Butler 2015; Louw et al., 2016). However, for pain outcomes non-clinically significant changes were demonstrated, and small clinically significant changes were demonstrated in disability, suggesting that future research may play an important role in deciding the cost-benefit of including PNE alongside physiotherapy treatment.

Limitations of this review:

Although this study includes eight moderate quality RCT studies, the heterogeneity in primary outcomes selected and outcome measure utilised limited the ability to pool all results in meta-analysis and increased the indirectness of effect. As such the limited ability to group studies results in increased influence of imprecision, and publication bias with 3 of the included studies authored by prominent PNE authors receiving royalties from PNE's promotion.

The lack of a registered protocol for this review is also recognised as a methodological shortcoming.

Implications for practice

There is moderate quality evidence that the use of PNE alongside physiotherapy interventions for CLBP probably reduce disability and pain in the short-term. The variety of interventions included in this review is reassuring, ensuring treatments can be tailored to patient's individual goals and preferences. There is low evidence for the use of PNE to reduce fear avoidance and pain catastrophizing.

As GPs are seeing a large proportion of first-contact patients and managing CLBP patients possibly more frequently than physiotherapists, future research should include training of GPs in the delivery of PNE to assist with increasing their familiarity with the biopsychosocial and PNE approach, as well as to evaluate whether there are differences in patient outcomes.

Conclusion

This study provides moderate quality evidence for the use of PNE as an adjunct to usual physiotherapy interventions in the improvement of disability and pain scores in CLBP in the short-term. We are uncertain whether PNE may improve long-term pain and disability. Future research should evaluate the cost-effectiveness of the addition of PNE to usual care.

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Table 1: Included Trials Characteristics

Authors		Sample	Intervention	Comparator	Outcomes	Timepoint of Assessment
Louw et al. 2016 USA	<i>Total</i> <i>Age (yrs)</i> <i>F/M(%)</i> <i>Duration</i> <i>Pain(mean)</i>	62 60.14 56/43 9.26 years	Manual therapy Maitland mobilisation with a PNE explanation for 5 minutes	Manual therapy Maitland mobilisation	Pain Intensity (NRS for leg and LBP); Lumbar flexion; SLR	Baseline and post- treatment (same day)
Malfliet et al. 2017 Belgium	<i>Total</i> <i>Age(yrs)</i> <i>F/M(%)</i> <i>Duration</i> <i>Pain(mean)</i>	120 EG 37.5 CG 42; EG63/37; CG 58/42 EG 97.0 /CG 67.0 months	PNE Education 3 sessions: 1 group session, 1 webinar session, 1 individual session	Biomedical Education 3 sessions: 1 group session, 1 webinar session, 1 individual session	Pain Disability Index; Illness Perceptions Questionnaire; Tampa Scale of Kinesiophobia; Pain Catastrophizing Scale	Baseline and Post- education (3 weeks)
Moseley 2002 Australia	<i>Total</i> <i>Age(yrs)</i> <i>F/M(%)</i> <i>Duration</i> <i>Pain</i>	57 EG 43±7, CG 38±7; EG 64/36, CG54/46 EG 39; CG 37 months	2 physiotherapy treatments per week for 4 weeks including manual therapy, motor control training and once weekly PNE in one-to-one format	GP care, no physiotherapy	Function (RMDQ), Low back pain (NRS); Health care utilisation	Baseline and post- treatment (average 29days); One year follow up data
Moseley et al. 2004 Australia	<i>Total</i> <i>Age(yrs)</i> <i>F/M(%)</i> <i>Duration</i> <i>Pain</i>	58 EG 42; CG 45. EG 58/42; CG 56/44. EG 29; CG 30 months	One to one education session on PNE for 3 hours	One to one education session on biomedical and anatomical education, 3 hours	Function (RMDQ); Survey of Pain Attitudes (revised) (SOPA); PCS; SLR, Lumbar Flexion, Abdominal	Baseline and 15 days later

					Drawing in Task	
Pires et al. 2015 <i>Portugal</i>	<i>Total</i> <i>Age(yrs)</i> <i>F/M(%)</i> <i>Duration</i> <i>Pain</i>	62 EG 50.9; CG 51.0; EG 67/33; CG 62/38 EG 80%>24 months; CG 75% >24 months	Aquatic exercise twice weekly, 6 weeks + 2 sessions PNE prior to aquatherapy	Aquatic exercise twice weekly 6 weeks only	Pain Intensity (VAS), disability (QBPDS) Secondary: Tampa Scale of Kinesiophobia (TSK)	Baseline, 6 weeks and 12 weeks
Télez-García et al. 2015 <i>Spain</i>	<i>Total</i> <i>Age(yrs)</i> <i>F/M(%)</i> <i>Duration</i> <i>Pain</i>	12 EG 36; CG 37; Female 66/36 EG 17; CG 19 months	Trigger-point dry needling with PNE (3 sessions, 2 with PNE)	Trigger point dry needling alone (3 sessions)	Pain Intensity (NRS), Disability (ODI, RMDQ), TSK and widespread pressure sensitivity (PPT)	Baseline, 1 week
Wälti et al. 2015 <i>Switzerland</i>	<i>Total</i> <i>Age(yrs)</i> <i>F/M (%)</i> <i>Duration</i> <i>Pain</i>	28 EG 41.57; CG 41.71. EG 64/36; CG 43/57 Unknown	MMT includes a) neurophysiological education b) sensory training of the lower trunk c) movement control of the trunk. 1-2 x week per 8 weeks	Usual physiotherapy 1-2 x week per 8 weeks	Primary: Pain (NRS) Secondary: Disability (RMDQ)	Baseline, 12 weeks
Werner et al. 2016 <i>Norway</i>	<i>Total</i> <i>Age(yrs)</i> <i>F/M(%)</i> <i>Duration</i> <i>Pain(mean)</i>	216 EG 38.1; CG 38.6 EG 55.3/ 43.7, CG 60/40 EG 6.8; CG 6.1 weeks	Explain Pain education program 4 x 30min sessions + Usual treatment	4 x 30 mins Anatomical education + Usual treatment	Primary: Function (RMDQ), Pain (NRS), Sick leave, Quality of life (EQ-5D)	Baseline, 4 weeks, 12 months

Table S2: Table to demonstrate the dosage and delivery of PNE in included trials

Author	Details of PNE delivery	Dosage of PNE
Louw et al., 2016	PNE alongside manual therapy	5-minute delivery, individualised.
Malfliet et al., 2017	PNE alone	One group session (30 minutes to one hour). One webinar session (one hour). One individualised session (30 minutes)
Moseley 2002	PNE and physiotherapy	Individualised PNE one hour once a week for four weeks.
Moseley et al., 2004	PNE alone	Individualised PNE for three hours.
Pires et al., 2015	PNE and aqua physiotherapy	Two group sessions 90 minutes each prior to aqua physiotherapy.
Tellez-Garcia et al., 2015	PNE and dry needling	Individualised PNE session 30 minutes, once a week for two weeks
Walti et al., 2015	PNE and multimodal treatment	Two to four individualized PNE sessions of unspecified duration
Werner et al., 2016	PNE alone	Individualized PNE, 30 minutes once a week for four weeks.

