

What outcome measures are commonly used for Complex Regional Pain Syndrome clinical trials? A systematic review of the literature

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Short title: Outcome measures used in CRPS clinical trials

Category: Review article

Database

- 104 papers have been found meeting the following inclusion criteria; published from January 2000 onwards, available in English, reporting primary data of an adult population (n>1) and evaluating an intervention directed at CRPS.

What does this review add?

- In this systematic review we have identified questionnaire format outcome measures which are patient or health professional reported, used in CRPS clinical trials since 2000, and those which have been developed specifically for a CRPS population.
- Information gained will inform an international consortium project to define a core outcome measurement set for CRPS Clinical trials.

Ethical Approval: Not required

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Abstract

Background and Objective

Complex Regional Pain Syndrome (CRPS) is a chronic pain condition, often triggered by trauma to a limb and characterised by sensory, motor, autonomic and trophic changes within the affected limb. Due to the multi-faceted nature of the condition there are a wide range of potential health outcome measures for use within CRPS related clinical trials. This aim of this systematic literature review was to identify which patient or health professional questionnaire format outcome measures have been used in CRPS specific clinical trials, and which of these have been developed specifically for use in CRPS populations. Information gained from this review will inform an international consortium project to define a Core Outcome measurement set for CRPS Clinical trials.

Databases and Data Treatment

The electronic databases EMBASE, Medline, PsycInfo, CINAHL and LILACS were systematically searched from January 2000 until April 2014.

Results

104 full text papers were obtained with 68 questionnaire outcome measures identified. Five of these outcome measures were validated for CRPS. Of those outcome measures used since 2000, those addressing physical functioning were most prevalent.

Conclusions

Currently CRPS clinical trials use a wide range of outcome measures making the potential to synthesise evidence problematic. There is no internationally agreed core measurement set. This diversity of outcome measures demonstrates a clear need for the development of a core measurement set to be used in CRPS clinical trials.

Introduction

Complex Regional Pain Syndrome (CRPS) is a chronic pain condition which predominantly occurs after trauma to a limb. Pain is disproportionate to the inciting injury and associated with motor, sensory, trophic and autonomic changes (Harden et al., 2010). In many cases CRPS will resolve within the first 6-13 months as indicated in prospective studies (Bean et al., 2014), however approximately 15-20% of individuals will develop long term disability significantly affecting their quality of life (Field et al., 1992; Geertzen et al., 1998).

CRPS clinical trials currently do not have a shared core measurement set of internationally agreed outcome measures. This lack of standardisation limits the value of the synthesis of clinical trial evidence and its translation to clinical practice (Tugwell et al., 2007; Boers et al., 2014; Macefield et al., 2014). The complex nature of the condition means researchers may consider a wide range of instruments to measure outcomes and, as a result, there is heterogeneity across studies. To address these challenges, an international consortium of patients, clinicians and researchers was established in 2013 (COMPACT*) to identify and agree a minimum core set of outcome measures to answer specific research questions agreed as internationally important for the advance of treatment of CRPS. Previous initiatives have advocated the use of core outcome measurement sets in pain and rheumatology clinical trials; Initiative on Methods Measurement and Pain Assessment in Clinical Trials (IMMPACT) and Outcome Measures in Rheumatology (OMERACT). Each initiative

* **COMPACT** Core Outcome Measures for complex regional PAin syndrome Clinical Trials.

identifies a number of core domains which should be considered when establishing a core set of health outcome measures (Turk et al., 2003; Boers et al., 2014). The six IMMPACT domains (Turk et al., 2003) are listed below;

- Pain
- Physical functioning
- Emotional functioning
- Participant ratings of global improvement
- Symptoms and adverse events
- Participant disposition

These are applicable to chronic pain clinical trials such as CRPS studies. The outcome measures identified from our literature search were mapped to the six IMMPACT domains to facilitate the selection of a core outcome measurement set thereby enabling future comparison across CRPS clinical trials.

Two previously published systematic literature reviews have been conducted which identified and evaluated outcome measures used for CRPS clinical trials (Schasfoort et al., 2000; Packham et al., 2012). Schasfoort et al., (2000) classified the outcome measures used in research for CRPS type I in the context of rehabilitation medicine. Both questionnaire outcome measures and objective clinical measures were included and assessed for relevance and objectivity. The authors found most outcome measures focused on sensory, motor, trophic and autonomic impairments with fewer measuring functional and social outcomes. Packham et al.,(2012) conducted a systematic review of the literature which evaluated the psychometric properties of outcome measures used for CRPS. Of those identified, no tool was

found to have been fully assessed for the comprehensive range of psychometric properties, resulting in no specific tool being recommended by the author for use in CRPS.

