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Outcome measures in randomized controlled trials of Neuropathic Pain conditions: A systematic review of systematic reviews and recommendations for practice

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Abstract:	Objectives: Neuropathic pain (NeP) is a prevalent, disabling, multi-dimensional condition with significant morbidity; however there appears to be a variable approach in the use of outcome measures in NeP trials. A search of systematic reviews of interventional randomized controlled trials for NeP was undertaken to investigate the range and types of outcome measures employed to determine treatment effects. Methods: Keywords and MESH searches were conducted in five electronic databases from inception to 31st January 2012. Full text English language reviews based on various acute and chronic NeP conditions were included. Two independent reviewers screened papers for inclusion, extracted data, and assessed the quality of reviews. Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines were used to critically appraise the reviews. Results: A total of 46 studies were identified: the majority of reviews (n=28/46, 61%) scored well on the PRISMA (PRISMA scores of 20-27/27). Change in levels or intensity of pain were used by the majority of studies as the primary outcome measure in intervention studies (n=40/46 studies, 87%). Few studies employed a functional outcome measure (FOM) as either a primary or secondary outcome measure (n=7/46, 15% of studies). Discussion: These results demonstrate that measures of pain are predominantly used in trials of NeP conditions and highlight the scant usage of FOMs. The lack of standardization for the diagnostic criteria in NeP trials is also an issue which needs to be considered for future research and guideline development.

Reviewer 1		
COMMENT	EXPLAINATION	MODIFICATIONS (Highlighted text)
It seems you missed my point. You included a review of disease modifying therapies (not symptomatic pain therapies) 1. You included a review and not the original articles 2. The review was of a disease modifying therapy - pain was not the primary efficacy endpoint in most or all of the trials in the review 3. If you feel that these interventions (i.e., disease modifying trials) are under your purview, there are dozens of articles that you have left out	We note the reviewer's concern here. Since this is a systematic review of systematic reviews, there is a potential that many other similar studies (based on disease modifying therapies) might have left out, so we have agreed to exclude Chalk C et al. systematic reviews from the manuscript.	Necessary modifications have been made in the sections of Abstract, Methodology (inclusion criteria), Results, Discussion, Figure, Tables 2, 4, 5, and Reference list.

INTRODUCTION

Defining 'Neuropathic Pain- NeP' has proved a challenge to health care,[1] due primarily to the lack of a 'gold standard' test to confirm the presence of this pain state[2] and resultant variability in diagnostic classifications among both clinicians and researchers. The original IASP (International Association for the Study of Pain) definition of NeP, "*pain initiated or caused by a primary lesion or dysfunction in the nervous system*"[3] has been proposed to be replaced by NeuPSIG (IASP Special Interest Group on NeP) with the wording of "*pain arising as a direct consequence of a lesion or disease affecting the somatosensory system*".[2] The rationale for this new definition is that 'dysfunction', which in itself is a very vague term, is not able to differentiate between NeP and other pain states such as inflammatory pain[4] and musculoskeletal pain.[5]

For chronic pain conditions, the Initiative on Methods, Measurement and Pain Assessment in Clinical Trials (IMMPACT) has recommended use of six core outcome domains in clinical trials: pain; physical functioning; emotional functioning; participant rating of improvement and satisfaction with treatment; symptoms and adverse events; and participant disposition.[6] Importantly, it has been found that due to the range and variability of outcome assessments employed in pain intervention studies, decisions on comparative effectiveness for available treatments remains problematic.[6] Thus, to measure the efficacy and effectiveness in clinical trials of chronic pain, a set of core outcome measures for each domain has also been recommended.[7] In addition, outcome measures are also recommended for use for specific chronic pain conditions such as osteoarthritis,[8] low back pain,[9, 10] and NeP.[5, 11]

Both the European Federation of Neurological Societies (EFNS)[5] and the Neuropathic Pain Special Interest Group (NeuPSIG)[11] have evaluated the existing evidence for methods of NeP assessment, and formulated guidelines for assessing and managing patients. For NeP intensity, usage of one-dimensional pain scales (e.g. Visual Analogue Scale and pain relief scales) were highly recommended over the use of non-specific multidimensional scales (e.g. McGill Pain Questionnaire).[5] It has also been previously stated that rating of severity and unpleasantness of pain should be done separately.[5, 12] Since these chronic conditions are multidimensional, both EFNS and NeuPSIG guidelines have recommended that, in conjunction to pain, quality of life (mood, sleep, anxiety and depression), as well as functional capacity (physical, cognitive, emotional and social), should also be assessed as secondary outcome measures. [5, 11]

Despite the extensive research base in NeP, and the availability of IMMPACT guidelines for chronic pain assessment and EFNS & NeuPSIG guidelines for NeP assessment, to our knowledge, outcomes used in NeP trials have not previously been investigated. Thus, the objective of this review was to systematically review systematic reviews of interventional RCTs for NeP to investigate the range and types of outcome measures used to determine treatment effect.

METHOD

Eligibility Criteria: Selection criteria for this review included systematic review designs of interventional RCTs in the symptomatic management of NeP conditions, as defined by the Clinical Resource Efficiency Support Team (CREST).[13] Systematic reviews of both acute (less than 3 months duration) and chronic pain conditions (3 months duration or more)[14] were

included. Narrative reviews or systematic reviews of non-RCTs were not included. Systematic reviews were restricted to those published in English.

Information Sources: The following electronic databases were searched: Ovid Medline, CINAHL, The Cochrane central register of controlled trials, AMED, and Web of Science (WOS) (from database inception to 31 January 2012). The search strategy for Ovid Medline is detailed in Table 1; this search strategy was amended for other databases. Reference lists of included systematic reviews were not searched for further systematic reviews.

Study Selection: Two reviewers (PM and LC), independently selected articles for potential eligibility at title and abstract stages. Full text articles of all potentially eligible abstracts were retrieved for application of the eligibility criteria. To determine the usability of Treede's Guidelines for reporting NeP, all recently published (2008 onwards) systematic reviews were graded for the level of certainty for the presence of NeP[2] independently by two reviewers (PM and LC). The grading system is detailed in Table 3.

Data collection process and data items: The following data were collected and tabulated from each of the included systematic reviews: study reference, objectives, population, number of RCTs, intervention type, primary and secondary outcome measures, and results. Data extraction was carried out independently by two reviewers (PM and SW) using standardised forms, with consensus meetings and opinions from other reviewers (LC and PH) to resolve any disagreements.

Risk of bias in individual reviews: The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA)[15] was independently used by two reviewers (PM and LC) to critically appraise the included reviews. The PRISMA has been used previously in other

systematic reviews of systematic reviews to critically appraise the quality of systematic reviews.[16] Disagreements regarding inclusion of individual reviews and PRISMA scoring were resolved by discussion with reviewers (PH and DB). Reviewers were not blind to the journal affiliation or authors of the systematic reviews. Reviews were not excluded based on their PRISMA scores.

Summary measures and data synthesis: Summary measures (mean difference (MD), weighted mean difference (WMD), Relative Risk Ratio (RRR), and Odds Ratio (OR)) were extracted for each outcome measure for each systematic review. Outcome measures used by each systematic review were grouped under the four recommended core chronic pain outcome domains: pain intensity, physical functioning, emotional functioning, and participant's rating of overall improvement (assessed by the Patient Global Impression of Change scale, PGIC).[7] Each domain was further sub-grouped based upon the summary measure used in the review, and the amount of change determined to be clinically relevant.

RESULTS

Study selection: Figure 1 summarises the study selection process. The search strategy resulted in 498 systematic reviews. After accounting for duplicate removal, title screening, abstract screening, and assessment of eligibility of full text articles, 61 systematic reviews were identified and retrieved for full text review.

Common reasons for exclusion (n=15) were: eight reviews were based on non- RCTs (Furlan AD 2010, Kuwabara S 2008, Mailis-Gagnon A 2004, Mulvey MR 2010, Sekula RF 2011, Simpson EL 2009, Sultan A 2008, and Watson CPN 2010); in five reviews, it was not clearly evident if patients had sensory involvement i.e. presence of pain (Allen D 2007,

Lancaster T 1995, Lockhart P 2009, Salinas RA 2010, and Teixeira LJ 2011); one review was excluded as it primarily included pain immediately after surgery (Toms L 2008); and one review was excluded as its focus was on disease modifying therapy not symptomatic pain therapy (Chalk C 2007). A total of 46 reviews remained after exclusion.

Characteristics of included reviews: Details of all 46 eligible reviews are given in Table 2. Systematic reviews fulfilled all selection criteria and presented data on various underlying neuropathic conditions.