Table to demonstrate Risk of Bias Assessment for included trials:

Trial Authors	Selection Bias		Performance Bias		Detection Bias	Attrition Bias	Reporting Bias		Other Bias					Score
	Random Sequence Generation: Was the allocation sequence adequately generated? Score "Low" if a random component in the sequence generation process is described; Score "High" when a nonrandom method is used. Score "Unclear" if not specified.	Allocation Concealment: Score "Low" if the unit of allocation was by institution, team or professional and allocation was performed on all units at the start of the study; or if the unit of allocation was by patient or episode of care and there was some form of centralised randomisation scheme, an on-site computer system or sealed opaque envelopes were used. Score "High" if this did not happen and "unclear" if not enough information	Blinding of participants and personnel: Score "Low" if measures are described to blind study participants or personnel from knowledge of which intervention a participant received. Score "High" if no blinding occurred. Score "unclear" if insufficient information is provided.	Blinding of care providers: Score "Low" if measures are described to blind deliverers of the intervention from knowledge of which intervention is active, score "High" if no blinding occurred, Score "Unclear" if insufficient information is provided	Blinding of outcome assessment: Score "Low" if measures are described to blind outcome assessors from knowledge of which intervention a participant received, score "High" if no blinding occurred, Score "Unclear" if insufficient information is provided	Drop Out Rate: Score Low if the drop out rate was described and acceptable, score high if the drop-out rate was not described or was unequal between groups. Score "unclear" if insufficient information was provided.	Were all participants analysed in the group they were randomised to? Score Low if this occurred, score "high" if this did not occur.	Selective Reporting: Score "Low" if the possibility of selective reporting was examined by review authors, score "High" if this was present. Score "Unclear" if it is uncertain whether this was examined.	Baseline similarities groups: Score "Low" if the baseline groups were similar, score "High" if there were statistically significant differences between groups, score "unclear" if there is insufficient information provided.	Co-interventions avoided: Score "Low" if co-interventions were avoided, score "high" if there was a likely co-intervention effect, score "unclear" if there is insufficient information provided.	Compliance: Score "low" if the compliance was acceptable in all groups, score "high" if the compliance was unacceptable in all groups. Score "unclear" if insufficient information was provided.	Timing of outcome assessment: Score "low" if all timings were the same across groups, score "high" if the timings varied across groups, score "unclear" if this was not clear.	Other Bias: State any other concerns about bias with a "High" and quote	/12
	Low	Unclear	Low	High	High	Low	Low	Low	High.	Low	Low	Low	High.	8

Louw et al., 2016	"Randomisation performed using an alternating blank envelope system for the PT"	Allocation concealment is not described. "Therapists were given identical blank envelopes which allocated the participant to a group."	"Participants were not aware of group allocation."	"Therapists were aware of group allocation due to treatment guidance for the manual therapy and therefore a greater element of bias existed."	"This had a higher risk of bias due to the treating therapist collecting outcome measures and performing the pre- and post-treatment outcome scores."	Acceptable	Yes	All data was reported and presented clearly with pre- and post- means and SD's displayed as well as interaction effect, time main effect and group main effect	Baseline characteristics are not displayed across the two groups.	Yes	Yes	Yes	Convenience sampling utilized.	
Malfliet et al., 2017	Low:	Unclear	Low	High	Low	Low	Low	Low	Low	Low	Low	Low	Unclear	10
	"Randomization was performed using a stratified permuted block allocation (block size of four) at the Biostatistics Unit (Ghent University) by an independent investigator using SAS 9.4"	Allocation concealment is not described	The study participants and the statistician (performing the data analyses) were blinded to the study hypothesis;	The therapists could not be blinded	"The outcomes assessor (collecting the data) was blinded for the randomization sequence."	Yes Described management of drop-out data in statistical analysis. Reasons provided for withdrawal,	Yes	All data provided at all time points	Groups were similar. Control group had slightly higher age scores than intervention group.	Yes.		Yes	Recruitment required volunteering for the trial again predisposing the trial to include those of moderate to milder disability and pain scores.	
	Low	Unclear	Unclear	High	Low	High	Low	Unclear	Low	High	Low	Low	High	6

Moseley 2002	"independent person allocated them to experimental group using a coin toss."	"strategy ensured that allocation was concealed from the subjects until after initial assessment, and from the assessors throughout the study." The allocation procedure is not adequately described.	No mention is made of blinding	Not mentioned	"Initial and final assessment was performed by the same two investigators, who were not otherwise involved in the study and were blinded to experimental group. One-year follow-up data were collected via telephone by separate assessors who were also blinded to experimental group. The	Adequate reasons are not provided for withdrawal. The pre-treatment data for those subjects included in the follow up showed no differences between the experimental groups.	Yes	It is not clear how long term results were calculated (accounting for drop outs) and not all results at 12 months are clearly presented (only treatment effect and NNT)	Age is slightly lower in control group and more people receiving compensation in control group.	Physiotherapy group with PNE compared to no intervention.	Yes	Yes	Recruitment bias present as patients "volunteered" for the trial. More patients withdrew from the intervention group than the control group (5 vs 3)	
Moseley et al., 2004	High Unclear what methods were used. "Concealed randomization was performed after the initial assessment in accordance with recommendations made in the literature."	Unclear Allocation concealment not detailed.	Low Subjects were blinded to experimental group.	Low Therapists were also informed as to the purpose of the study but were told that the other type of education was the control intervention.	High Of 3 objective measures, only one is reported to be blinded assessed "Correct performance was monitored and recorded by a trained physiotherapist, who was blinded to treatment group"	Low Similar across groups..	Unclear Pre-intervention data from the subjects that did not complete the study was removed, which did not cause a change in group mean	Low All results are reported for all time points.	Low Similar baseline results between groups	Low Yes	Low Yes	Low Yes	High Subjects attending a private rehabilitation clinic were invited to attend - not generalizable to	8

et al., 2015	Computer generated table of randomised numbers pre-allocated.	"Concealed allocation was performed by using a computer-generated randomized table of numbers created prior to the start of data collection by a researcher" However this is not well described.	Unclear if participants or personnel blinded to group allocation, however it is unlikely that either group was blinded due to the study design	Unclear if participants or personnel blinded to group allocation, however it is unlikely that either group was blinded due to the study design.	Blinded assessor examined participants maintaining a low risk of bias	N/A No attrition	N/A	All results reported	Both groups similar	None	Yes	Yes	None noted.	
Walti et al., 2015	Low	Unclear	High	High	Low	Low	Low	Low	Low	High	Low	Low	Low	8
	Electronically generated block randomisation	No detail regarding how allocation concealment was maintained.	No mention made of blinding either participants or personnel.	No mention made of blinding.	Independent blinded assessors utilised to assess outcomes.	Similar across groups Drop-outs with reasons given was performed, but statistical analyses were not performed between those that completed the study and those lost to drop-out.	Yes	All results were reported, with group mean difference and between group mean differences reported for all outcomes with 95% confidence intervals and p-values	Similar baseline characteristics	Very different treatment interventions provided, thus the active component providing the change is difficult to elicit.	Yes	Yes	None noted	
	Low	Low	Low	High	Low	High	Low	Low	High	Low	High	low	Low	8