This presented systematic literature review was required to identify the potential range of health outcome measure questionnaires that could be included within the CRPS core outcome measurement set.

METHODS

Data sources and search strategy

CRPS clinical trials were identified from January 2000 onwards. A comprehensive literature search was conducted by 2nd April 2014 using electronic databases; EMBASE, Medline, PsycInfo, CINAHL and LILACS. Search terms comprised the study population combined with intervention terms. The study population terms were informed by the key word Complex Regional Pain Syndrome and its acronyms, synonyms and truncations, listed in Appendix S1. CRPS Type I and II were included (without/with associated nerve damage). The terms were mapped to a thesaurus for completeness. Search terms to identify the clinical trials were informed by a Cochrane systematic review of interventions for treating pain and disability in adults with CRPS (O'Connell et al., 2013), consultation with an academic librarian and colleagues with expertise in the area . An intervention study was defined according to O'Connell et al., (2013) as; "any intervention aimed at treating pain or disability or both". To capture clinical trials, the first 200 results of the study population search in EMBASE were reviewed and subject headings relating to study design classification identified. These terms were reviewed by the author and another researcher to

ensure comprehensiveness and then used to identify the clinical trials. Appendix S2 lists the key terms.

Selection criteria

The following inclusion criteria were applied to the search results;

1. Paper available in the English language
2. Human subjects
3. Primary data only
4. Study population aged 18 and over
5. Papers published from January 2000 until date of search
6. Studies evaluating an intervention directed at CRPS
7. Studies with more than one participant

There were no restrictions on study design applied as the intention was to capture all questionnaire outcome measures used for CRPS clinical trials regardless of methodology. The inclusion criteria were applied using the limiters available on the database where possible, and then applied to the title and abstract. SG reviewed all search results except Medline (LJ). Papers were identified from 2000 onwards as around this time the International Association for the Study of Pain (IASP) criteria were validated for standardising diagnosis of CRPS (Bruehl et al., 1999). In addition, this builds on work in a similar area (Schasfoort et al., 2000). To ensure all clinical trials were captured and for completeness, the search results were checked against papers identified in previous systematic reviews (Cossins et al., 2013; O'Connell et al., 2013), an unpublished systematic literature review and Trauma RElated Neuronal

Dysfunction (TREND) publications; a Dutch clinical and academic consortium (accessed from <http://www.trendconsortium.nl/research/publications>).

Identifying outcome measures

The full text of each paper meeting the inclusion criteria was examined and all patient reported and health professional reported questionnaire outcome measures were identified. In instances where an instrument appeared to be referenced under different measure names, for example; Walking Ability Questionnaire (Roorda et al., 2005b), Walking Questionnaire and the Walking Skills Questionnaire, further clarification was sought from academic papers or the author directly. Objective clinical measures were not captured for the purposes of this review. Where possible the aim and scope of each outcome measure was recorded, licence access restrictions if any, and the language options available; this information was for later use to inform the COMPACT project.

Classification of CRPS clinical trials

Clinical trials were classified according to the three core elements of CRPS treatment described by O'Connell et al., (2013); pain management, rehabilitation and psychological therapy. Each element incorporates many different therapeutic options; for example, pain management includes pharmacological approaches, surgical interventions and neuromodulation techniques, rehabilitation includes physiotherapy and occupational therapy, and psychological therapy includes education and cognitive behaviour therapy (O'Connell et al., 2013). The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)

recommendations for reporting systematic literature reviews have not been used as the papers were not assessed for methodological quality (Moher et al., 2009).

Application to domains

The outcome measures identified were mapped to the six core IMMPACT domains to inform the future selection process of a final core measurement set for the COMPACT consortium.

RESULTS

Study selection

Initial searches generated a total of 3591 records. After eligibility criteria were applied and duplicates removed, 133 papers remained. Papers were selected if the full text was available electronically or from the librarian, resulting in 104 papers being included in the review (Appendix S3 for a list of included papers). Figure 1 depicts the process. Appendix S4 lists the papers we were unable to access in full text. The 104 papers were classified according to the three core elements of CRPS treatment described by O'Connell et al (O'Connell et al., 2013); pain management (n=82), rehabilitation (n=22) and psychological therapy (n=0). The clinical trials identified incorporated a broad range of methodologies including randomised controlled trials (RCT), open label studies, observational and pilot studies. Prospective and retrospective studies were included.