Half, 57% (26/46) of systematic reviews included the following study populations: diabetic neuropathy (Chen W 2011,[17] Hurley RW 2008,[18] Ites KI 2011,[19] Li H 2008,[20] and Wong MC 2007[21]), post herpetic neuralgia (Alper BS 2002,[22] Hempenstall K 2005,[23] Khaliq W 2007,[24] and Volmink J 1996[25]), trigeminal neuralgia (Chole R 2007,[26] Liu H 2010,[27] Lopez BC 2004,[28] Yang M 2011,[29] and Zakrzewska JJM 2008[30]), or mixed NeP where all the covered conditions were well tabulated (Challapalli V 2005,[31] Collins SL 2000,[32] Eccles NK 2005,[33] Gill D 2011,[34] Goodyear-Smith F 2009,[35] Häuser W 2011,[36] McQuay HJ 1996,[37] Moore RA 2009,[38] Moore RA 2011,[39] Straube S 2008,[40] Straube S 2010,[41] and Wiffen PJ 2011[42]). The systematic reviews based on mixed NeP populations were only included if a sub-group analysis of the underlying conditions was performed.

Half of the remaining reviews (10/20 systematic reviews) were heterogeneous studies which included NeP of any aetiology (Ang CD 2008,[43] Eisenberg E 2005,[44] Eisenberg E 2006,[45] Eisenberg E 2006,[46] Hollingshead J 2006,[47] Lunn MP 2009,[48] Mason L 2004,[49] Moore RA 2005,[50] Papaleontiou M 2010,[51] Pittler MH 2008,[52] Plested M 2010,[53] Saarto T 2007,[54] Seidel S 2008,[55] Tremont-Lukats IW 2005,[56] White CM 2004,[57] and Wiffen PJ 2011[58]). There were four more reviews based on different conditions; Herpes Zoster (Cao H 2010[59]), Painful

HIV-associated sensory neuropathy (Phillips TJC 2010[60]), Entrapment Neuropathy (Caliandro P 2011[61] and Traumatic Spinal cord injury & Central NeP (Denkers MR 2002[62]).

Grading system for the presence of NeP: As Treede's guidelines for reporting NeP were published in 2008, only recently published systematic reviews (after 2008) were graded for the presence of a clear statement criterion for the diagnosis of NeP.[2] Of those 18 systematic reviews, we could identify only three reviews that met the criteria for definite (Chen W 2011),[17] probable (Moore RA 2009),[38] or possible (Straube S 2010)[41] NeP (Table 3). The rest of the reviews (15/18) did not provide sufficient or clear information for a NeP grade (Table 2) to be given; we were therefore unable to classify those reviews under any designated NeP category.

It has been observed that pain and other neurological symptoms due to peripheral or central nervous system disease or injury present in very similar ways, and this observation has led to a group designation for NeP.[3] However the study population for the current systematic review covered within the included reviews all the common conditions associated with NeP (CREST, 2008).[13]

Critical appraisal of included reviews: PRISMA scoring for the reviews are detailed in Table 4: 28 out of 46 reviews achieved 20-27 points on the PRISMA, 14 scored 10-19 points, and four scored 9 points or less. Higher scores reflect higher internal validity of the systematic review.[15]

Outcome measures

Pain intensity: Changes in levels of pain intensity were used as the primary outcome measure in 40 out of 46 (87%) included systematic reviews (Table 2). A variety of pain scales

were used to measure intensity of pain (or its relief): Visual Analogue Scales (VAS), Verbal Rating Scales (VRS), Likert pain rating scales, the McGill Pain Questionnaire (MPQ), and Numerical Rating Scales (NRS).

Physical functioning: Only 7 of the 46 (15%) included systematic reviews used a functional outcome measure as a primary or secondary outcome measure (Table 5). Ten different functional outcome measures were reported: Disability of the Arm, Shoulder and Hand questionnaire (DASH), Pain Disability Index, SF-36: physical functional component, daily activities measured by Video Relay Service (VRS), function interference measured by NRS, Western Ontario and McMaster Osteoarthritis Index (WOMAC): functional component, timed scored functional activity, functional reach test, timed meter to walk test (6m and 15m walking speed), and interference with daily activities.

Emotional functioning: 10/46 (i.e. 22%) systematic reviews assessed the emotional domain (Alper BS 2002, Caliandro P 2011, Chen W 2011, Lunn MP 2009, Papaleontiou M 2010, Plested M 2010, Saarto T 2007, Seidel S 2008, White CM 2004, and Zakrzewska JJM 2011). A range of measures were employed including scales for Quality of Life to evaluate depression, anxiety, and sleep, as part of the Health Survey (SF-36), (SF-12), and (SF-MCQ).

Participant's rating of overall improvement: The PGIC (Patient global impression of change) score was employed in 15/46 (33%) systematic reviews. The outcome was described by the number of patients with a "moderate", "good" or "notable" improvement in their global response to treatment, or 'at least moderate pain relief' on a suitable categorical scale.

Subgrouping these reviews on the basis of summary measures adopted, demonstrated that 16/46 (35%) reviews used different forms of means to describe their treatment effects, including mean difference (MD), weighted mean difference (WMD) and standardized mean difference (SMD) at 95% of confidence interval levels (CIs). Relative Risk Ratio (RRR) and Odds Ratio (OR) were alternatively used to summarize the results; of the 33 (26 and 7) systematic reviews which adopted RR or OR (respectively), 16 (14 and 2) reviews could be simply categorized into a dichotomous response of yes/no (i.e. 50% pain relief or not). Six systematic reviews described their results narratively, and 13 reviews also calculated the Number Needed to Treat (NNT).

DISCUSSION

To our knowledge, this is the first systematic review of systematic reviews to investigate the usage of various pain and functional outcome measures in intervention trials of NeP conditions. The most interesting finding from the current review is that, although the majority of reviews scored highly on the PRISMA scale for internal validity, their focus in outcome measures were almost exclusively on pain intensity and not within other domains, recommended by IMMPACT,[7] EFNS,[5, 63-65] and NeuPSIG.[11] Thus the findings from the current review were in contrast to other areas of pain management, where the aim is more commonly focussed on reduction of disability (e.g. inactivity) and enabling the person to achieve independence.[66] Changes in level or intensity of pain was the most commonly used primary endpoint in NeP trials, with the majority of studies using either the VAS and/or the NRS pain measurement scales. This particular finding was in accordance with NeuPSIG guidelines in which VAS and NRS are highly recommended to assess intensity of pain and treatment effect.[11]

Despite our expectations for the usage of multidimensional pain scales, our results showed that one-dimensional measurements of pain were employed in 40/46 systematic reviews. An international, informally organized network aimed at improving Outcome Measurement in Rheumatology (OMERACT)[8] recommended a core set of four domains (pain, physical function, patient global assessment and, for studies of at least one year: joint imaging) for outcome assessment, for future clinical trials of hip, knee and hand osteoarthritis. However a recent systematic review of chronic musculoskeletal pain outcomes,[67] reported that over half (54%) of all pain outcome measures were based on uni-dimensional measures such as VAS. In contrast, only 16% used multidimensional scales (e.g. MPQ) and 27% were multi-item scales that measured one dimension of pain (e.g. Neck Disability Index). The results of the current review demonstrate that the use of single item pain measures as the primary outcome measure is a common finding in the majority of chronic pain studies. There may be a number of reasons behind this finding, such as: the time required for assessment of other related domains (i.e. physical functioning, emotional impact, and global improvement), the patient burden associated with lengthy assessment procedures, or alternatively because research is focussed exclusively on pain intensity.[67]

Additionally, for the recently published systematic reviews, we determined the level of certainty for the presence of NeP in accordance with Treede's grading system.[2] There was little consistency across recent reviews with respect to Treede's guidelines for reporting NeP. Given that these criteria were published relatively recently (in 2008), the reviews published in or before 2008 were not evaluated for this property. However, even for these recently published systematic reviews, only a small number of studies followed the specified assessment and diagnostic criteria (Table 2). The majority of studies provided insufficient/

unclear information about diagnosis and therefore according to this grading system, if a patient's inclusion criterion does not fulfil the criteria for any of the three grading levels, then the study population is classified as unlikely to have a NeP condition. According to the IASP revised definition of NeP, it is a clinical description (and not a diagnosis) and there is a requirement for a lesion of the nervous system to be present, as a precursor to the pain state.[14] However, others state that when no lesion can be demonstrated, the limits of current diagnostic technology do not always allow the possibility of NeP to be excluded.[68] Thus, it can be argued that there is a need to adopt and utilise validated criteria to define and grade NeP in research, as well as clinical practice.

