Outcome Measures in Randomized-controlled Trials of Neuropathic Pain Conditions

A Systematic Review of Systematic Reviews and Recommendations for Practice

Poonam Mehta, MPT, Leica Claydon, PhD, Paul Hendrick, PhD, Stanley Winser, MPT, and G. David Baxter, D.Phil

Objectives: Neuropathic pain (NeP) is a prevalent, disabling, multidimensional 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 used to determine treatment effects.

Methods: Keywords and MESH searches were conducted in 5 electronic databases from inception to January 31, 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 used a functional outcome measure 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 functional outcome measures. The lack of standardization for the diagnostic criteria in NeP trials is also an issue that needs to be considered for future research and guideline development.

Key Words: neuropathic pain, systematic review, pain, physical function, outcome measures

Received for publication February 12, 2013; revised April 7, 2014; accepted February 14, 2014.

From the School of Physiotherapy, University of Otago, Dunedin, New Zealand.

The authors declare no conflict of interest.

Reprints: Poonam Mehta, MPT, School of Physiotherapy, University of Otago, Dunedin, 9054 New Zealand (e-mail: poonam_2585@yahoo.com).

Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal’s Website, www.clinicalpain.com.

Copyright © 2014 Wolters Kluwer Health, Inc. All rights reserved.

DOI: 10.1097/AJP.0000000000000088

www.clinicalpain.com | 169
review was to review reviews of interventional randomised control trails (RCT) for NeP systematically to investigate the range and types of outcome measures used to determine treatment effect.

**METHODS**

**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. Systematic reviews of both acute (<3 month duration) and chronic pain conditions (≥3 month duration) 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 January 31, 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 (P.M. and L.C.) 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 independently by 2 reviewers (P.M. and L.C.). The grading system is detailed in Table 2.

**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 2 reviewers (P.M. and S.W.) using standardized forms, with consensus meetings and opinions from other reviewers (L.C. and P.H.) to resolve any disagreements.

**Risk of Bias in Individual Reviews**

The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) was independently used by 2 reviewers (P.M. and L.C.) to appraise the included reviews critically. The PRISMA had been used previously in other systematic reviews of systematic reviews to appraise the quality of systematic reviews. Disagreements regarding the inclusion of individual reviews and PRISMA scoring were resolved by discussion with reviewers (P.H. and D.B.). Reviewers were not blind to the journal affiliation or authors of the systematic reviews. Reviews were not excluded on the basis of their PRISMA scores.

**Summary Measures and Data Synthesis**

Summary measures (mean difference, weighted mean difference, relative risk ratio, and odds ratio) were extracted for each outcome measure for each systematic review. Outcome measures used by each systematic review were grouped under the 4 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). Each domain was further subgrouped based on the summary measure used in the review and the amount of change determined to be clinically relevant.

**RESULTS**

**Study Selection**

Figure 1 summarizes 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.

---

**TABLE 1. Search Strategy**

| Step | Database Search | Results |
|------|-----------------|---------|
| 1    | (neuropathic pain OR neuropathy OR neurodynia OR nerve pain OR neuralgia).mp. | 61,826 |
| 2    | (activit* daily living OR funct* outcome OR funct* OR funct* abilit* OR measur* OR scale OR parameter*).mp. | 1,045,383 |
| 3    | (systematic review OR systematic reviews).mp. | 24,973 |
| 4    | systematic review.mp_titl. | 16,352 |
| 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 |

**TABLE 2. 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 1 confirmatory test‡ |
| 4   | Demonstration of the relevant lesion or disease by at least 1 confirmatory test§ |

* 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 neurological examination, these tests confirm the presence of negative or positive neurological 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 neurological examination, these tests confirm the diagnosis of the suspected lesion/disease. These confirmatory tests depend on which lesion/disease is causing NeP.

Grading of definite NeP indicates all (1 to 4); possible NeP, 1 and 2, without confirmatory evidence from 3 or 4; probable NeP, 1 and 2; plus either 3 or 4.
CNS indicates central nervous system; NeP, neuropathic pain.
Common reasons for exclusion (n = 15) were: 8 reviews were based on non-RCTs; in 5 reviews, it was not clearly evident whether patients had sensory involvement, that is, the presence of pain; 1 review was excluded as it primarily included pain immediately after surgery; and 1 review was excluded as its focus was on disease-modifying therapy not symptomatic pain therapy. A total of 46 reviews remained after exclusion.

Characteristics of Included Reviews

Details of all 46 eligible reviews are given in Table, Supplemental Digital Content 1, http://links.lww.com/CJP/A108.17–62 Systematic reviews fulfilled all selection criteria and presented data on various underlying neuropathic conditions.