Werner et al., 2016	Cluster group, computer generated randomisation	Stratification of each clinician	The patients and study statistician were blinded to group allocation	Not possible due to study type	The patients and study statistician were blinded to group allocation	Statistical analysis was provided for non-responders at 4 weeks and 12 months. There was a particularly high drop out of those attending the GP sessions. There was a particularly high drop out of those attending the GP sessions. Statistical analysis was provided for non-responders at 4 weeks and 12 months.	Yes	All results were reported.	The GP group had smaller proportion of employed participants, with lower level of education and increased obesity, more likely to be smokers (in comparison to the physiotherapy groups). The intervention versus control group had similar values.	Low Yes.	It is mentioned in the text that although thorough training was provided on the content of sessions to be included, it was mentioned that there was uncertainty about the providers' compliance with the intervention manual			
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Risk of Bias Summary:

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of care providers	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Baseline similarities groups	Co-interventions Avoided?	Other bias
Louw et al. 2016	-	?	+	-	-	+	+	-	+	-
Malfliet et al., 2017	+	-	+	-	+	+	+	+	+	-
Moseley 2002	?	-	-	-	+	-	-	+	-	-
Moseley et al. 2004	-	-	+	+	-	-	+	+	+	-
Pires et al. 2015	+	+	-	-	+	+	+	+	+	+
Tellez-Garcia et al., 2015	+	+	?	?	+	+	+	+	+	+
Walti et al., 2015	+	?	-	-	+	-	+	+	-	+
Werner et al., 2016	+	+	+	-	+	-	+	-	+	+

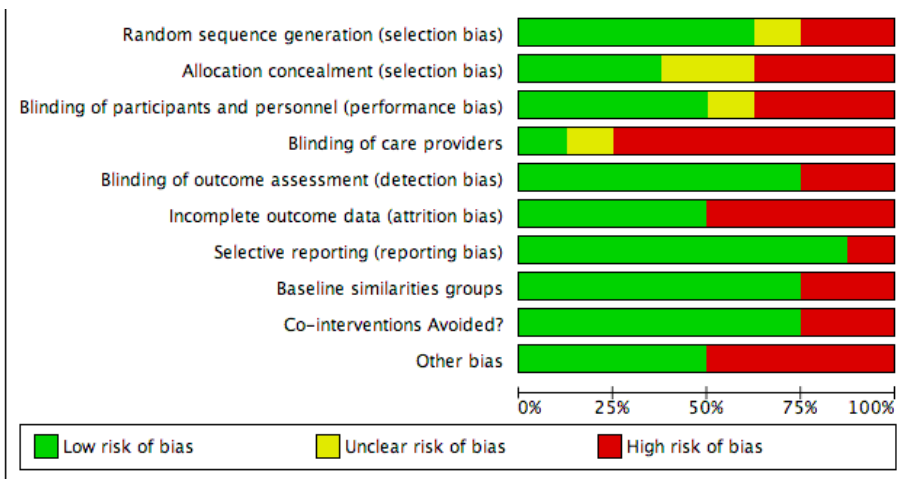


Table to demonstrate Risk of Bias Assessment for included trials:

Trial Author s	Selection Bias		Performance Bias		Detection Bias	Attrition Bias	Reporting Bias	Other Bias		
	Random Sequence Generation: Was the allocation sequence adequately generated? Score "Low" if a random component in the sequence generation process is described; Score "High" when a nonrandom method is used. Score "Unclear" if not specified.	Allocation Concealment: Score "Low" if the unit of allocation was by institution, team or professional and allocation was performed on all units at the start of the study; or if the unit of allocation was by patient or episode of care and there was some form of centralised randomisation scheme, an on-site computer system or sealed opaque	Blinding of participants and personnel: Score "Low" if measures are described to blind study participants or personnel from knowledge of which intervention a participant received. Score "High" if no blinding occurred. Score "unclear" if insufficient information	Blinding of care providers: Score "Low" if measures are described to blind deliverers of the intervention from knowledge of which intervention is active, score "High" if no blinding occurred, Score "Unclear" if insufficient information is provided	Blinding of outcome assessment: Score "Low" if measures are described to blind outcome assessors from knowledge of which intervention a participant received, score "High" if no blinding occurred, Score "Unclear" if insufficient information is provided	Incomplete Outcome Data: Score "Low" if each main outcome includes attrition and exclusion from analysis information (as well as reasons for the above) and any re-inclusions in analysis; Score "High" if this information is not provided and Score unclear if insufficient data is available to make a judgement	Selective Reporting: Score "Low" if the possibility of selective reporting was examined by review authors, score "High" if this was present . Score "Unclear" if it is uncertain whether this was examined.	Baseline similarities groups: Score "Low" if the baseline groups were similar, score "High" if there were statistically significant differences between groups, score "unclear" if there is insufficient information provided.	Co-interventions avoided: Score "Low" if co-interventions were avoided, score "high" if there was a likely co-intervention effect, score "unclear" if there is insufficient information provided.	Other Bias: : State any other concerns about bias with a "High" and quote

		envelopes were used. Score "High" if this did not happen and "unclear" if not enough information	n is provided.							
Louw et al., 2016	High	Unclear	Low	High	High	Low.	Low	High.	Low	High.
	“Randomisation performed using an alternating blank envelope system for the PT”	Allocation concealment is not described. “Therapists were given identical blank envelopes which allocated the participant to a group.”	“Participants were not aware of group allocation.”	“Therapists were aware of group allocation due to treatment guidance for the manual therapy and therefore a greater element of bias existed.”	“This had a higher risk of bias due to the treating therapist collecting outcome measures and performing the pre- and post-treatment outcome scores.”	There were no exclusions or attritions.	All data was reported and presented clearly with pre- and post-means and SD's displayed as well as interaction effect, time main effect and group main effect	Baseline characteristics are not displayed across the two groups.	Yes	Convenience sampling utilized.
Malfliet et al., 2017	Low:	High:	Low	High	Low	Low:	Low	Low	Low	Unclear
	“Randomization was performed using a stratified permuted block allocation (block size of four) at the Biostatistics	Allocation concealment is not described	The study participants and the statistician (performing the data analyses) were	The therapists could not be blinded	“The outcomes assessor (collecting the data) was blinded for the randomization sequence.”	Described management of drop-out data in statistical analysis. Reasons provided for	All data provided at all time points	Groups were similar. Control group had slightly higher age scores than	Yes.	Recruitment required volunteering for the trial again predisposing the trial to include