In order to determine clinically important differences in pain intensity, IMMPACT also proposed criteria to determine the patient's evaluation of change. It has been suggested that a raw score change of approximately 1 point represents 15-20% change and signifies "less important change" in the pain scores. Changes of approximately 2 points i.e. 30-36% change represent "much better", "much improved", or "meaningful" decrease in chronic pain. Finally, a decrease of ≥4 points denoting ≥50% change appears to represent a "very much improved", "treatment success", or "satisfactory improvement" of pain.[7] Because of the ease of administration, it has become a "gold standard" of outcome in chronic pain research.[69] It is noteworthy that of the 40 reviews which employed pain as the primary outcome measure, only 23 followed the benchmarks provided by IMMPACT. Nine reviews selected ≥50% pain relief, as their primary outcome variable, while the other eight employed pain intensity reduction of ≥30- 50%.

Pain has always been considered as a risk factor for, as well as a cause of disability.[70] It has also been shown that functional losses as well as mood disturbances are directly

related to an increased severity of peripheral NeP.[71] Moreover, it is not only activities of daily living which are affected by this multi-disabling condition, but also the individual's work potential, raising the economic burden both at individual and society level.[72] Beyond this, the relationship between pain and functional limitation is varied and moderated by a number of factors, including psychological and social issues, and level of emotional support.[69] Our results emphasise that multi-dimensional pain scales and measures of functional and emotional responses to pain are needed to better evaluate response to pain interventions, and also to allow better modelling of the factors which mediate and moderate such relationships. Multi-dimensional measures would also help to better evaluate how and why patients fail to respond to specific interventions and also potentially allow targeting of the key factors which are driving the patient's response to the intervention.

Strengths and limitations: A number of strengths and limitations in this review should be acknowledged.

Firstly, it is acknowledged that 'Neuropathic Pain conditions' is an umbrella term which covers a number of different conditions such as diabetic neuropathy, trigeminal neuralgia, and post herpetic neuralgia.[13] For the search strategy, MESH terms/ key words indexed for neuropathy, neuralgia, and neurodynia were used to be as inclusive as possible. It is acknowledged that each health condition could have been separately searched and potentially this may have lessened the chances of missing systematic reviews. However, it is anticipated that these reviews would have been identified during the hand search process.

Secondly, as this was a systematic review of systematic reviews, the emphasis was at the review level, rather than investigating individual RCTs. Each systematic review included

numerous RCTs, for example Hauser W (2011)[36] reviewed 142 RCTs. Each systematic review detailed (usually in table format) each outcome measure used in the included RCTs. However, it is possible that not all outcome measures employed in the RCTs were fully described. Another possible reason for the usage of pain outcome measure in isolation may be that many included studies were apparently industry-driven, and therefore aimed at approval or registration, or new indication for a drug, rather than investigating the full profile of the effects.

Thirdly, we rated the recently published reviews for the presence of NeP based on an internationally recommended grading criteria[2] and found that the majority of reviews simply stated the condition, without clear or sufficient information regarding the likelihood of NeP being present. The remainder of the studies (published before 2008) were not assessed as these could not be expected to meet the same criteria. As the main aim of this systematic review was to investigate the range and type of outcome measures used in (RCTs) of NeP, it can be argued that the presence/ absence of an NeP grading system does not affect the quality or types of outcome measures employed. Thus systematic reviews were not excluded based on these criteria.

Lastly, internationally recommended systematic review reporting guidelines (PRISMA) were followed for scoring the internal validity or methodological reporting of included reviews. Other methodological quality checklists of systematic reviews are also available including: Critical Appraisal Skills Program of systematic reviews (CASP),[73] Aggressive Research Intelligence Facility (ARIF),[74] and Assessment of Multiple Systematic Reviews (AMSTAR).[16] However instances of poor reporting of key information published in systematic reviews has been identified as an issue, which diminishes their value to clinicians

and researchers.[15] As the PRISMA checklist has already been used to check out the methodological quality of the Cochrane review,[75] to report the methodological quality, its use was preferred.

Conclusion: We have presented extensive data which demonstrates that measures of pain are predominantly used in trials of NeP conditions and highlight the scant usage of physical FOMs. Since NeP is a multi-disabling condition with significant associated morbidity, usage of physical and emotional functional measures along with severity of pain as core outcomes is a key recommendation for future research in NeP intervention studies.

Our analysis also showed that in recently published reviews, there is a lack of standardization of diagnostic criteria in NeP trials. Since appropriate diagnosis followed by the earliest appropriate management remains the primary target to minimise the risks of comorbidities and disabilities, this issue needs to be considered for future research and guidelines development.

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All authors declare that there exist no conflicts of interest associated with the current study.

FIGURE LEGEND

Figure 1. Flow diagram summarising systematic search and study selection process

REFERENCES

1. International Association for the Study of Pain. Diagnosis and Classification of Neuropathic Pain [Web Page]. Available at http://www.iasp-pain.org/AM/AMTemplate.cfm?Section=Home,Home&TEMPLATE=/CM/ContentDisplay.cfm&SECTION=Home,Home&CONTENTID=15084.

2. Treede RD. Redefinition of neuropathic pain and a grading system for clinical use: consensus statement on clinical and research diagnostic criteria. *Neurology* 2008;70:1630.

3. Merskey H and Bogduk N. *Classification of Chronic Pain: Descriptions of Chronic Pain Syndromes and Definitions of Pain Terms*. Seattle: IASP Press, 1994.

4. Backonja MM. Defining neuropathic pain. *Anesthesia and Analgesia* 2003;97:785-790.

5. Cruccu G, Sommer C, Anand P, et al. EFNS guidelines on neuropathic pain assessment: Revised 2009. *European Journal of Neurology* 2010;17:1010-1018.

6. Turk DC, Dworkin RH, Allen RR, et al. Core outcome domains for chronic pain clinical trials: IMMPACT recommendations. *Pain* 2003;106:337-345.

7. Dworkin RH. Interpreting the Clinical Importance of Treatment Outcomes in Chronic Pain Clinical Trials: IMMPACT Recommendations. *The journal of pain* 2008;9:105-121.

8. Bellamy N, Kirwan J, Boers M, et al. Recommendations for a core set of outcome measures for future phase III clinical trials in knee, hip, and hand osteoarthritis. Consensus development at OMERACT III. *Journal of Rheumatology* 1997;24:799-802.

9. Deyo RA, Battie M, Beurskens AJHM, et al. Outcome measures for low back pain research: A proposal for standardized use. *Spine* 1998;23:2003-2013.

10. Ostelo RWJG and de Vet HCW. Clinically important outcomes in low back pain. *Best Practice and Research: Clinical Rheumatology* 2005;19:593-607.

11. Haanpää M, Attal N, Backonja M, et al. NeuPSIG guidelines on neuropathic pain assessment. *PAIN* 2011;152:14-27.

12. Smith WB. The meaning of pain: cancer patients' rating and recall of pain intensity and affect. *Pain (Amsterdam)* 1998;78:123-129.

13. Clinical Resource Efficiency Support Team (CREST). Guidelines on the management of neuropathic pain [Web Page]. Available at http://www.thblack.com/links/RSD/CRESTManagementNeuropathicPainGuidelines.pdf. Accessed Sept, 2012.

14. Merskey H and Bogduk N. *Classification of Chronic Pain, Part III: Pain Terms, A Current List with Definitions and Notes on usage* Seattle: IASP Press, 2011.

15. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: Explanation and elaboration. *PLoS Medicine* 2009;6.

16. Shea BJ, Grimshaw JM, Wells GA, et al. Development of AMSTAR: A measurement tool to assess the methodological quality of systematic reviews. *BMC Medical Research Methodology* 2007;7.

17. Chen W, Zhang Y and Liu JP. Chinese herbal medicine for diabetic peripheral neuropathy. *Cochrane database of systematic reviews (Online)* 2011.

18. Hurley RW, Lesley MR, Adams MCB, et al. Pregabalin as a Treatment for Painful Diabetic Peripheral Neuropathy: A Meta-Analysis. *Regional Anesthesia and Pain Medicine* 2008;33:389-394.

19. Ites KI, Anderson EJ, Cahill ML, et al. Balance interventions for Diabetic Peripheral Neuropathy: A systematic review. *Journal of Geriatric Physical Therapy* 2011;34:109-116.

20. Li H. Effectiveness of the anodyne therapy system in treating diabetic peripheral neuropathy: a systematic review. *Physical therapy reviews* 2008;13:395-404.

21. Wong MC, Chung JWY and Wong TKS. Effects of treatments for symptoms of painful diabetic neuropathy: Systematic review. *BMJ* 2007;335:87-90.

22. Alper BS and Lewis PR. Treatment of postherpetic neuralgia: A systematic review of the literature. *Journal of Family Practice* 2002;51:121-128.

23. Hempenstall K, Nurmikko TJ, Johnson RW, et al. Analgesic therapy in postherpetic neuralgia: A quantitative systematic review. *PLoS Medicine* 2005;2:0628-0644.