Half, that is, 57% (26/46), of the systematic reviews included the following study populations: diabetic neuropathy,17–21 postherpetic neuralgia,53–56 trigeminal neuralgia,58–62 or mixed NeP where all the covered conditions were well tabulated.22–33 The systematic reviews based on mixed NeP populations were only included if a subgroup analysis of the underlying conditions was performed.

Half of the remaining reviews (10/20) were heterogeneous studies that included NeP of any etiology.36–51 There were 4 more reviews based on different conditions: herpes zoster,35 painful HIV-associated sensory neuropathy,52 entrapment neuropathy,34 and traumatic spinal cord injury and central NeP.57

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 3 that met the criteria for definite,17 probable,29 or possible32 NeP (Table 2). The rest of the reviews (15/18) did not provide sufficient or clear information for a NeP grade (Table, Supplemental Digital Content 1, http://links.lww.com/CJP/A108) 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 because of peripheral or central nervous system disease or injury present in very similar ways, and this observation has led to a group designation for NeP. However, the study population for the current systematic review covered within the included reviews all the common conditions associated with NeP (Clinical Resource Efficiency Support Team, 2008).

Critical Appraisal of Included Reviews

PRISMA scoring for the reviews are detailed in Table 3: 28 of the 46 reviews achieved 20 to 27 points on the PRISMA, 14 scored 10 to 19 points, and 4 scored ≤9 points. Higher scores reflect higher internal validity of the systematic review.

Outcome Measures

Pain Intensity
Changes in levels of pain intensity were used as the primary outcome measure in 40 of the 46 (87%) included systematic reviews (Table, Supplemental Digital Content 1, http://links.lww.com/CJP/A108). A variety of pain scales were used to measure the intensity of pain (or its relief): visual analog scales (VAS), Verbal Rating Scales, 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 4). Ten different functional outcome measures were reported: Disability of the Arm, Shoulder, and Hand questionnaire, Pain Disability Index, SF-36: physical functional component, daily activities measured by Video Relay Service, function interference measured by NRS, Western Ontario and McMaster Arthritis Index: functional component, timed scored functional activity, functional reach test, timed meter to walk test (6 and 15 m walking speed), and interference with daily activities.

Emotional Functioning

Of the 46 (ie, 22%) systematic reviews, 10 assessed the emotional domain. A range of measures were used 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 Patient Global Impression of Change score was used 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, weighted mean difference, and standardized mean difference at 95% of confidence interval levels, relative risk ratio, and OR were alternatively used to summarize the results; of the 33 (26 and 7) systematic reviews that adopted RR or OR (respectively), 16 (14 and 2) reviews could be simply categorized into a dichotomous response of yes/no (ie, 50% pain relief or not). Six systematic reviews described their results narratively, and 13 reviews also calculated the Number Needed to Treat.

DISCUSSION

To the best of our knowledge, this is the first systematic review 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 the 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, EFNS, and NeuPSIG. Thus, the findings from the current review were in contrast with other areas of pain management, where the aim is more commonly focused on reduction of disability (eg, inactivity) and enabling the person to achieve independence. Changes in level or intensity of pain was the most commonly used

---

**TABLE 3. Summary of Reviews Using “Physical Functional Outcome Measures” as an Outcome Measure**

| References      | Treede’s NeP Grading | Functional Outcome Measure Tools/Scales                                      | No. RCTs | Studies Using Functional Outcome Measure |
|-----------------|----------------------|---------------------------------------------------------------------------|----------|-----------------------------------------|
| Ites et al      | UNCLEAR              | Functional reach test                                                     | 6        | 1                                       |
| Eccles          | NA                   | 15 m walking speed, Pain Disability Index, functional status, physical functions, WOMAC, effects on function | 21       | 7                                       |
| Calandro et al  | UNCLEAR              | Disability of the Arm, Shoulder and Hand questionnaire                    | 6        | 6                                       |
| Papaleontiou et al | UNCLEAR          | Pain Disability Index and SF-36: physical component                      | 43       | 2                                       |
| Plested         | UNCLEAR              | Daily activities measured by VRS and function interference measured by NRS | 17       | 2                                       |
| White et al     | NA                   | WOMAC: functional component, 1- and 5-time scored functional activity, sub-scale of SF-36, 6 m comfortable walking speed or 6 m gait speed | 3        | 3                                       |
| Denkers et al   | NA                   | Improvement in functional capacity                                        | 11       | 1                                       |

