



Management of Chronic Central Neuropathic Pain Following Traumatic Spinal Cord Injury

Summary

Overview

Pain has been recognized for more than 50 years as one of the many symptoms experienced by persons who have suffered traumatic spinal cord injuries (TSCI). Efforts to estimate the prevalence, severity, and duration of pain after TSCI have led to variable results. This variation has been explained by differences among studies in terms of pain definitions, terminology, classification, inclusion criteria, variability in reporting methods, as well as several etiologic, demographic, and cultural factors.

Great variability and little consensus have also plagued the classification of pain in persons with TSCI. In 1997, however, a group of investigators developed a classification that appears to be gaining widespread acceptance. The first axis of this classification includes four major categories or divisions of pain: musculoskeletal, visceral, neuropathic, and other. These categories are based on the system affected, which can be readily identifiable in clinical settings. Neuropathic pain is the focus of this report.

Neuropathic pain is defined as pain that occurs following damage to the central or peripheral nervous system. This pain can be identified by site (region of sensory disturbance) and by features (sharp, shooting, electric, burning, stabbing). Neuropathic pain can be further broken down by site (Axis 2) into neuropathic pain “at level” (pain that occurs at the level of the spinal cord injury, in a segmental pattern with neuropathic features) and neuropathic pain “below level” (diffuse pain that is described by the words “burning,” “tingling,” “aching,” “shooting,” or “stabbing” and that should be present at least three segments below the level of injury). Neuropathic pain “at level” can be subdivided further into radicular (when it can be attributed to nerve root pathology) or central (when it is due

to changes within the spinal cord or possible supraspinal structures), although the value of this subdivision has been questioned.

Neuropathic pain not only is one of the most challenging conditions in chronic pain management and one of the most promising areas in pain research, but also it may have even greater impact on the quality of life of patients than the extent of the injury itself.

This evidence report was developed by the McMaster University’s (MU) Evidence-based Practice Center (EPC). The objectives of the report were to conduct a comprehensive systematic review of the literature on this important topic and to support guideline development initiatives by the Consortium for Spinal Cord Medicine (CSCM) and other interested organizations, while building on existing work and focusing on answerable, clinically relevant questions.

Reporting the Evidence

A set of questions was initially proposed by the CSCM and further refined with input from members of the MU-EPC and the Task Order Officer. All questions, unless otherwise specified, relate to the assessment or management of chronic central neuropathic pain (CNP) following TSCI in adults and adolescents.

After multiple consultations, the following questions were selected as the focus of the evidence report. To maximize the efficiency of the process, they were grouped by theme.

Group I. Issues Related to Assessment.

1. What are the measurement properties (reliability, validity, and responsiveness) of:
 - a) Assessment approaches for chronic CNP per se (including criteria and tools such as inventories, questionnaires, and scales)?

- b) Other outcome measures or assessments (related to the experience of pain)?
 - c) Assessment approaches (including criteria and tools such as inventories, questionnaires, and scales) to identify new onset musculoskeletal pain against a background of chronic CNP?
2. What is the strength of evidence for strategies for the differential diagnosis of chronic CNP from other types of pain?

Group II. Issues Related to Natural History.

3. What is the strength of evidence for identifying the prevalence of acute and chronic CNP, and factors that could predict the development of chronic CNP?

Group III. Issues Related to Interventions for Treatment.

4. What is the evidence for the effectiveness and safety of each of the following classes of medications:
- a) Simple analgesics (including NSAIDs and acetaminophen), antidepressants (including tricyclics and selective serotonin reuptake inhibitors [SSRIs]), antiseizure medication, narcotics, muscle relaxants, N-methyl-D-aspartate (NMDA) antagonists, and local anesthetics?
 - b) How do these classes of medication compare with each other?
 - c) What is the strength of evidence for the effectiveness and safety of treatment algorithms including these classes of medication?
5. What is the evidence of effectiveness and safety of:
- a) Transcutaneous electrical nerve stimulation (TENS).
 - b) Nerve blocks (regional anesthetic interventions).
 - c) Surgery, including dorsal root entry zone (DREZ).
 - d) Multidisciplinary pain treatment approaches.
 - e) Pain management approaches.
 - f) Comprehensive pain management clinics.
 - g) Psychosocial interventions.
6. What is the evidence for the effectiveness and safety of self-management approaches to chronic pain management (e.g., Catalano's workbook, Caudill's workbook, Aspen's pain management education manual, Tollison's pain management patient guide)?

The Technical Expert Panel (TEP) for this report included individuals who represented professional organizations, providers of health care, purchasers of health services, researchers, and consumers. These individuals are recognized as national and international leaders in the management of pain or in issues related to spinal cord injury.