24. Khaliq W, Alam S and Puri N. Topical lidocaine for the treatment of postherpetic neuralgia. *Cochrane Database of Systematic Reviews* 2007.

25. Volmink J, Lancaster T, Gray S, et al. Treatments for postherpetic neuralgia: A systematic review of randomized controlled trials. *Family Practice* 1996;13:84-91.

26. Chole R, Patil R, Degwekar SS, et al. Drug Treatment of Trigeminal Neuralgia: A Systematic Review of the Literature. *Journal of Oral and Maxillofacial Surgery* 2007;65:40-45.

27. Liu H, Li H, Xu M, et al. A systematic review on acupuncture for trigeminal neuralgia. *Alternative therapies in health and medicine* 2010;16:30-35.

28. Lopez BC, Hamlyn PJ, Zakrzewska JM, et al. Systematic Review of Ablative Neurosurgical Techniques for the Treatment of Trigeminal Neuralgia. *Neurosurgery* 2004;54:973-983.

29. Yang M, Zhou M, He L, et al. Non-antiepileptic drugs for trigeminal neuralgia. *Cochrane database of systematic reviews (Online)* 2011;1.

30. Zakrzewska JJM and Linskey ME. Neurosurgical interventions for the treatment of classical trigeminal neuralgia. *Cochrane Database of Systematic Reviews* 2008.

31. Challapalli V, Tremont-Lukats IW, McNicol ED, et al. Systemic administration of local anesthetic agents to relieve neuropathic pain. *Cochrane database of systematic reviews (Online)* 2005.

32. Collins SL, Moore RA, McQuay HJ, et al. Antidepressants and anticonvulsants for diabetic neuropathy and postherpetic neuralgia: A quantitative systematic review. *Journal of Pain and Symptom Management* 2000;20:449-458.

33. Eccles NK. A critical review of randomized controlled trials of static magnets for pain relief. *Journal of Alternative and Complementary Medicine* 2005;11:495-509.

34. Gill D, Derry S, Wiffen PJ, et al. Valproic acid and sodium valproate for neuropathic pain and fibromyalgia in adults. *Cochrane database of systematic reviews (Online)* 2011.

35. Goodyear-Smith F and Halliwell J. Anticonvulsants for neuropathic pain: Gaps in the evidence. *Clinical Journal of Pain* 2009;25:528-536.

36. Häuser W, Bartram-Wunn E, Bartram C, et al. Systematic review: Placebo response in drug trials of fibromyalgia syndrome and painful peripheral diabetic neuropathy - Magnitude and patient-related predictors. *Pain* 2011;152:1709-1717.

37. McQuay HJ, Tramèr M, Nye BA, et al. A systematic review of antidepressants in neuropathic pain. *Pain* 1996;68:217-227.

38. Moore RA, Straube S, Wiffen PJ, et al. Pregabalin for acute and chronic pain in adults. *Cochrane Database of Systematic Reviews* 2009.

39. Moore RA, Wiffen PJ, Derry S, et al. Gabapentin for chronic neuropathic pain and fibromyalgia in adults. *Cochrane database of systematic reviews (Online)* 2011;3.

40. Straube S, Derry S, McQuay HJ, et al. Enriched enrolment: Definition and effects of enrichment and dose in trials of pregabalin and gabapentin in neuropathic pain. A systematic review. *British Journal of Clinical Pharmacology* 2008;66:266-275+334.

41. Straube S, Derry S, Moore RA, et al. Cervico-thoracic or lumbar sympathectomy for neuropathic pain and complex regional pain syndrome. *Cochrane database of systematic reviews (Online)* 2010;7.

42. Wiffen PJ, Derry S and Moore RA. Lamotrigine for acute and chronic pain. *Cochrane database of systematic reviews (Online)* 2011;2.

43. Ang CD, Alviar MJM, Dans AL, et al. Vitamin B for treating peripheral neuropathy. *Cochrane Database of Systematic Reviews* 2008.

44. Eisenberg E, McNicol ED and Carr DB. Efficacy and safety of opioid agonists in the treatment of neuropathic pain of nonmalignant origin: Systematic review and meta-analysis of randomized controlled trials. *JAMA* 2005;293:3043-3052.

45. Eisenberg E, McNicol ED and Carr DB. Efficacy of mu-opioid agonists in the treatment of evoked neuropathic pain: Systematic review of randomized controlled trials. *European Journal of Pain* 2006;10:667-676.

46. Eisenberg E, McNicol E and Carr DB. Opioids for neuropathic pain. *Cochrane database of systematic reviews (Online)* 2006;3.

47. Hollingshead J, Dühmke RM and Cornblath DR. Tramadol for neuropathic pain. *Cochrane database of systematic reviews (Online)* 2006;3.

48. Lunn MP, Hughes RA and Wiffen PJ. Duloxetine for treating painful neuropathy or chronic pain. *Cochrane database of systematic reviews (Online)* 2009.

49. Mason L, Moore RA, Derry S, et al. Systematic review of topical capsaicin for the treatment of chronic pain. *BMJ* 2004;328:991-994.

50. Moore RA and McQuay HJ. Prevalence of opioid adverse events in chronic non-malignant pain: systematic review of randomised trials of oral opioids. *Arthritis research & therapy* 2005;7:R1046-1051.

51. Papaleontiou M, Henderson Jr CR, Turner BJ, et al. Outcomes associated with opioid use in the treatment of chronic noncancer pain in older adults: A systematic review and meta-analysis. *Journal of the American Geriatrics Society* 2010;58:1353-1369.

52. Pittler MH and Ernst E. Complementary therapies for neuropathic and neuralgic pain: Systematic review. *Clinical Journal of Pain* 2008;24:731-733.

53. Plested M. Pregabalin, the lidocaine plaster and duloxetine in patients with refractory neuropathic pain: A systematic review. *BMC neurology* 2010;10:116.

54. Saarto T and Wiffen PJ. Antidepressants for neuropathic pain. *Cochrane Database of Systematic Reviews* 2007.

55. Seidel S, Aigner M, Ossege M, et al. Antipsychotics for acute and chronic pain in adults. *Cochrane Database of Systematic Reviews* 2008.

56. Tremont-Lukats IW, Challapalli V, McNicol ED, et al. Systemic administration of local anesthetics to relieve neuropathic pain: A systematic review and meta-analysis. *Anesthesia and Analgesia* 2005;101:1738-1749.

57. White CM, Pritchard J and Turner-Stokes L. Exercise for people with peripheral neuropathy. *Cochrane database of systematic reviews (Online)* 2004.

58. Wiffen PJ, Derry S, Moore RA, et al. Carbamazepine for acute and chronic pain in adults. *Cochrane database of systematic reviews (Online)* 2011;1.

59. Cao H, Zhu C and Liu J. Wet cupping therapy for treatment of herpes zoster: a systematic review of randomized controlled trials. *Alternative therapies in health and medicine* 2010;16:48-54.

60. Phillips TJC, Cherry CL, Cox S, et al. Pharmacological treatment of painful HIV-associated sensory neuropathy: A systematic review and meta-analysis of randomised controlled trials. *PLoS ONE* 2010;5.

61. Caliandro P, La Torre G, Padua R, et al. Treatment for ulnar neuropathy at the elbow. *Cochrane database of systematic reviews (Online)* 2011;2.

62. Denkers MR, Biagi HL, Ann O'Brien M, et al. Dorsal root entry zone lesioning used to treat central neuropathic pain in patients with traumatic spinal cord injury: a systematic review. *Spine* 2002;27:E177-184.

63. Cruccu G, Anand P, Attal N, et al. EFNS guidelines on neuropathic pain assessment. *European Journal of Neurology* 2004;11:153-162.

64. Attal N, Cruccu G, Haanpää M, et al. EFNS guidelines on pharmacological treatment of neuropathic pain. *European Journal of Neurology* 2006;13:1153-1169.

65. Attal N, Cruccu G, Baron R, et al. EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. *European Journal of Neurology* 2010;17:1113-e88.

66. Brandsma JW, Lakerveld-Heyl K, Van Ravensberg CD, et al. Reflection on the definition of impairment and disability as defined by the World Health Organization. *Disability and Rehabilitation* 1995;17:119-127.

67. Litcher-Kelly L, Martino SA, Broderick JE, et al. A Systematic Review of Measures Used to Assess Chronic Musculoskeletal Pain in Clinical and Randomized Controlled Clinical Trials. *Journal of Pain* 2007;8:906-913.

68. Dworkin RH, Backonja M, Rowbotham MC, et al. Advances in Neuropathic Pain: Diagnosis, Mechanisms, and Treatment Recommendations. *Archives of Neurology* 2003;60:1524-1534.