NA indicates 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.
| 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 | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | 24 |
| 1.1 Chen et al²⁷ | x | | | | | | | | | | | | | | | | | | | | | | | | | | 21 |
| 1.2 Hurley et al²⁶ | x | | | | | | | | | | | | | | | | | | | | | | | | | | 21 |
| 1.3 Isgaard et al⁴⁹ | x | | | | | | | | | | | | | | | | | | | | | | | | | | 16 |
| 1.4 Li²⁶ | x | | | | | | | | | | | | | | | | | | | | | | | | | | 16 |
| 1.5 Wong et al⁵⁰ | x | | | | | | | | | | | | | | | | | | | | | | | | | | 21 |
| 2           | Diabetic neuropathy, postherpetic neuralgia, trigeminal neuralgia, poststroke pain, Phantom limb pain, fibromyalgia, CRPS, and GB syndrome | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | 16 |
| 2.1 Challapalli et al²² | | | | | | | | | | | | | | | | | | | | | | | | | | | 19 |
| 2.2 Collens et al⁵¹ | | | | | | | | | | | | | | | | | | | | | | | | | | | 16 |
| 2.3 Eccles⁵² | | | | | | | | | | | | | | | | | | | | | | | | | | | 9 |
| 2.4 Gill et al⁵³ | | | | | | | | | | | | | | | | | | | | | | | | | | | 24 |
| 2.5 Goodyear-Smith and Halliwell⁵⁴ | | | | | | | | | | | | | | | | | | | | | | | | | | | 11 |
| 2.6 Hauser et al⁵⁵ | | | | | | | | | | | | | | | | | | | | | | | | | | | 27 |
| 2.7 McQuay et al⁵⁶ | | | | | | | | | | | | | | | | | | | | | | | | | | | 15 |
| 2.8 Moore et al⁵⁷ | | | | | | | | | | | | | | | | | | | | | | | | | | | 24 |
| 2.9 Moore et al⁵⁸ | | | | | | | | | | | | | | | | | | | | | | | | | | | 22 |
| 2.10 Straube et al⁵⁹ | | | | | | | | | | | | | | | | | | | | | | | | | | | 19 |
| 2.11 Straube et al⁵⁰ | | | | | | | | | | | | | | | | | | | | | | | | | | | 20 |
| 2.12 Wiffen et al⁶¹ | | | | | | | | | | | | | | | | | | | | | | | | | | | 26 |
| 3           | Entrapment neuropathy | | | | | | | | | | | | | | | | | | | | | | | | | | | 20 |
| 3.1 Calandrino et al⁶² | | | | | | | | | | | | | | | | | | | | | | | | | | | 25 |
| 4           | Herpes zoster | | | | | | | | | | | | | | | | | | | | | | | | | | | 20 |
| 4.1 Cao et al⁶³ | | | | | | | | | | | | | | | | | | | | | | | | | | | 20 |
| 5           | Neuropathic pain of any etiology | | | | | | | | | | | | | | | | | | | | | | | | | | | 20 |
| 5.1 Ang et al⁶⁴ | | | | | | | | | | | | | | | | | | | | | | | | | | | 22 |
| 5.2 Eisenberg et al²⁷ | | | | | | | | | | | | | | | | | | | | | | | | | | | 20 |
| 5.3 Eisenberg and colleagues³⁸,³⁹ | | | | | | | | | | | | | | | | | | | | | | | | | | | 20 |
| 5.4 Eisenberg and colleagues³⁸,³⁹ | | | | | | | | | | | | | | | | | | | | | | | | | | | 20 |
| 5.5 Hollingshead et al⁶⁰ | | | | | | | | | | | | | | | | | | | | | | | | | | | 25 |
| 5.6 Lunn et al⁶¹ | | | | | | | | | | | | | | | | | | | | | | | | | | | 21 |
| 5.7 Mason et al⁶² | | | | | | | | | | | | | | | | | | | | | | | | | | | 20 |
| 5.8 Moore and McQuay⁴⁵ | | | | | | | | | | | | | | | | | | | | | | | | | | | 15 |
| 5.9 Papadomakou et al⁶⁴ | | | | | | | | | | | | | | | | | | | | | | | | | | | 23 |
| 5.10 Pittler and Ernst⁴⁵ | | | | | | | | | | | | | | | | | | | | | | | | | | | 6 |
| 5.11 Plested⁴⁶ | | | | | | | | | | | | | | | | | | | | | | | | | | | 16 |
| 5.12 Saarinen and Waffner⁶⁷ | | | | | | | | | | | | | | | | | | | | | | | | | | | 20 |
| 5.13 Seidel et al⁶⁸ | | | | | | | | | | | | | | | | | | | | | | | | | | | 23 |
| 5.14 Temont-Lukats et al⁶⁹ | | | | | | | | | | | | | | | | | | | | | | | | | | | 25 |
| 5.15 White et al⁷⁰ | | | | | | | | | | | | | | | | | | | | | | | | | | | 23 |
| 5.16 Wiffen et al⁷¹ | | | | | | | | | | | | | | | | | | | | | | | | | | | 19 |
| 6           | Painful HIV-associated sensory neuropathy | | | | | | | | | | | | | | | | | | | | | | | | | | | 18 |
| 6.1 Phillips et al²² | | | | | | | | | | | | | | | | | | | | | | | | | | | 18 |
| 7           | Postherpetic neuralgia | | | | | | | | | | | | | | | | | | | | | | | | | | | 20 |
| 7.1 Alper and Lewis⁵⁵ | | | | | | | | | | | | | | | | | | | | | | | | | | | 16 |
| 7.2 Hempenstall et al⁷² | | | | | | | | | | | | | | | | | | | | | | | | | | | 19 |
| 7.3 Khalig et al⁷³ | | | | | | | | | | | | | | | | | | | | | | | | | | | 23 |
| 7.4 Volmink et al⁷⁶ | | | | | | | | | | | | | | | | | | | | | | | | | | | 17 |
| 8           | Traumatic spinal cord injury and central NeuP | | | | | | | | | | | | | | | | | | | | | | | | | | | 15 |
| 8.1 Denkers et al⁷⁵ | | | | | | | | | | | | | | | | | | | | | | | | | | | 15 |
| 9           | Trigeminal neuralgia | | | | | | | | | | | | | | | | | | | | | | | | | | | 15 |
| 9.1 Chole et al⁷⁶ | | | | | | | | | | | | | | | | | | | | | | | | | | | 9 |
| 9.2 Lin et al⁷⁷ | | | | | | | | | | | | | | | | | | | | | | | | | | | 9 |
| 9.3 Lopez et al⁷⁸ | | | | | | | | | | | | | | | | | | | | | | | | | | | 9 |
| 9.4 Yang et al⁷⁹ | | | | | | | | | | | | | | | | | | | | | | | | | | | 14 |
| 9.5 Zakrzewska and Linsey⁸⁰ | | | | | | | | | | | | | | | | | | | | | | | | | | | 23 |