INSERT FIGURE 1 HERE

Outcome Measures

68 outcome measures were identified from the 104 papers included in the review (Table 1). Four measures were adapted specifically for CRPS; Brief Pain Inventory adapted for CRPS (van der Vusse et al., 2004), CRPS Limb Symptom Scale (Goebel et al., 2010) and global impression of change of CRPS signs and symptoms, both patient reported (Munts et al., 2009; Munts et al., 2010) and health professional reported (Munts et al., 2009; Munts et al., 2010; van der Plas et al., 2011; van der Plas et al., 2013). 64 measures were generic. Five outcome measures were validated for CRPS; Radboud Skills Questionnaire (Oerlemans et al., 2000), Rising and Sitting Questionnaire (Roorda et al., 2005a), Walking Stairs Questionnaire (Roorda et al., 2004), the Walking Ability Questionnaire (Roorda et al., 2005b) and the Neuropathic Pain Scale (Galer and Jensen 1997).

INSERT TABLE 1 HERE

Mapping to the IMMPACT domains

The content of some of the identified outcome measures spanned more than one of the IMMPACT domains. For example, The Short Form-36 (Ware and Sherbourne 1992) includes measures relating to physical functioning and mental health. For the purpose of this review a decision was made by the authors to classify outcome measures into the domain that best represented the majority of the outcome measure items.

The number of studies included in this review which use each outcome measure is identified in brackets in the following text.

Pain

Nineteen different outcome measures were identified for this domain. The most frequently used were the visual analogue scale (n= 53 studies) and numeric rating scale (n=33) which are used to assess pain intensity on a scale of 0-10. The McGill Pain questionnaire was also frequently used (n=24), assessing both intensity and quality of pain (Melzack 1975). Other pain measures were used much less frequently (≤ 5 studies for each measure) such as the Neuropathic Pain Scale (Galer and Jensen 1997), Pain Disability Index (Pollard 1984) and Brief Pain Inventory (Cleeland 1989). All outcome measures identified in this domain were patient self-report.

Physical Functioning

Twenty-nine different outcome measures were used to capture physical functioning. Most frequently used were the EuroQol EQ-5D (EuroQol Group 1990) (n=11), Radboud Skills Questionnaire (Oerlemans et al., 2000) (n=10) and the Rising and Sitting Questionnaire (Roorda et al., 2005a) (n=10). The Short-Form 36 (Ware and Sherbourne 1992) (n=9), Walking Ability Questionnaire (Roorda et al., 2005b) (n=8) and the Disabilities of Arm, Shoulder and Hand questionnaire (Hudak et al., 1996) (n=6) were also used frequently. Many outcome measures were used in only one study, for example the International Physical Activity questionnaire (Sjöström et al., 2002) and the Rivermead Mobility Index (Collen et al., 1991). 90% (n= 26) of outcome measures identified were patient reported.

Emotional Functioning

Ten outcome measures were identified for this domain, five of which were designed to assess depression. Other measures included those used to measure an individual's emotional response to pain, such as the Pain Anxiety Symptoms Scale (McCracken et al., 1992) and the Pain Catastrophizing Scale (Sullivan et al., 1995). The Tampa Scale for Kinesiophobia was the most widely used measure in the emotional functioning domain (n=4). This scale was originally designed to measure fear of movement related to lower back pain (Miller et al., 1991). All measures are patient reported except the Hamilton Rating Scale for Depression (Hamilton 1980) (n=1).

Participant Rating of Global Improvement

Eight outcome measures were identified for this domain. The most frequently used were the Patient Global Impression of Change questionnaire (PGIC) (n=6) and the Global Perceived Effect (n=6). Other measures included the PGIC of CRPS Signs and Symptoms (n=2) and Response to Treatment (n=1). One health professional rating scale was used in several studies; Clinician Rating of Global Impression of Change in CRPS Signs and Symptoms (n=4). Only one rehabilitation study reported using an outcome measure from this domain (Lagueux et al., 2012), with more frequent use demonstrated in studies relating to pain management.

Symptoms and Adverse Events

Two studies (Wallace et al., 2000; Kiefer et al., 2008) recorded the occurrence and intensity of side effects using a visual analogue scale (0-100mm). Participants were asked to rate any side effects which may occur as a result of the intervention; from no side effect to worst imaginable side effect or intolerable.

Patient disposition

This domain includes those participants who withdrew from a study or who were lost to follow up. Although, it is acknowledged that these data are important to report, the studies identified within this literature review did not use questionnaire outcome measures to capture these data.