69. Seres JL. The fallacy of using 50% pain relief as the standard for satisfactory pain treatment outcome. *Pain Forum* 1999;8:183-188.

70. Covinsky KE. Pain, Functional Limitations, and Aging PAIN, FUNCTIONAL LIMITATIONS, AND AGING. *Journal of the American Geriatrics Society (JAGS)* 2009;57:1556-1561.

71. van Seventer R, Serpell M, Bach FW, et al. Relationships between changes in pain severity and other patient-reported outcomes: Andn analysis in patients with posttraumatic peripheral neuropathic pain. *Health and Quality of Life Outcomes* 2011;9.

72. Gore M, Brandenburg NA, Hoffman DL, et al. Burden of Illness in Painful Diabetic Peripheral Neuropathy: The Patients' Perspectives. *Journal of Pain* 2006;7:892-900.

73. Oxman AD, Cook DJ and Guyatt GH. Users' guides to the medical literature: VI. How to use an overview. *JAMA* 1994;272:1367-1371.

74. University of Birmingham. Aggressive Research Intelligence Facility (ARIF) Checklist [Web Page]. Available at http://www.birmingham.ac.uk/research/activity/mds/projects/HaPS/PHEB/ARIF/index.aspx . Accessed April 2012.

75. Shah PB. Interventions for treating community-acquired pneumonia: an overview of Cochrane systematic reviews. *Cochrane Database of Systematic Reviews* 1996.

Figure
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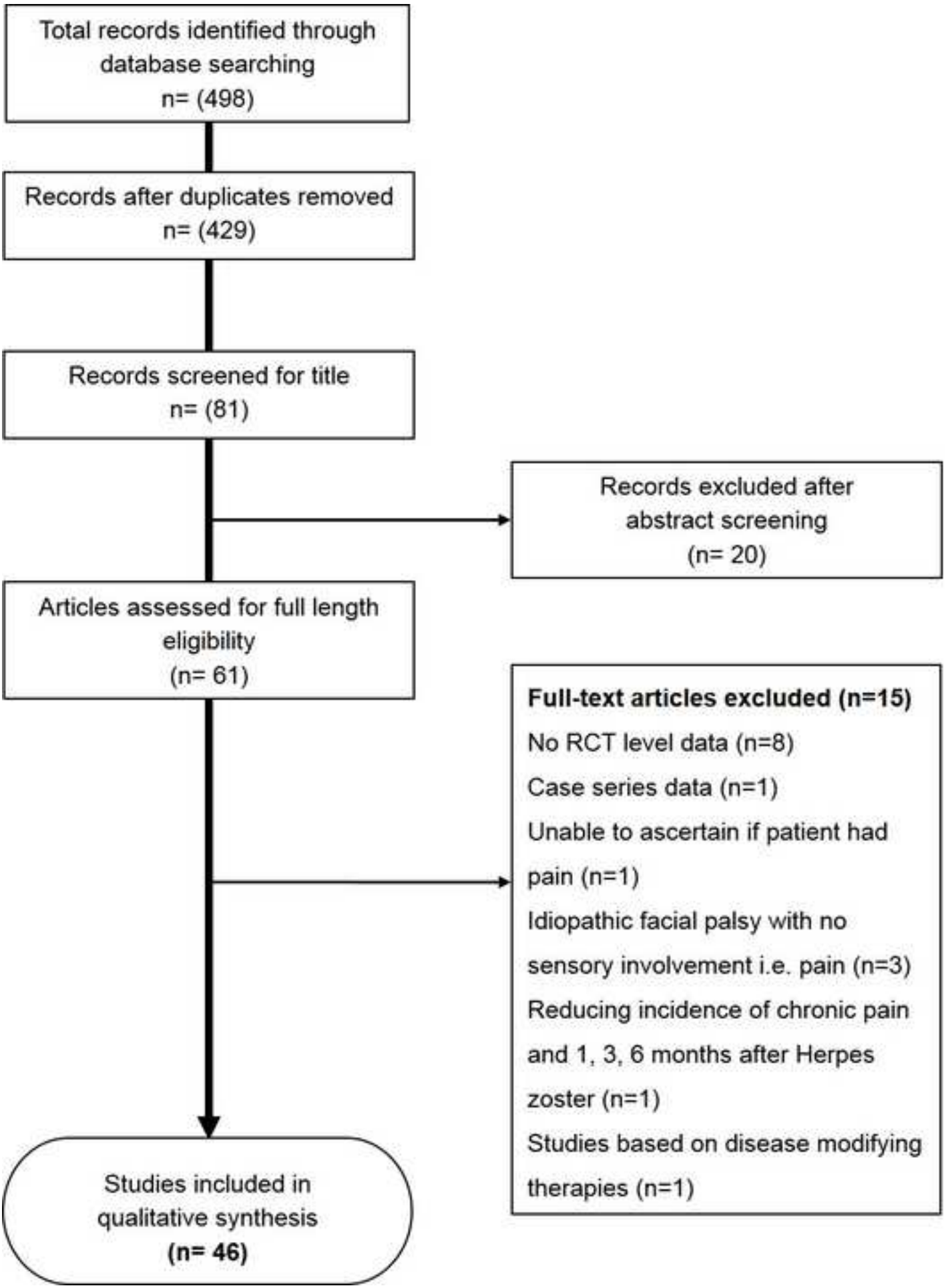

2.3 Table 1. Search Strategy

Step	Database search	Results
1	(neuropathic pain OR neuropathy OR neurodynia OR nerve pain OR neuralgia).mp.	61826
2	(activit* daily living OR funct* outcome OR funct* activit* OR funct* abilit* OR measur* OR scale OR parameter*).mp.	1045383
3	(systematic review OR systematic reviews).mp.	24973
4	systematic review.m_titl.	16352
5	(RCT OR randomised control trial OR randomized control trial).mp.	7569
6	1 AND 2 AND 4 AND 5	29
7	limit 6 to (English language and humans)	29
8	remove duplicates from 7	27

[mp = protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]

Table 2. Summary characteristics of included reviews

Study reference	Population (Treede's Definition of NeP)	No. of RCT's	Outcome Measures	Statistical Approach used by included studies	Level of Change used by included studies
Diabetic Neuropathy					
Chen W et al. 2011	Diabetic peripheral neuropathy (DEFINITE NeP)	39	Primary outcome: Improvement of 30% in VAS or total symptom score, Global symptom improvement and changes in nerve conduction velocity. Secondary outcomes: Quality of life by SF-36 scales, Change in or absolute values of motor or sensory nerve conduction velocity, Adverse events.	MD, WMD and RR with 95% CIs	NA
Hurley RW et al. 2008	Diabetic peripheral neuropathy (NA)	3	Pain score (with and without 50% reduction), PGIC rating at end point and adverse events.	RR and WMD with 95% CIs	50%
Ites KI et al. 2011	Diabetic peripheral neuropathy (UNCLEAR)	6	Measure of balance (question about balance, perception of falls risk and number of falls, Tinnetti Balance Assessment, Sway parameters, tendem stance, single leg stance, functional reach, ABC scale, failure rate during weight transfer task to unipedal stance with a tilting support surface).	Effect size with 95% CIs and NNT	NA

Li H 2008	Diabetic peripheral neuropathy (NA)	10	Sensory impairment level, hot-cold temperature discrimination, current perception threshold, and pain levels using VAS.	Narrative synthesis	NA
Wong MC et al. 2007	Painful diabetic neuropathy (NA)	25	Primary: 50% reduction in pain and 'moderate', 'good', or 'notable' improvement in PGIC. Secondary: 30% reduction in pain and the number of patients who withdrew as a result of side effects.	OR with 95% CI using a random effect model	30-50%
Diabetic neuropathy, post herpetic neuralgia, trigeminal neuralgia, post stroke pain, Phantom limb pain, Fibromyalgia, CRPS and GB syndrome					
Challapalli V et al. 2005	Painful peripheral neuropathy, Plexopathy or radiculopathy, CRPS type I and II, Central pain from cerebrovascular lesions or tumours, Spinal cord injuries, Multiple sclerosis and other demyelinating diseases, Trigeminal neuralgia, Post-amputation pain, Fibromyalgia (NA)	30	Intensity of spontaneous pain or its relief measured by any validated measurement tool and Adverse effects with enough intensity to cause study withdrawal or to decrease the dose of the drug.	WMD and OR in a random effects model	NA
Collins SL et al. 2000	Diabetic neuropathy, post herpetic neuralgia (NA)	19	Point global scale of pain relief or effectiveness or improvement and 50% or more reduction on VAS of pain intensity.	RR and RB with 95% CI using fixed effect model	≥50%