* indicates no; √, yes; NeuP, neuropathic pain.
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 multi-dimensional pain scales, our results showed that 1-dimensional measurements of pain were used in 40/46 systematic reviews. An international, informally organized network aimed at improving Outcome Measurement in Rheumatology9 recommended a core set of 4 domains (pain, physical function, patient global assessment and, for studies of at least 1 y: 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 unidimensional measures such as VAS. In contrast, only 16% used multidimensional scales (eg, MPQ) and 27% were multi-item scales that measured 1 dimension of pain (eg, 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 majority of chronic pain studies. There may be a number of reasons behind this finding, such as: the time required for the assessment of other related domains (ie, physical functioning, emotional impact, and global improvement), the patient burden associated with lengthy assessment procedures, or alternatively because research is focused exclusively on pain intensity.62

In addition, 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, Supplemental Digital Content 1, http://links.lww.com/CJP/A108). 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 fulfill the criteria for any of the 3 grading levels, then the study population is classified as unlikely to have an NeP condition. According to the IASP revised definition of NeP, it is a clinical description (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 the 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 utilize validated criteria to define and grade NeP in research, as well as clinical practice.

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% to 20% change and signifies “less important change” in the pain scores. Changes of approximately 2 points, that is, 30% to 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 that used 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, whereas the other 8 employed pain intensity reduction of ≥ 30% to 50%.

Pain has always been considered a risk factor for as well as a cause of disability.70 It has also been shown that functional losses and mood disturbances are directly related to an increased severity of peripheral NeP.71 Moreover, it is not only activities of daily living that are affected by his multidisabling 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 emphasize that multidimensional pain scales and measures of functional and emotional responses to pain are needed to evaluate response to pain interventions better, and also to allow better modeling of the factors that 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 that are driving the patient’s response to the intervention.

Strengths and Limitations

A number of strengths and limitations in this review should be acknowledged. First, it is acknowledged that “Neuropathic Pain conditions” is an umbrella term that covers a number of different conditions such as diabetic neuropathy, trigeminal neuralgia, and postherpetic 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.

Second, 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 et al17 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 used 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.

Third, we rated the recently published reviews for the presence of NeP based on an internationally recommended grading criteria2 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.

Finally, 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,73 Aggressive Research Intelligence Facility,74 and Assessment of Multiple Systematic Reviews.15 However, instances of poor reporting of key information published in systematic reviews have 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.