DISCUSSION

This systematic literature review provides a comprehensive summary of patient reported and health professional reported questionnaire outcome measures used in published CRPS intervention studies conducted between January 2000 and April 2014. There is clear evidence of a shift in utilisation of outcome measures compared to the findings of previous work (Schasfoort et al., 2000). Prior to 2000 there was little emphasis on health outcomes related to daily functioning in the context of rehabilitation medicine. In the literature review by Schasfoort et al., (2000) the majority of outcome measures related to sensory, motor, trophic and autonomic impairments but in contrast, in this current review, outcome measures related to physical functioning comprised 43% of identified tools. Furthermore, some measures which were classified within other domains also incorporate aspects of physical functioning e.g. West Haven-Yale Multidimensional Pain Inventory (Kerns et al., 1985). The change in diagnostic criteria since publication of the Schasfoort review (2000) may account for this change. Current IASP diagnostic criteria have a stronger emphasis on motor function which may have encouraged a greater focus on the assessment of physical function in recent studies.

The studies included in this current review encompass a wide range of therapeutic interventions within the area of pain management and rehabilitation described by

O'Connell et al., (2013). Several studies investigated pain exposure therapy in a rehabilitation context and were therefore classified as rehabilitation rather than psychological interventions; confirmed by correspondence with the authors (Ek et al., 2009; van de Meent et al., 2011; Barnhoorn et al., 2012). The cross-over between the rehabilitation and psychological classification is acknowledged however with both approaches addressing aspects of the other. There was an absence of studies reporting other psychological interventions which was unexpected as these were recommended as best-practice in the IASP treatment algorithm and have been considered a core part of CRPS rehabilitation treatment for some time now (Stanton-Hicks et al., 1998; Harden et al., 2013). National guidelines within the UK also advocate psychological interventions as one of the four pillars of care along with pharmacological, physical and vocational rehabilitation, and patient education/self-management interventions (Goebel et al., 2012).

The diversity of outcome measures identified across the research studies demonstrates the challenge of synthesising research evidence at a national or international level. The heterogeneity of outcome measures may compromise potential meta-analysis and interpretation of results demonstrating the need for more consistency across clinical trials (Duncan et al., 2000). However, it is apparent that some instruments are utilised for several studies by the same researcher or research team, making within research group synthesis or across these specific research groups more feasible. In addition, there may be cultural factors which influence the selection of specific measures. Patient reported outcome measures developed for a particular cultural group may increase the response rate therefore influencing the choice of a particular measure, however validation for the specific population is required (Weldring and Smith 2013). Health professional reported

outcome measures comprised only 9% of those identified. These provide objective clinical judgements of the patient's signs, impairment and disability but cannot report symptoms and experiences only known to the patient (Black and Jenkinson 2009). The prominence of patient reported outcomes is largely a consequence of clinical interventions aiming to improve aspects of the condition which can only be experienced and reported by the patient. In addition the nature of a chronic pain condition means objective measures of a patient's pain experience are not available (Turk et al., 2006). As expected there are no health professional reported outcome measures identified in the pain domain within this review.

Of the outcome measures identified in the review, only five were validated for CRPS; Radboud Skills Questionnaire (Oerlemans et al., 2000), Rising and Sitting Questionnaire (Roorda et al., 2005a), Walking Stairs Questionnaire (Roorda et al., 2004), the Walking Ability Questionnaire (Roorda et al., 2005b) and the Neuropathic Pain Scale (Galer and Jensen 1997). This indicates a need for further disease specific measures to be validated as they provide greater face validity and credibility than generic measures (Black 2013).

Limitations/Risk of Bias

This review was not without limitations. Papers were confined to English language only as translation services were unavailable. The literature search was reviewed predominantly by one researcher (SG) except Medline (SG and LJ). Access to full text papers was limited by availability of online resources via electronic databases. The academic library was unable to provide unlimited support to access additional papers as no specific funding was available for this. The full text of 29 papers was unobtainable for these reasons and there is a possibility that outcome measures not

previously identified may be included in these papers. No intervention studies were identified relating to psychological therapy and consideration should be given to revisiting the search strategy in collaboration with a psychologist to confirm the search result.

Conclusion

A broad range of patient reported outcome measures are used to evaluate the impact of interventions for CRPS, with fewer utilised outcome measures being health professional reported. This diversity of outcome measures demonstrates a clear need for the development of a specific CRPS core outcome measurement set to facilitate the synthesis of evidence, particularly in this relatively rare condition which would benefit from large scale studies.

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Supporting Information

Appendix S1 Key search terms for CRPS

Appendix S2 Key search terms for clinical trials

Appendix S3 Final papers included in the systematic literature review.

Appendix S4 Papers not included in SLR as full text unavailable.

FIGURE AND TABLE LEGENDS

Table 1: Outcome Measures identified from the systematic literature review

Figure 1: Study Flow

Authorship statement of responsibility: CM and SG conceived the study; NW advised on methodology; SG conducted searches; SG and LJ reviewed search results; all authors reviewed the final paper.