Eccles NK 2005	Acute pain induced by heat, foot pain from plantar fasciitis, postsurgical foot pain, chronic shoulder and neck pain, post-polio pain, low back pain, postsurgical wound pain, intractable neuropathic pain, chronic knee, and back pain, fibromyalgic pain, rheumatoid arthritic knee pain, osteoarthritic knee pain, chronic headache, wrist pain, carpal tunnel syndrome, chronic pelvic pain and monthly dysmenorrhea (NA)	21	Level of pain was assessed using the McGill Pain and VAS, VRS, 11 point NRS, WOMAC, 15 m walking speed.	Narrative review	NA
Gill D et al. 2011	Painful diabetic neuropathy, Post-herpetic neuralgia, Trigeminal neuralgia, Phantom limb pain, Postoperative or traumatic neuropathic pain, CRPS, Cancer-related neuropathy, Guillain Barré, HIV-neuropathy, Spinal cord injury, Fibromyalgia (UNCLEAR)	3	Primary outcomes: Patient-reported pain relief of 30%-50% or greater, PGIC much or very much improved. Secondary outcomes: Any pain-related outcome indicating some improvement, Withdrawals due to lack of efficacy, Participants experiencing any adverse event, Withdrawals due to adverse events, somnolence and dizziness.	RR with 95% CI using fixed effect model	≥30-50%
Goodyear-Smith F & Halliwell J 2009	Diabetic neuropathy, post herpetic neuralgia, trigeminal neuralgia, and post stroke pain (UNCLEAR)	70	Pain relief (UNCLEAR)	Narrative synthesis	NA

Hauser W et al. 2011	Fibromyalgia and painful diabetic peripheral neuropathy (UNCLEAR)	142	Rating of pain intensity- VAS, NRS, summary scores including non-painful symptoms (Paraesthesia and sleep numbness of feet).	WMD and RR with 95% CI using fixed effect model	<10, 10-20 AND 20-27 point change
McQuay HJ et al. 1996	Diabetic neuropathy, post herpetic neuralgia, atypical facial pain and central pain (NA)	17	Patient global judgement (excellent/good), Pain intensity (no pain/ slight pain or 50% decrease from 'neuropathy' scale) or relief (good/ excellent), Improved or marked improvement and minor and major adverse effects.	OR at 95% CIs in a fixed effect model	>50%
Moore RA et al. 2009	Chronic or neuropathic pain including diabetic neuropathy, post herpetic neuralgia (PHN), phantom limb pain, Guillain Barré, and spinal cord injury (PROBABLE NeP)	19	Patient reported pain relief of 30%- 50% or greater, PGIC, Pain on movement, Pain at rest, Any other pain related measure, Adverse effects.	RR with 95% CI using fixed effect model	>30-50%
Moore RA et al. 2011	Painful diabetic neuropathy, Post herpetic neuralgia, Trigeminal neuralgia, Phantom limb pain, Postoperative or traumatic neuropathic pain, CRPS, Cancer-related neuropathy, HIV-neuropathy, Spinal cord injury, Fibromyalgia (UNCLEAR)	29	Primary outcomes: Patient reported pain intensity reduction of 30%- 50% or greater, PGIC much or very much improved, Secondary outcomes: Any pain-related outcome indicating some improvement, Withdrawals due to lack of efficacy, Participants experiencing any adverse event, Withdrawals due to adverse events, somnolence and dizziness.	RR with 95% CI using fixed effect model	30-50%
Straube S et al.	Post herpetic neuralgia, painful diabetic	21	At least 50% pain relief, PGIC: much or very much	NNT, RR and RB with	50%

2008	neuropathy, fibromyalgia and neuropathic pain after spinal cord injury (NA)		improved, Withdrawals due to lack of efficacy, Withdrawals due to adverse events, Somnolence and Dizziness.	95% CIs using fixed effect model	
Straube S et al. 2010	Neuropathic pain and CRPS (POSSIBLE NeP)	1	Primary outcomes: Participants with 30% pain relief, or at least "much improved" in PGIC, Participants with 50% pain relief, or "very much improved" in PGIC. Secondary outcomes: Participants with < 30% or "mild" pain relief, or undefined improvement, Pain relief lasting < 4 weeks, Adverse events and complications, Occurrence of persistent serious new or expanded pain.	RR with 95% CI using fixed effect model	<30%, ≥30%, ≥50%
Wiffen PJ et al. 2011	Acute, chronic or cancer pain (UNCLEAR)	15	Patient reported pain relief of 50% or greater, PGIC, Pain on movement, Pain on rest or spontaneous pain and any other pain related outcomes, Adverse events.	NNT and RR with 95% CI using fixed effect model	30-50%
Entrapment Neuropathy					
Caliandro P et al. 2011	People with clinical symptoms suggesting the presence of UNE with or without neurophysiological evidence of entrapment (UNCLEAR)	6	Primary outcomes: Improvement in function measured by Disability of the Arm, Shoulder and Hand questionnaire or the UNE questionnaire. Secondary outcomes: Change in neurological impairment, Change from baseline of the motor nerve	MD, OR (random effect model) and RR with 95% CI using fixed effect model	NA

			conduction velocity across the elbow, Change from baseline in the nerve diameter, Change in quality of life and Adverse events.		
Herpes Zoster					
Cao H et al. 2010	Herpes zoster (UNCLEAR)	8	Reduction in severity of pain, Duration of relief of pain, Percentage of cured patients and Incidence rate of PHN.	RR and MD with 95% CI using fixed effect model	NA
Neuropathic pain of any aetiology					
Ang CD et al. 2008	Generalized peripheral neuropathy (NA)	13	Primary outcomes: VAS and a neuropathy impairment score. Secondary outcomes: Long-term (after more than three months) change in pain intensity or impairment, Short-term and long-term change in neuropathic symptoms, Short-term and long-term change in nerve conduction study parameters, Serious adverse events.	RR with 95% CI using fixed effect model and MD with 95% CIs	NA
Eisenberg E et al. 2005	Central or peripheral neuropathic pain of any aetiology (NA)	9	Differences in pain intensity, pain relief, and the incidence and severity of adverse effects.	WMD with 95% CIs	NA
Eisenberg E et al. 2006	Peripheral neuropathic pain of any aetiology (NA)	22	Pain intensity using a VAS; type and amount of opioid and control used; and incidence of adverse effects	RR with 95% CI using fixed effect model	NA

			during treatment with opioid or control.	and MD with 95% CIs	
Eisenberg E et al. 2006	Central or peripheral neuropathic pain of any aetiology (NA)	23	Visual Analogue Scale.	NNT with 95% CI using fixed effect model	NA
Hollinshead J et al. 2006	Peripheral neuropathy (NA)	7	Primary outcomes: The primary outcome measure was 50% or more pain relief, or 50% or more reduction of the score on a validated pain scale. Secondary outcomes: 50% or more reduction in touch-evoked pain after at least two weeks of treatment, Adverse events, which are life threatening, prolong or require hospitalisations, or lead to death.	RR and NNT with 95% CI using fixed effect model	50%
Lunn MP et al. 2009	Any form of painful peripheral neuropathy or chronic pain (UNCLEAR)	6	Primary outcomes: VAS and categorical scales. Secondary outcomes: Long-term (more than 12 weeks) improvement of pain, Improvement in short-term and long-term pain of at least 30% compared with baseline, Improvement in any validated Quality of Life Score of more than 30% compared to the baseline, Adverse events during treatment.	RR, NNT and WMD with 95% CI using fixed effect model	30-50%
Mason L et al. 2004	Chronic pain from neuropathic or	14	50% reduction in pain. This was the number of patients	NNT, RR and RB with	50%

	musculoskeletal disorders (NA)		with either a “good” or “excellent” global assessment of treatment or “none” or “slight” pain on rest or movement measured on a suitable categorical scale.	95% CI using fixed effect model	
Moore RA & McQuary HJ 2005	Arthritis/ musculoskeletal/ neuropathic pain/ Mixed (NA)	34	Adverse event rates	Adverse event rate with 95% CI	NA
Papaleontiou M et al. 2010	Osteoarthritis, neuropathic pain, or other pain-producing disorders (UNCLEAR)	43	Pain (UNSPECIFIED) and physical function outcomes by WOMAC, physical quality of life by SF-36 physical component, mental quality of life and sleep.	NNT and RR with 95% CI using fixed effect model	NA
Pittler MH & Ernst E 2008	Neuropathic pain or neuralgic pain (NA)	15	Pain relief (UNSPECIFIED).	NNT and RR with 95% CI using fixed effect model	NA
Plested M 2010	Refractory NeP (central or peripheral) (UNCLEAR)	17	Pain relief (VAS), Overall quality of life (SF-MPQ total, sensory and affective scores and SF-12), function interference, sleep interference, interference of mood, daily activities and pain associated distress, safety, tolerability.	Narrative synthesis	NA
Saarto T & Wiffen PJ 2007	Any neuropathic pain (NA)	61	Measures of effectiveness: patient-reported global improvement or pain relief, or both. Overall quality of life measures, Adverse effects measures, sleep	RR with 95% CI using fixed effect model	NA