	Unit (Ghent University) by an independent investigator using SAS 9.4”		blinded to the study hypothesis;			withdrawal, loss to follow up similar across groups.		intervention group.		those of moderate to milder disability and pain scores.
Moseley 2002	Low “independent person allocated them to experimental group using a coin toss.”	High “strategy ensured that allocation was concealed from the subjects until after initial assessment, and from the assessors throughout the study.” The allocation procedure is not adequately described.	Unclear No mention is made of blinding	High Not mentioned	Low “Initial and final assessment was performed by the same two investigators, who were not otherwise involved in the study and were blinded to experimental group. One-year follow-up data were collected via telephone by separate assessors who were also blinded to experimental group. The	Unclear The pre-treatment data for those subjects included in the follow up showed no differences between the experimental groups. However adequate reasons are not provided for withdrawal.	Unclear It is not clear how long term results were calculated (accounting for drop outs) and not all results at 12 months are clearly presented (only treatment effect and NNT)	Low Age is slightly lower in control group and more people receiving compensation in control group.	High Physiotherapy group with PNE compared to no intervention. Co-interventions occurred regardless of treatment group allocation and were accounted for but not controlled for.	High Recruitment bias present as patients “volunteered” for the trial. More patients withdrew from the intervention group than the control group (5 vs 3).
Moseley et al., 2004	High Unclear what methods were used. “Concealed	High Allocation concealment not detailed.	Low Subjects were blinded to	Low Therapists were also informed as to the	High Of 3 objective measures, only one is reported to be	High Pre-intervention data from the subjects	Low All results are reported	Low Similar baseline results	Low Adherence not described.	High Subjects attending a private rehabilitatio

	randomization was performed after the initial assessment in accordance with recommendations made in the literature.”		experimental group.	purpose of the study but were told that the other type of education was the control intervention.	blinded assessed “Correct performance was monitored and recorded by a trained physiotherapist, who was blinded to treatment group”	that did not complete the study was removed, which did not cause a change in group mean pre-intervention scores (P > 0.47). No further comparisons or information provided.	for all time points.	between groups		n clinic were invited to attend - not generalizable to wider community. Higher rate of drop out in intervention group (3 vs 1).
Pires et al., 2015	Low	Low	Unclear	Unclear	Low	Low	Low	Low	Low	Low
	“Balanced block randomisation performed.”	“Allocation concealment maintained with allocation via central telephone registration service.”	No mention is made of blinding either participants or staff delivering intervention.	No mention is made of blinding either participants or staff delivering intervention.	An independent assessor was utilised to gather all data thereby reducing the risk of bias.	Dropout participants showed similar characteristics of those completing the study. The only exception was the QBPDS where statistical comparison showed that those who	All results were described in test with group mean difference and between group mean differences for all outcomes with 95% confidence intervals	No differences between groups	Yes	None noted. Adherence appeared satisfactory.

						dropped out had a higher level of self-reported disability, thereby increasing the risk of bias. Reasons provided for those who withdrew. Similar across groups.	and p-values reported.			
Tellez-Garcia et al., 2015	Low	High	High	High	Low	Low	Low	Low	Low	Low
	Computer generated table of randomised numbers pre-allocated.	“Concealed allocation was performed by using a computer-generated randomized table of numbers created prior to the start of data collection by a researcher” However this is not	Unclear if participants or personnel blinded to group allocation, however it is unlikely that either group was blinded due to the study design	Unclear if participants or personnel blinded to group allocation, however it is unlikely that either group was blinded due to the study design.	Blinded assessor examined participants maintaining a low risk of bias	No attrition.	All results reported	Both groups similar	No co-interventions	None noted.

		well described.								
Walti et al., 2015	Low	High	High	High	Low	High	Low	Low	High	Low
	Electronically generated block randomisation	No detail regarding how allocation concealment was maintained.	No mention made of blinding either participants or personnel.	No mention made of blinding.	Independent blinded assessors utilised to assess outcomes.	Drop-outs with reasons given was performed, but statistical analyses were not performed between those that completed the study and those lost to drop-out. Similar across groups.	All results were reported, with group mean difference and between group mean difference s reported for all outcomes with 95% confidence intervals and p-values	Similar baseline characteristics	Very different treatment interventions provided, thus the active component providing the change is difficult to elicit.	High initial exclusion (90% interested persons excluded). Adherence similar across groups.
Werner et al., 2016	Low	Low	Low	High	Low	High	Low	High	Low	High
	Cluster group, computer generated randomisation	Stratification of each clinician	The patients and study statistician were blinded to group allocation	Not possible due to study type	The patients and study statistician were blinded to group allocation	There was a particularly high drop out of those attending the GP sessions. Statistical analysis was provided for non-	All results were reported.	The GP group had smaller proportion of employed participants, with lower level of education and increased	Low Yes.	It is mentioned in the text that although thorough training was provided on the content of sessions to be

						responders at 4 weeks and 12 months.		obesity, more likely to be smokers (in comparison to the physiotherapy groups). The intervention versus control group had similar values.		included, it was mentioned that there was uncertainty about the providers' compliance with the intervention manual. Compliance similar across groups.
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Table S5: Table to demonstrate GRADE criteria (taken from Ryan and Hill, 2016)

GRADE category	GRADE Assessment Criterion		
Risk of Bias	<p>Systematically assess the outcome against the following criteria (most are elements of the RCT risk of bias tool) for each of the studies that contribute to it to determine whether the quality of the evidence is affected: Inadequate methods of sequence generation.</p> <ul style="list-style-type: none"> • Lack of allocation concealment. • Lack of blinding of each of: participants, providers, outcome assessors. The more subjective an outcome is, the more important effective blinding becomes. For example, symptom improvement is a more subjective outcome than mortality, and is therefore more likely to be biased if unblinded. • Loss to follow up. There is no simple rule of thumb on which to base judgements about this item. The seriousness of losses from a study must be judged based on both the numbers of participants lost and the reasons for these losses, looking particularly at whether these are unbalanced across the study groups. • Failure to follow intention to treat principles in analyses. • Selective outcome reporting of outcomes and/or analyses. • Other sources of bias such as stopping the trial for benefit, design specific issues relating to non-standard trial designs, such as cluster or crossover studies 		
	Risk of bias across studies	Considerations	GRADE assessment
	Most information is from studies at low risk of bias	Most information is from studies at low risk of bias	Most information is from studies at low risk of bias
	The proportion of information from studies at high risk of bias is sufficient to affect the interpretation of results.	The proportion of information from studies at high risk of bias is sufficient to affect the interpretation of results.	The proportion of information from studies at high risk of bias is sufficient to affect the interpretation of results.
	Plausible bias unlikely to seriously alter the results	Plausible bias unlikely to seriously alter the results	Plausible bias unlikely to seriously alter the results
Inconsistency	Consider how much variability there is in the results of studies contributing to the outcome you are assessing.		

	<p>1. For meta-analysed data, consider whether:</p> <ul style="list-style-type: none"> • there is wide variation in the effect estimates across studies • there is little or no overlap of confidence intervals associated with the effect estimates • statistical tests that suggest heterogeneity is present, for example: <ul style="list-style-type: none"> Chi2 test (testing the null hypothesis that the studies in the meta-analysis have the same underlying effect size) has a low p value I2 statistic (which quantifies the degree of variability between studies) is large -but please note the I2 statistic is only one of several things to be considered when assessing heterogeneity, and the thresholds below are only a rough guide. As an approximate guide, an I2 of: <ul style="list-style-type: none"> o 0% to 40% might not be important (low heterogeneity) o 30% to 60% might represent moderate heterogeneity o 50% to 90% might represent substantial heterogeneity o 75% to 100% might represent considerable heterogeneity. <ul style="list-style-type: none"> • whether any heterogeneity has been adequately explained. <p>2. Decide whether to downgrade on the basis of variability in the results:</p> <ul style="list-style-type: none"> • not at all (inconsistency does not seem to be an issue); • one point (some inconsistency exists); or • two points (severe inconsistency is present).
Indirectness	<p>1.Consider again the question your review set out to address. Did the included studies provide broad answers to the question? Are there restrictions based on what was found, and that might affect applicability of the findings, in terms of: • population? • intervention? • comparator? • outcomes?</p> <p>2.Decide whether the evidence that was found is more restrictive than the review question. If so, then the evidence may not directly</p>