CONCLUSIONS

We have presented extensive data that demonstrate that measures of pain are predominantly used in trials of NeP conditions and highlight the scant usage of physical functional outcome measures. As NeP is a multidisabling 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. As appropriate diagnosis followed by the earliest appropriate management remains the primary target to minimize the risks for comorbidities and disabilities, this issue needs to be considered for future research and guidelines development.

ACKNOWLEDGMENT

The authors thank and acknowledge Professor Chad Cook, Department of Physical Therapy, Walsh University, North Canton; for his suggestions, invaluable constant assistance, and helping with the constructive feedback on drafts of the manuscript.

REFERENCES

1. International Association for the Study of Pain. Diagnosis and Classification of Neuropathic Pain [Web Page]. Available at http://iasp.files.cms-plus.com/Content/ContentFolders/Publications2/PainClinicalUpdates/Archives/PCU_18-7_final_1390_200761555_9.pdf. Accessed December 9, 2011.
2. Treede RD. Redefinition of neuropathic pain and a grading system for clinical use: consensus statement on clinical and research diagnostic criteria. *Neurology*. 2008;70:1630–1635.
3. Merskey H, 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. *Anesth Analg*. 2003;97:785–790.
5. Cruccu G, Sommer C, Anand P, et al. EFNS guidelines on neuropathic pain assessment: revised 2009. *Eur J Neurol*. 2010;17:1010–1017.
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. *J 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. *J Rheumatol*. 1997;24:799–802.
9. Deyo RA, Battie M, AJ Beurskens, et al. Outcome measures for low back pain research: a proposal for standardized use. *Spine*. 1998;23:2003–2013.
10. Ostelo RWJG, de Vet HC. Clinically important outcomes in low back pain. *Best Pract Res Clin Rheumatol*. 2005;19:593–607.
11. Haampää 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*. 1998;78:123–129.
13. Clinical Resource Efficiency Support Team (CREST). Guidelines on the management of neuropathic pain [Web Page]. Available at http://www.tbblack.com/links/RSD/CRESTManagementNeuropathicPainGuidelines.pdf. Accessed September 6, 2012.
14. Merskey H, 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 Med*. 2009;6:e1000100.
16. Shea BJ, Grimshaw JM, Wells GA, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMJ Med Res Methodol*. 2007;7:10.
17. Chen W, Zhang Y, Liu JP. Chinese herbal medicine for diabetic peripheral neuropathy. *Cochrane Database Syst Rev*. 2013;10:CD007796.
18. Hurley RW, Lesley MR, Adams MCB, et al. Pregabalin as a treatment for painful diabetic peripheral neuropathy: a meta-analysis. *Reg Anesth Pain Med*. 2008;33:389–394.
19. Itses KI, Anderson EJ, Cahill ML, et al. Balance interventions for diabetic peripheral neuropathy: a systematic review. *J Geriatr Phys Ther*. 2011;34:109–116.
20. Li H. Effectiveness of the anodyne therapy system in treating diabetic peripheral neuropathy: a systematic review. *Phys Ther Rev*. 2008;13:395–404.
21. Wang MC, Chung JWY, Wong TKS. Effects of treatments for symptoms of painful diabetic neuropathy: systematic review. *BMJ*. 2007;335:87–90.
22. Chiallappali V, Tremont-Lukas JW, McNicol ED, et al. Systemic administration of local anesthetic agents to relieve neuropathic pain. *Cochrane Database Syst Rev*. 2005;CD003345.
23. Collins SL, Moore RA, McQuay HJ, et al. Antidepressants and anticonvulsants for diabetic neuropathy and postherpetic neuralgia: a quantitative systematic review. *J Pain Symptom Manage*. 2000;20:449–458.
24. Eccles NK. A critical review of randomized controlled trials of static magnets for pain relief. *J Altern Complement Med*. 2005;11:495–509.
25. Gill D, Derry S, Wiffen PJ, et al. Valproic acid and sodium valproate for neuropathic pain and fibromyalgia in adults. *Cochrane Database Syst Rev*. 2011:CD009183.
26. Goodyear-Smith F, Halliwell J. Anticonvulsants for neuropathic pain: gaps in the evidence. *Clin J Pain*. 2009;25:528–536.
27. 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.
28. McQuay HJ, Tramer M, Nye BA, et al. A systematic review of antidepressants in neuropathic pain. *Pain*. 1996;68:217–227.
29. Moore RA, Straube S, Wiffen PJ, et al. Pregabalin for acute and chronic pain in adults. *Cochrane Database Syst Rev*. 2009:CD007076.