			parameters, Depression scales.		
Seidel S et al. 2008	Acute, chronic or both pains (NA)	11	Primary outcomes: The reduction in pain intensity as measured by VAS, self-reported global scale, VRS, NRS or categorical pain relief scale, and self-reported pain relief. Secondary outcomes: adverse effects. Additional outcomes: Attrition, Measures of satisfaction or patient preference and assessment of quality of life.	WMD and RR with 95% CI using fixed effect model	NA
Tremont-Lukats IW et al. 2005	Neuropathic pain of any aetiology (NA)	27	A change in the 0–100 mm VAS, Adverse events.	WMD and OR in a random effect model	NA
White CM et al. 2004	Peripheral neuropathy, including sensory, motor and combined sensory and motor neuropathies (NA)	3	Primary outcomes: Functional ability (walking, stair climbing and running), functional use of the affected arm/s and/or independence in activities of daily living such as washing, dressing, preparing food etc. Secondary outcomes: Muscle strength, Endurance, Psychological status or quality of life, Return to work, Relapse and use, or increased use, of analgesics.	WMD and RR at 95% CIs in a random effect model	NA

Wiffen PJ et al. 2011	Painful diabetic neuropathy, Post herpetic neuralgia, Trigeminal neuralgia, Phantom limb pain, Postoperative or traumatic neuropathic pain, CRPS, Cancer-related neuropathy, HIV-neuropathy, Spinal cord injury, fibromyalgia (UNCLEAR)	17	Primary outcomes: Patient reported pain intensity reduction of 30%- 50% or greater, PGIC much or very much improved. Secondary outcomes: Any pain-related outcome indicating some improvement, Withdrawals due to lack of efficacy, Participants experiencing any adverse event, Withdrawals due to adverse events, somnolence and dizziness.	NNT and RR with 95% CI using fixed effect model	30-50%
Painful HIV-associated sensory neuropathy					
Phillips TJC et al. 2010	Painful HIV-Associated Sensory Neuropathy (UNCLEAR)	14	Pain improvement (UNCLEAR)	NNT with 95% CIs	≥30%, ≥50%
Post herpetic Neuralgia					
Alper BS & Lewis PR 2002	Post herpetic neuralgia (NA)	27	Pain resolution, VAS, Quality of life and adverse effects.	Narrative synthesis	50%
Hempenstall K et al. 2005	Post herpetic neuralgia (NA)	35	Patient related global scale for pain relief and VAS or 11 point NRS for pain intensity.	RB and NNT with 95% CI using fixed effect	≥50%

				model	
Khaliq W et al. 2007	Post herpetic neuralgia (NA)	12	Primary outcomes: Mean improvement in patients' reports of pain relief measured by a categorical scale. Secondary outcome: Mean reduction in VAS scores, Highest recorded blood lidocaine level, The proportion of participants with one or more adverse skin reactions.	RR, NNT and MD with 95% CI using fixed effect model	NA
Volmink J et al. 1996	Post herpetic neuralgia (NA)	3	Pain relief by VAS and VRS.	OR at 95%CIs in a random effect model	NA
Traumatic Spinal Cord Injury & Central NeP					
Denkers MR et al. 2002	Traumatic spinal cord injury and central neuropathic pain (NA)	11	Rating of pain relief, Decreased usage of pain medication, Interference with daily activities.	Narrative synthesis	NA
Trigeminal Neuralgia					
Chole R et al. 2007	Trigeminal neuralgia (NA)	21	Adverse effects.	RB with 95% CI using fixed effect model	NA

Liu H et al. 2010	Trigeminal neuralgia (UNCLEAR)	12	Cured rate (UNSPECIFIED), Adverse effects.	OR with 95% CIs	NA
Lopez BC et al. 2004	Trigeminal neuralgia (NA)	31	Pain relief (UNSPECIFIED) and Complications.	Narrative synthesis	NA
Yang M et al. 2011	Trigeminal Neuralgia, both idiopathic and symptomatic (UNCLEAR)	4	Primary outcomes: Immediate improvement in pain relief evaluated as decreased pain intensity or TN scores i.e. number of attacks per day and their intensity. Secondary outcomes: Improvement in pain intensity or TN scores at least 12 weeks after the start of treatment and Adverse effects.	MD and RR with 95% CI using fixed effect model	NA
Zakrzewska JJM & Linskey ME 2008	Trigeminal neuralgia (NA)	11	Primary outcomes: Complete pain relief. Secondary outcomes: Surgical morbidity, Quality of life, Patient satisfaction and adverse events.	RR and MD with 95% CI using fixed effect model	NA

CIs= Confidence intervals, MD= Mean difference, NA= Not Applicable, NNT= Number Needed to Treat, NRS= Numerical Rating Scale, OR= Odds Ratio, PGIC= Patient Global Impression of Change, RB= Relative Benefit Ratio, RR= Relative Risk Ratio, SF 36 / 12= The Medical Outcome Study Short Form Health Survey-36 / 12, SF-MPQ= Short Form-McGill Pain Questionnaire, SMD= Standardized mean difference, TN= Trigeminal Neuralgia, UNE= Ulnar Neuropathy at Elbow, VAS= Visual Analog Scale, VRS= Verbal Rating Scale, WOMAC= The Western Ontario and McMaster Universities Arthritis Index, WMD= Weighted mean difference

Table 3. Treede's (2008) Grading system for the level of certainty for the presence of NeP

No.	Criteria to be evaluated for each patient
1	Pain with a distinct neuroanatomically plausible distribution*
2	A history suggestive of a relevant lesion or disease affecting the peripheral or central somatosensory system†
3	Demonstration of the distinct neuroanatomically plausible distribution by at least one confirmatory test‡
4	Demonstration of the relevant lesion or disease by at least one confirmatory test§

Grading of definite NeP: all (1 to 4); probable NeP: 1 and 2, plus either 3 or 4; possible NeP: 1 and 2, without confirmatory evidence from 3 or 4.

*A region corresponding to a peripheral innervation territory or to the topographic representation of a body part in the CNS.

†The suspected lesion or disease is reported to be associated with pain, including a temporal relationship typical for the condition.

‡As part of the neurologic examination, these tests confirm the presence of negative or positive neurologic signs concordant with the distribution of pain. Clinical sensory examination may be supplemented by laboratory and objective tests to uncover subclinical abnormalities.

§As part of the neurologic examination, these tests confirm the diagnosis of the suspected lesion/ disease. These confirmatory tests depend on which lesion/ disease is causing NeP.

Table 4. Summary of reviews using 'Physical Functional Outcome Measures' as an outcome measure

Reference	Treede's NeP Grading	Functional Outcome Measure Tools/ Scales	No of RCT's	Studies using FOM
Ites KI et al. 2011	UNCLEAR	Functional reach test	6	1
Eccles NK 2005	NA	15m walking speed, pain disability index, functional status, physical functions, WOMAC, effects on function	21	7
Caliandro P et al. 2011	UNCLEAR	Disability of the Arm, Shoulder and Hand questionnaire	6	6
Papaleontiou M et al. 2010	UNCLEAR	Pain disability index and SF-36: physical component	43	2
Plested M 2010	UNCLEAR	Daily activities measured by VRS and Function interference measured by NRS.	17	2
White CM et al. 2004	NA	WOMAC: functional component, One and five time	3	3

		scored functional activity, Sub scale of SF-36, 6m comfortable walking speed or 6m gait speed.		
Denkers MR et al. 2002	NA	Improvement in functional capacity.	11	1

NA= Not Applicable, NRS= Numerical Rating Scale, SF-36= The Medical Outcome Study Short Form Health Survey-36, VRS= Verbal Rating Scale, WOMAC= The Western Ontario and McMaster Universities Arthritis Index

Table

Table 5. PRISMA items and criteria (Liberati A 2009). √=YES ×=NO:

	Particulars	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	Total (√)
1	Diabetic Neuropathy																												
1.1	Chen W et al. 2011	×	√	√	×	√	√	√	√	√	√	√	×	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	**24**
1.2	Hurley RW et al. 2008	√	√	√	√	×	√	√	√	√	√	√	×	√	√	√	×	√	√	×	√	√	√	×	√	×	√	√	**21**
1.3	Ites KI et al. 2011	√	√	√	×	×	√	√	×	√	×	√	√	√	×	×	×	√	√	√	√	×	×	×	√	√	√	×	**16**
1.4	Li H 2008	√	√	√	×	×	×	√	√	√	√	√	√	√	√	√	×	√	√	√	√	×	√	×	√	√	√	√	**21**
1.5	Wong MC et al. 2007	√	√	√	×	×	√	√	√	√	√	×	√	√	√	×	√	√	√	√	√	√	×	√	√	×	√	√	**21**
2	Diabetic neuropathy, post herpetic neuralgia, trigeminal neuralgia, post stroke pain, Phantom limb pain, Fibromyalgia, CRPS and GB syndrome																												
2.1	Challapalli V et al. 2005	√	√	√	√	×	√	√	×	√	√	√	√	√	√	×	√	√	√	√	√	√	√	√	√	×	√	√	**23**
2.2	Collins SL et al. 2000	√	√	√	√	×	√	√	×	×	×	√	√	√	×	×	×	√	√	×	√	×	×	√	√	×	√	√	**16**
2.3	Eccles NK 2005	×	√	√	×	×	×	√	×	×	×	×	√	×	×	×	×	×	√	√	×	×	×	×	√	×	√	√	**9**
2.4	Gill D et al. 2011	×	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	×	√	√	√	×	√	√	√	√	√	√	**24**
2.5	Goodyear-Smith F & Halliwell J 2009	×	√	√	×	×	×	√	√	×	√	×	√	×	×	×	×	√	×	×	×	×	×	×	√	√	√	√	**11**
2.6	Hauser W et al. 2011	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	**27**
2.7	McQuay HJ et al. 1996	√	√	√	×	×	√	√	×	√	×	×	√	√	×	×	×	×	√	√	√	×	×	√	√	×	√	√	**15**
2.8	Moore RA et al. 2009	×	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	×	√	√	√	√	×	√	√	√	√	√	**24**
2.9	Moore RA et al. 2011	×	√	√	×	√	√	√	√	√	√	√	√	√	×	×	√	×	√	√	√	√	√	√	√	√	√	√	**22**

2.10	Straube S et al. 2008	√	√	√	√	×	√	√	√	×	×	√	√	√	√	√	×	×	√	√	×	√	×	√	√	×	√	√	**19**
2.11	Straube S et al. 2010	×	√	√	√	√	√	√	√	√	√	√	×	√	√	√	√	×	√	√	√	×	×	×	√	×	√	√	**20**
2.12	Wiffen PJ et al. 2011	×	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	**26**
3	Entrapment Neuropathy																												
3.1	Caliandro P et al. 2011	×	√	√	×	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	**25**
4	Herpes Zoster																												
4.1	Cao H et al. 2010	√	√	√	×	×	√	√	×	√	√	×	√	√	√	√	×	√	√	√	√	√	√	×	√	×	√	√	**20**
5	Neuropathic pain of any aetiology																												
5.1	Ang CD et al. 2008	×	√	√	√	√	√	√	√	√	√	×	√	√	√	√	√	×	√	√	√	√	×	√	√	×	√	√	**22**
5.2	Eisenberg E et al. 2005	×	√	√	×	√	√	√	√	√	√	√	√	√	√	×	×	√	√	√	√	√	×	×	√	×	√	√	**20**
5.3	Eisenberg E et al. 2006	√	√	√	√	×	√	√	√	×	√	×	√	√	√	×	√	√	√	×	√	√	×	√	√	×	√	√	**20**
5.4	Eisenberg E et al. 2006	√	√	√	√	×	√	√	×	√	√	√	√	√	√	×	×	√	√	√	√	√	×	√	√	√	√	√	**22**
5.5	Hollingshead J et al. 2006	×	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	×	√	√	**25**
5.6	Lunn MP et al. 2009	×	√	√	×	√	×	√	√	√	√	×	√	√	√	√	√	√	√	√	√	√	×	√	√	×	√	√	**21**
5.7	Mason L et al. 2004	√	√	√	√	×	√	√	√	×	√	√	√	√	√	×	×	√	√	√	√	√	×	×	√	√	√	×	**20**
5.8	Moore RA & McQuary HJ 2005	√	√	√	×	×	√	√	×	×	×	√	√	×	×	×	√	×	√	×	√	√	×	√	√	×	√	√	**15**
5.9	Papaleontiou M et al.	√	√	√	√	×	√	√	×	√	√	√	√	√	√	√	√	√	√	×	×	√	√	√	√	√	√	√	**23**

	2010																												
5.10	Pittler MH & Ernst E 2008	√	√	×	×	×	×	√	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	√	√	√	**6**
5.11	Plested M 2010	√	√	√	×	×	√	√	√	√	√	×	√	×	×	×	×	√	√	×	√	×	×	×	√	√	√	√	**16**
5.12	Saarto T & Wiffen PJ 2007	×	√	√	×	√	√	√	√	√	√	√	×	√	√	×	√	×	√	√	√	√	×	√	√	×	√	√	**20**
5.13	Seidel S et al. 2008	×	√	√	√	√	√	√	√	√	√	√	√	√	×	×	√	√	√	√	√	√	×	√	√	√	√	√	**23**
5.14	Tremont-Lukats IW et al. 2005	×	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	×	√	√	√	√	√	√	√	√	√	√	**25**
5.15	White CM et al. 2004	×	√	√	√	√	√	√	√	√	√	√	×	√	√	×	√	√	√	√	√	√	×	√	√	√	√	√	**23**
5.16	Wiffen PJ et al. 2011	×	√	√	×	√	√	√	√	√	√	×	√	√	×	×	×	×	√	√	√	√	×	√	√	√	√	√	**19**
6	Painful HIV-associated sensory neuropathy																												
6.1	Phillips TJC et al. 2010	√	√	√	×	×	×	√	×	√	√	√	√	√	√	×	√	√	√	×	√	√	×	×	√	×	√	√	**18**
7	Post herpetic Neuralgia																												
7.1	Alper BS & Lewis PR 2002	√	√	√	×	×	√	√	√	×	√	×	√	×	×	×	×	√	√	√	√	×	×	×	√	√	√	√	**16**
7.2	Hempenstall K et al. 2005	√	√	√	×	×	√	√	×	√	√	×	√	√	√	×	√	√	√	×	√	√	×	√	√	×	√	√	**19**
7.3	Khaliq W et al. 2007	×	√	√	√	√	√	√	√	√	√	√	×	√	×	√	√	√	√	√	√	√	√	×	√	√	√	√	**23**
7.4	Volmink J et al. 1996	×	√	√	×	×	√	×	×	×	√	√	√	√	√	×	×	×	√	√	√	√	×	√	√	√	√	√	**17**

8	Traumatic SCI & Central NeP																												
8.1	Denkers MR et al. 2002	√	√	√	√	×	√	√	×	√	√	√	×	×	×	×	×	×	√	×	√	×	×	×	√	√	√	√	**15**
9	Trigeminal Neuralgia																												
9.1	Chole R et al. 2007	√	√	√	×	×	×	√	√	×	×	×	×	×	×	×	×	√	√	×	×	×	×	×	√	×	√	×	**9**
9.2	Liu H et al. 2010	√	√	√	×	×	×	√	√	×	×	√	×	×	×	×	×	×	√	×	×	×	×	×	√	×	√	×	**9**
9.3	Lopez BC et al. 2004	√	√	√	×	×	×	√	×	×	√	√	√	√	×	×	×	√	√	√	×	×	×	×	√	×	√	√	**14**
9.4	Yang M et al. 2011	×	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	×	√	√	√	√	×	×	√	√	√	√	**23**
9.5	Zakrzewska JJM & Linskey ME 2008	×	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	×	√	√	√	×	×	×	√	×	√	√	**21**

1. Title: Identify the report as a systematic review, meta-analysis, or both.

2. Structured summary: Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.

3. Rationale: Describe the rationale for the review in the context of what is already known.

4. Objectives: Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).

5. Protocol and registration: 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.

6. Eligibility criteria: 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.

7. Information sources: 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.

8. Search: Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.

9. Study selection: State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).

10. Data collection process: Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.

11. Data items: List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.

12. Risk of bias in individual studies: 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.

13. Summary measures: State the principal summary measures (e.g., risk ratio, difference in means).

14. Synthesis of results: Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.

15. Risk of bias across studies: Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).

16. Additional analyses: Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.

17. Study selection: 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.

18. Study characteristics: For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.

19. Risk of bias within studies: Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).

20. Results of individual studies: 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.

21. Synthesis of results: Present results of each meta-analysis done, including confidence intervals and measures of consistency.

22. Risk of bias across studies: Present results of any assessment of risk of bias across studies (see Item 15).

23. Additional analysis: Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).

24. Summary of evidence: 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).

25. Limitations: 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).

26. Conclusions: Provide a general interpretation of the results in the context of other evidence, and implications for future research.

27. Funding: Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.

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