	<p>answer the review question and you may downgrade for indirectness:</p> <ul style="list-style-type: none"> not at all (indirectness does not appear to be an issue) one point (some indirectness exists), or two points (indirectness is severe, or there is indirectness from several sources). <p>When considering the degree of indirectness, bear in mind that these judgements are often not clear cut, and not simply additive. A problem with indirectness of outcomes will often trigger downgrading, but all judgements need careful consideration.</p>
Imprecision	<p>1. Assess whether there is enough information (large enough sample size, or large enough number of events) to calculate a precise effect estimate.</p> <p>For continuous outcomes information is likely to be insufficient if:</p> <ul style="list-style-type: none"> • total number of participants is less than 400 (a “rule of thumb”). <p>2. Look at the precision of the effect estimate.</p> <p>Do the upper and lower limits include both meaningful benefit and harm (consistent or inconsistent messages) about the effect of the intervention? If the limits of confidence intervals represented the true effect, would they give the same message about the intervention, or not (e.g. does one end indicate a meaningful benefit, and the other no effect or even a harm)?</p> <p>Does the 95% CI (or alternative estimate of precision) around the pooled or best estimate of effect include both little or no effect and appreciable benefit or appreciable harm?</p> <p>For continuous outcomes, GRADE suggests that the thresholds are the minimal important difference (MID), either for benefit or harm. If the MID is not known, we suggest downgrading if the upper or lower confidence limit crosses the effect size (eg SMD) of 0.5 in either direction.</p> <p>3. Decide whether there is imprecision in the results, based on your assessments of points 1 and 2 above, and if so, to what extent. Make a decision about whether to downgrade:</p> <ul style="list-style-type: none"> not at all (imprecision does not appear to be an issue) one point (some imprecision exists), or two points (very serious imprecision exists).
Publication Bias	<ol style="list-style-type: none"> 1. Consider the size of the included studies (and number of events they include). If all results come from small studies, publication bias may be present. 2. Consider constructing a funnel plot, which graphs precision against the size of the effect. If the plot is asymmetrical (skewed) then publication bias may be present. Note,

	<p>however, that asymmetry of the plot does not always indicate publication bias.</p> <p>3. As it is difficult to entirely rule out the presence of publication bias, and ways of assessing it are uncertain, the GRADE recommendation is to only downgrade one level at a maximum (not two) on the basis of suspected publication bias. If publication bias is: a. undetected, do not downgrade b. strongly suspected, downgrade one level.</p>
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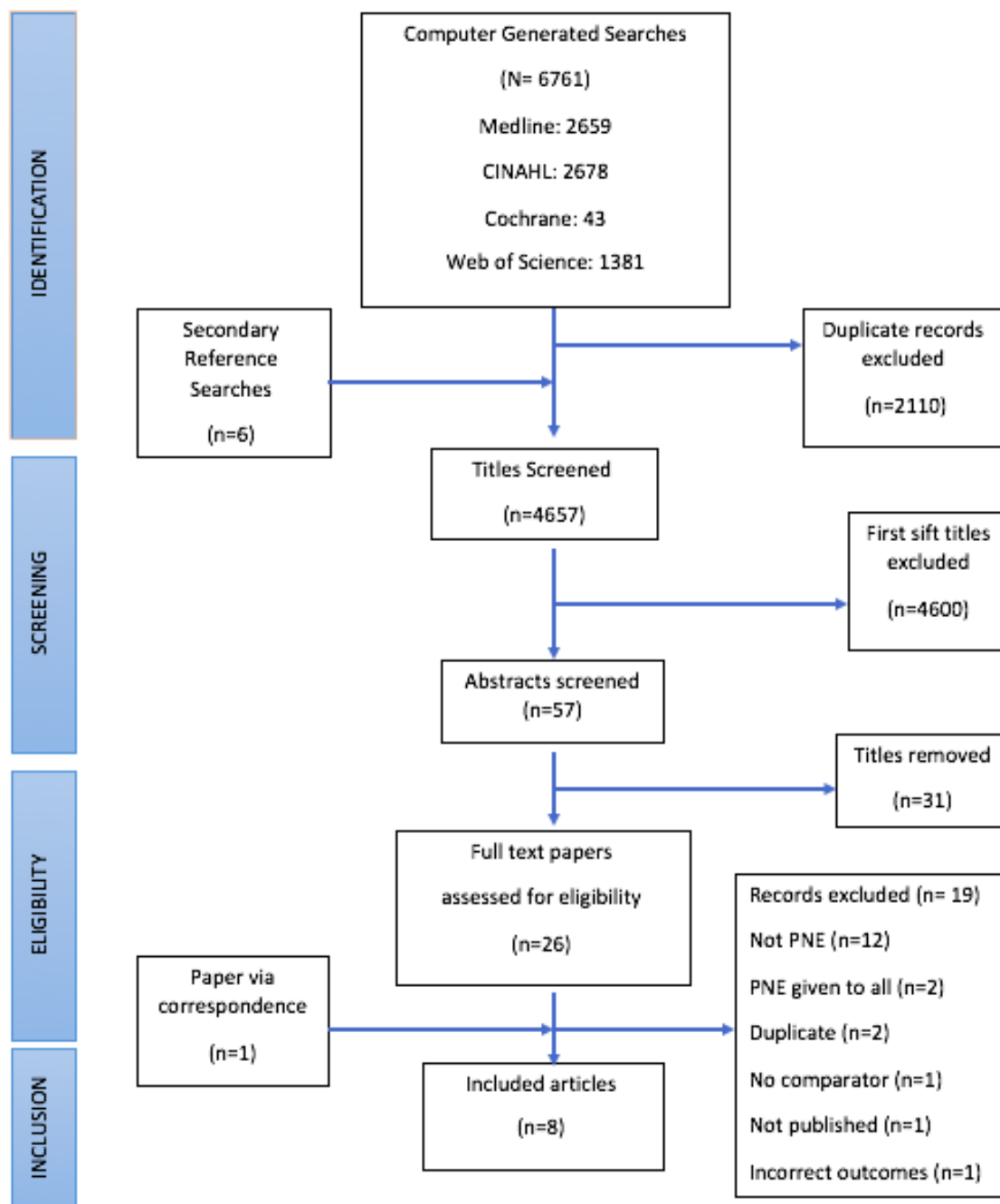
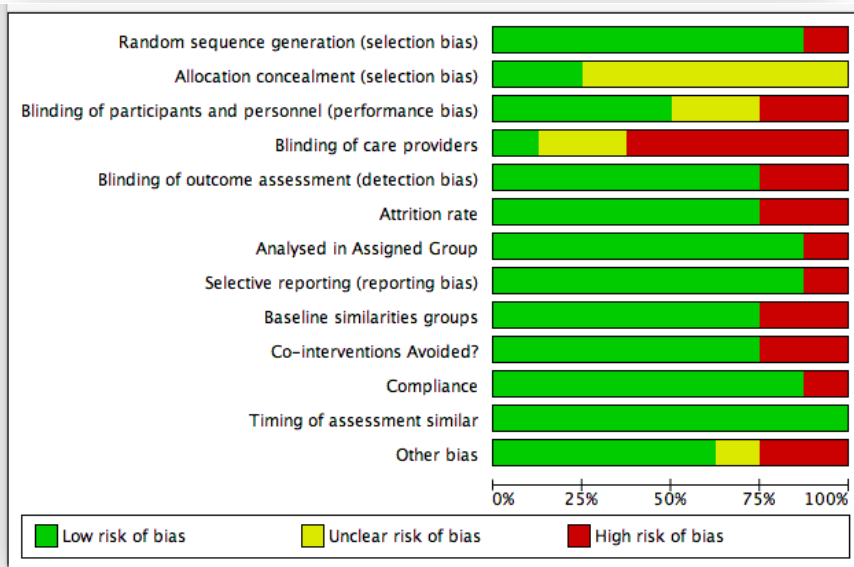


Figure 1: PRISMA flow chart demonstrating study search results.

Figure 2: Risk of Bias

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of care providers	Blinding of outcome assessment (detection bias)	Attrition rate	Analysed in Assigned Group	Selective reporting (reporting bias)	Baseline similarities groups	Co-interventions Avoided?	Compliance	Timing of assessment similar	Other bias
Louw et al. 2016	+	?	+	-	-	+	+	+	-	+	+	+	+
Malfliet et al., 2017	+	?	+	-	+	+	+	+	+	+	+	+	?
Moseley 2002	+	?	?	?	+	+	+	-	+	-	+	+	-
Moseley et al. 2004	-	?	+	+	-	+	-	+	+	+	+	+	-
Pires et al. 2015	+	+	?	?	+	-	+	+	+	+	+	+	+
Tellez-Garcia et al., 2015	+	?	-	-	+	+	+	+	+	+	+	+	+
Walti et al., 2015	+	?	-	-	+	+	+	+	+	-	+	+	+
Werner et al., 2016	+	+	+	-	+	-	+	+	-	+	-	+	+



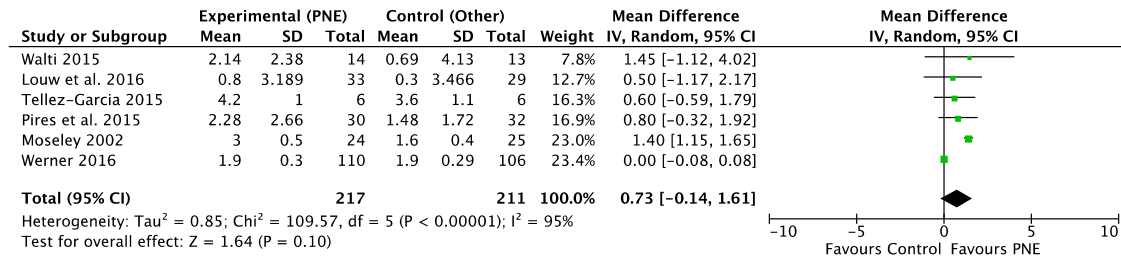


Figure 3: Forest plot of PNE versus alternative intervention in short-term

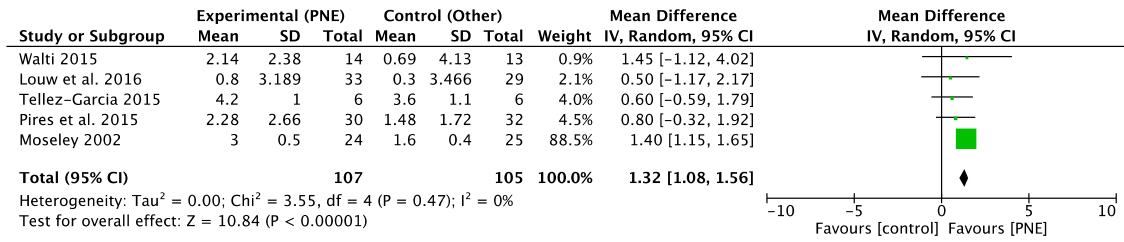


Figure 4: Forest plot of PNE with physiotherapy intervention versus PNE

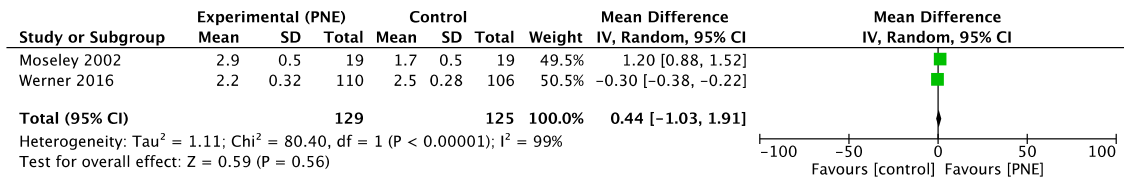


Figure 5: Forest plot to depict PNE versus alternative intervention at 12 months

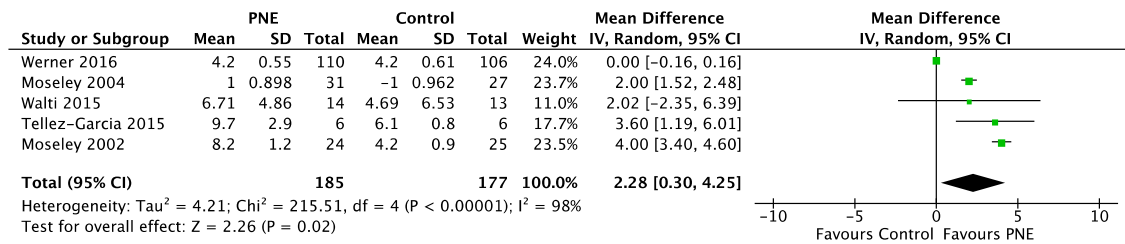


Figure 6: Forest Plot to depict combined RMDQ scores for PNE compared to alternative intervention in short-term

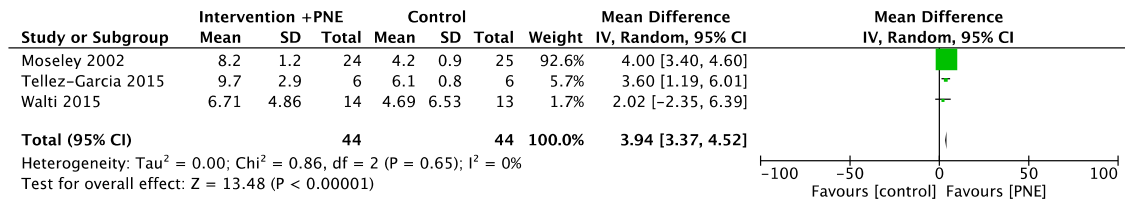


Figure 7: Forest plot to depict combined RMDQ scores for PNE in addition to physiotherapy intervention compared to physiotherapy interventions alone

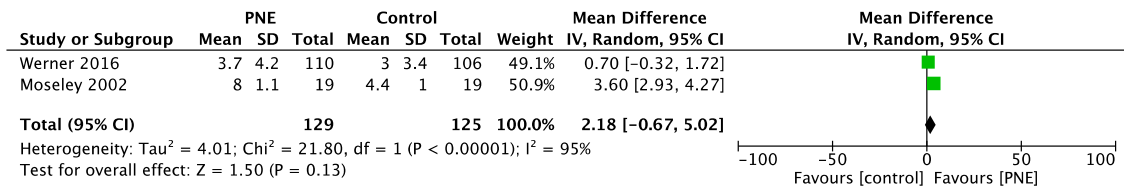


Figure 8: Forest plot to demonstrate the long-term effect of the addition of PNE compared to **controls on RMDQ disability scores**

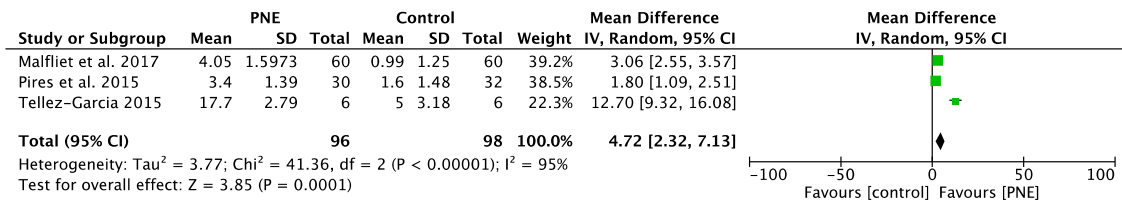


Figure 9: Forest plot to depict the effect of addition of PNE compared to controls on the TSK

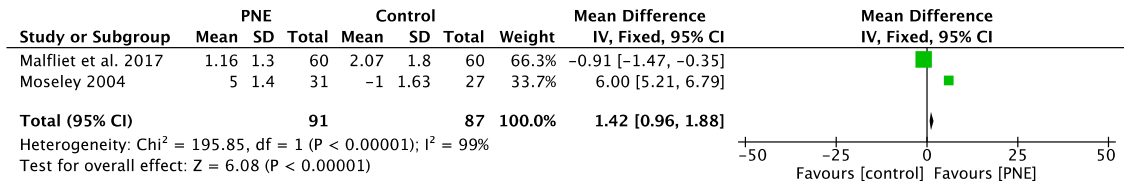


Figure 10: Forest plot to depict the effect of the addition of PNE compared to **controls on the PCS**

Figure S11

GRADE Analysis:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pain neuroscience education	no pain neuroscience education	Relative (95% CI)	Absolute (95% CI)		
Pain Short term (follow up: mean 31.8 days; assessed with: NRS; Scale from: 0 to 10)												
6	randomised trials	not serious 1,2,3,4,5,6,a	not serious	serious 1,2,3,4,5,6,b	serious 2,3,4,5,6,c	none	217	211	-	MD 0.73 higher (0.14 lower to 1.61 higher)	⊕⊕○○ LOW	
Pain ST (PNE+INTERVENTION_) (follow up: mean 32.6 days; assessed with: NUMERIC PAIN RATING SCALE; Scale from: 0 to 10)												
5	randomised trials	not serious 1,3,4,5,6,a	not serious	not serious	serious 3,4,5,6,c	none 1,6,d	107	105	-	MD 1.32 higher (1.08 higher to 1.56 higher)	⊕⊕⊕○ MODERATE	
RMDQ Short-term (follow up: mean 32.8 days; assessed with: RMDQ; Scale from: 0 to 24)												
5	randomised trials	not serious 1,2,3,5,7,a	not serious	serious 1,2,3,5,7,b	not serious	none	185	177	-	MD 2.28 higher (0.3 higher to 4.25 higher)	⊕⊕⊕○ MODERATE	
RMDQ LT (follow up: mean 12 months; assessed with: RMDQ; Scale from: 0 to 24)												
2	randomised trials	not serious 1,2,a	not serious	serious 1,2,a	serious 2,c	publication bias strongly suspected 1,f	129	125	-	MD 2.18 higher (0.67 lower to 5.02 higher)	⊕○○○ VERY LOW	
RMDQ Intervention +PNE (follow up: mean 40 days; assessed with: RMDQ; Scale from: 0 to 24)												
3	randomised trials	not serious 1,3,5,a	not serious	not serious	serious 9	none	44	44	-	MD 3.94 higher (3.37 higher to 4.52 higher)	⊕⊕⊕○ MODERATE	
Pain Long Term (follow up: mean 12 months; assessed with: NRS; Scale from: 0 to 10)												
2	randomised trials	not serious 1,2,a	serious 1,2,h	serious 1,2,i	not serious	publication bias strongly suspected 1,f	129	125	-	MD 0.44 higher (1.03 lower to 1.91 higher)	⊕○○○ VERY LOW	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pain neuroscience education	no pain neuroscience education	Relative (95% CI)	Absolute (95% CI)		
Tampa Scale of Kinesiophobia (follow up: mean 3.33 weeks; assessed with: Tampa Scale of Kinesiophobia; Scale from: 13 to 52)												
3	randomised trials	not serious	very serious ^{4,5,8,j}	not serious	very serious ^{4,5,8,k}	none	96	98	-	MD 4.72 higher (2.32 higher to 7.13 higher)	⊕○○○ VERY LOW	
PCS ST (follow up: mean 2.5 weeks; assessed with: Pain Catastrophizing Scale; Scale from: 0 to 52)												
2	randomised trials	not serious	very serious ^{7,8,l}	not serious	very serious ^{7,8,m}	none	91	87	-	MD 1.42 higher (0.96 higher to 1.88 higher)	⊕○○○ VERY LOW	

CI: Confidence interval; MD: Mean difference

Explanations

- a. All included studies had poor or unclear blinding of personnel, providers and or participants resulting in an increased level of bias.
- b. All studies apart from 2 compared various interventions alongside PNE against a control group. There were no direct comparisons of the same interventions with PNE.
- c. There is a small sample size and large confidence interval (crossing 0) suggesting poor precision of results.
- d. The authors of two included studies are prominent authors promoting the use of PNE and receiving royalties for its use
- e. One study compared PNE-only to education only, the other provided PNE alongside physiotherapy in comparison to a waiting list control.
- f. One of the studies included was authored by a prominent author in the PNE movement, receiving royalties for its use.
- g. Given the small total sample size, (<400) the domain of imprecision cannot be met
- h. The findings of the two studies were in direct opposition to each other.
- i. One study provided education only to both groups, whereas the other study provided physiotherapy treatment with or without a PNE explanation for a manual therapy technique.
- j. There is a large confidence interval, with minimal overlap between studies. There is also a high degree of heterogeneity (I²=95%)
- k. For a continuous outcome; there is a small sample size (<400) resulting in imprecision; further the effect size confidence interval is smaller than the minimal important difference (5.5 (Monticone et al., 2016))
- l. There is a significant variety in effect size and direction between the two studies. There is also significant heterogeneity.
- m. For a continuous outcome, there is a small sample size and an effect size less than the threshold of the MID of 12.8 points (Fernandes et al., 2012)

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3. Wälti P., Kool J., Luomajoki H. (2015). Short-term effect on pain and function of neurophysiological education and sensorimotor retraining compared to usual physiotherapy in patients with chronic or recurrent non-specific low back pain, a pilot randomized controlled trial. *BMC Musculoskelet Disord* 16(83)
4. Pires D., Cruz E.B., Caeiro C. (2015) Aquatic exercise and pain neurophysiology education versus aquatic exercise alone for patients with chronic low back pain: a randomised controlled trial. *Clin Rehabil* 29(6) 538-547.
5. Tellez-Garcia M., De-la-Llave-Rincon A., Salom-Moreno J., Palacios-Ceña M, Ortega-Santiago R. et al. (2015). Neuroscience education in addition to trigger point dry needling for the management of patients with mechanical chronic low back pain: a preliminary clinical trial. *J Bodyw Mov Ther* 19 464-472
6. Louw A., Farrell K., Landers M., Barclay M., Goodman E., et al. (2016). The effect of manual therapy and neuroplasticity education on chronic low back pain: a randomized clinical trial. *J Man Manip Ther* Sept 22 1-8
7. Moseley G.L., Nicholas M., Hodges P. (2004). A randomized controlled trial of intensive neurophysiology education in chronic low back pain. *Clin J Pain* 20 (5) 324-330.
8. Malfliet A., Kregel J., Meeus M., Rousset N., Danneels L., et al. (2017). Blended learning pain neuroscience education for people with chronic spinal pain: a randomized-controlled multi-centre trial. *Phys Ther* Awaiting Publication

List of Figures:

Figure 1: PRISMA flow chart demonstrating study search results.

Figure 2: Risk of Bias Summary

Figure 3: Forest plot of PNE versus alternative intervention in short-term

Figure 4: Forest plot of PNE with physiotherapy intervention versus PNE

Figure 5: Forest plot to depict PNE versus alternative intervention at 12 months

Figure 6: Forest Plot to depict combined RMDQ scores for PNE compared to alternative intervention in short-term

Figure 7: Forest plot to depict combined RMDQ scores for PNE in addition to physiotherapy intervention compared to physiotherapy interventions alone

Figure 8: Forest plot to demonstrate the long-term effect of the addition of PNE compared to control group on RMDQ disability scores

Figure 9: Forest plot to depict the effect of addition of PNE compared to control group on the TSK

Figure 10: Forest plot to depict the effect of the addition of PNE compared to control group on the PCS

Figure 11: GRADE analysis and explanation

#	Query	Limiters/Expanders	Last Run Via	Results
S17	S8 AND S16	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - AMED - The Allied and Complementary Medicine Database; MEDLINE;PsycINFO;SPORTDiscus with Full Text;AgeLine;CINAHL Plus with Full Text;PsycARTICLES	2,437
S16	S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - AMED - The Allied and Complementary Medicine Database; MEDLINE;PsycINFO;SPORTDiscus with Full Text;AgeLine;CINAHL Plus with Full Text;PsycARTICLES	61,308
S15	(explain pain)	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - AMED - The Allied and Complementary Medicine Database; MEDLINE;PsycINFO;SPORTDiscus with Full Text;AgeLine;CINAHL Plus with Full Text;PsycARTICLES	1,928
S14	(pain biology education)	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - AMED - The Allied and Complementary Medicine Database; MEDLINE;PsycINFO;SPORTDiscus with Full Text;AgeLine;CINAHL Plus with Full Text;PsycARTICLES	5
S13	(therapeutic neuroscience education)	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - AMED - The Allied and Complementary Medicine Database; MEDLINE;PsycINFO;SPORTDiscus with Full Text;AgeLine;CINAHL Plus with Full Text;PsycARTICLES	20
S12	(pain neuroscience education)	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - AMED - The Allied and Complementary Medicine Database; MEDLINE;PsycINFO;SPORTDiscus with Full Text;AgeLine;CINAHL Plus with Full Text;PsycARTICLES	90
S11	(pain neurophysiology education)	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - AMED - The Allied and Complementary Medicine Database; MEDLINE;PsycINFO;SPORTDiscus with Full Text;AgeLine;CINAHL Plus with Full Text;PsycARTICLES	45
S10	(pain education)	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - AMED - The Allied and Complementary Medicine Database; MEDLINE;PsycINFO;SPORTDiscus with Full Text;AgeLine;CINAHL Plus with Full Text;PsycARTICLES	5,542
S9	(MH "Patient Education")	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - AMED - The Allied and Complementary Medicine Database; MEDLINE;PsycINFO;SPORTDiscus with Full Text;AgeLine;CINAHL Plus with Full Text;PsycARTICLES	54,337
S8	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - AMED - The Allied and Complementary Medicine Database; MEDLINE;PsycINFO;SPORTDiscus with Full Text;AgeLine;CINAHL Plus with Full Text;PsycARTICLES	677,033

S7	backache OR (back ache)	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - AMED - The Allied and Complementary Medicine Database;MEDLINE;PsycINFO;SPORTDiscus with Full Text;AgeLine;CINAHL Plus with Full Text;PscARTICLES	11,250
S6	spine	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - AMED - The Allied and Complementary Medicine Database;MEDLINE;PsycINFO;SPORTDiscus with Full Text;AgeLine;CINAHL Plus with Full Text;PscARTICLES	177,884
S5	spinal	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - AMED - The Allied and Complementary Medicine Database;MEDLINE;PsycINFO;SPORTDiscus with Full Text;AgeLine;CINAHL Plus with Full Text;PscARTICLES	472,237
S4	lumbago	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - AMED - The Allied and Complementary Medicine Database;MEDLINE;PsycINFO;SPORTDiscus with Full Text;AgeLine;CINAHL Plus with Full Text;PscARTICLES	1,498
S3	lumbar	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - AMED - The Allied and Complementary Medicine Database;MEDLINE;PsycINFO;SPORTDiscus with Full Text;AgeLine;CINAHL Plus with Full Text;PscARTICLES	143,679
S2	(back pain)	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - AMED - The Allied and Complementary Medicine Database;MEDLINE;PsycINFO;SPORTDiscus with Full Text;AgeLine;CINAHL Plus with Full Text;PscARTICLES	103,563
S1	(MH "Low Back Pain")	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - AMED - The Allied and Complementary Medicine Database;MEDLINE;PsycINFO;SPORTDiscus with Full Text;AgeLine;CINAHL Plus with Full Text;PscARTICLES	32,106



PRISMA 2009 Checklist ----- EUROPEAN JOURNAL OF PAIN



Section/topic	#	Checklist item	Reported on page #
TITLE PAGE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
Funding	2	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review on your title page.	1
Bulleted statements	3	'Database?' and ' what does this review add?'.	1
ABSTRACT			
Structured summary	4	Provide a structured summary including, as applicable: background and objective; databases and data treatment; results, conclusion; systematic review registration number.	2
INTRODUCTION			
Rationale	5	Describe the rationale for the review in the context of what is already known.	4, 5
Objectives	6	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5, 6
METHODS			
Protocol and registration	7	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	8	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5,6
Information sources	9	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	10	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
Study selection	11	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	12	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	13	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	14	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7



PRISMA 2009 Checklist ----- EUROPEAN JOURNAL OF PAIN



Section/topic	#	Checklist item	Reported on page #
Summary measures	15	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	16	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I ²) for each meta-analysis.	8
Risk of bias across studies	17	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8
Additional analyses	18	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	19	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9
Study characteristics	20	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9,10
Risk of bias within studies	22	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	11
Results of individual studies	23	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	11-15
Synthesis of results	24	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	11-15
Risk of bias across studies	25	Present results of any assessment of risk of bias across studies (see Item 15).	15
Additional analysis	26	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	27	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	16
Limitations	28	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	17,19
Conclusions	29	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	19,20

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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