Methodology

Selection Criteria and Screening Process

Initially, EPC researchers used very liberal selection criteria. They regarded as potentially eligible any article that described a study: a) in humans; and, b) about the cause, management, or measurement of CNP in persons after TSCI. There was no exclusion based on study design.

They excluded reports that were not primary studies, studies where the sample consisted of persons without a TSCI, those without chronic neuropathic pain, or children younger than 13 years. They also excluded primary studies that did not contain data in the published report, and studies in which the sample included persons with TSCI as well as other types of CNP (but where the results were not presented separately for persons with TSCI). In addition, the researchers excluded studies that only used the term "chronic pain" without any other description of the pain experienced by the persons in the study sample that could have helped them judge it as central and neuropathic.

They accepted any definition for CNP provided by the primary study authors. They also developed a list of descriptions of CNP based on their preliminary searches. This list was used to guide the research team during the two-step screening process with six raters working in pairs. The first step was based on the information available in titles and abstracts (where available) and was conducted by the same two raters working independently. The second step of the screening was based on full-text reports and involved all six raters randomly paired. (Discrepancies were resolved by discussion.)

Literature Search

Citations of potentially eligible studies were identified through a systematic search of:

- MEDLINE, EMBASE, and PsycINFO from the date of their release to the end of May 2000.
- CINAHL, HEALTHStar, and Sociological Abstracts. These databases were searched from the date of their release to November 1999.
- The Cochrane Library (issue 4, 1999).
- The reference lists of any eligible article identified in any of the cited sources.
- Personal files of all members of the local research team and the TEP.

The development and refinement of the search strategy followed an iterative process using MEDLINE. The refined MEDLINE strategy was modified to meet the specific features of CINAHL, EMBASE, and PsycINFO.

Data Extraction

All data extraction forms were developed, pilot-tested, and revised by members of the local research team including the team statisticians. After consultations with the TEP, Task Order Officer, and project partners, the forms were approved for content. A general data extraction form was used with all studies, while individual forms were used for RCTs, observational studies, and case reports. Items related to the quality of different study designs were embedded within the data extraction forms. Two reviewers completed data extraction independently for all studies except the case reports. For these studies, data were extracted by one reviewer and checked by another. Any disagreements were resolved by consensus. Following consensus on each item, the data forms were scanned into a Microsoft® Access database using TELEform® software.

Data Synthesis

Descriptive statistics were calculated for all fields of the database. Evidence tables were constructed to describe the most salient features of the included studies according to the review question. These tables are found at the end of each chapter of the full evidence report (along with the relevant supplementary tables).

The local research team at the MU-EPC, in consultation with members of the partner organizations and the Task Order Officer, evaluated the overall quantity and quality of the data available. This evaluation led to the conclusion that meta-analysis would be inappropriate to summarize the evidence on each of the research questions or for each of the main categories of interest. The main reasons for this decision were substantial clinical heterogeneity across the studies (e.g., interventions evaluated, patient samples, duration), inconsistency in outcome measurements, low methodologic quality and incomplete data reporting (detailed descriptions within each category are included in the full evidence report). Therefore, this report represents a systematic qualitative review of the existing evidence, emphasizing the implications for clinical practice and the directions that future researchers could take to fill existing knowledge gaps.

For the purposes of this evidence report, the evidence syntheses were grouped in five chapters that included:

- The yield of the literature and general characteristics of all included studies.
- Studies on the diagnosis, assessment, and natural history of CNP after TSCI.
- Pharmacologic interventions.
- Spinal cord and deep brain stimulation techniques.

- Dorsal root entry zone (DREZ) lesions and other surgical interventions.

Findings

The analysis of the yield of the literature and general characteristics of the studies showed that:

- A total of 591 full articles were retrieved and screened. After screening, 158 studies met the inclusion criteria. Of the 158 studies, 19 were reported in more than one publication. After several iterations, a total of 132 unique studies were included. These form the basis for the evidence report.
- Six studies were randomized controlled trials (RCTs), and 126 were observational studies including 47 case series and at least 56 single or multiple case reports.
- Overall, numerous deficiencies in the reporting of the studies limited the assessment of their validity, relevance, precision, and therefore, their clinical application. More than 50 percent of studies did not provide a definition for neuropathic pain, report the cause of the injuries, describe the use of surgical stabilization, state the onset time for pain after injury, or highlight the duration of pain. Fifty-four percent of the studies did not report the time from the injury to the inclusion in the study, the completeness of the injury, or the area of the body affected by pain.
- There was little information on the management of CNP following TSCI in women and adolescents.
- Thirty percent of studies had fewer than 25 patients. This limited their power to detect meaningful clinically important differences among the interventions.
- There were no studies evaluating the role of treatment algorithms or multidisciplinary approaches. Only two studies evaluated self-management strategies in cases of CNP following TSCI.
- Comparison or synthesis of data across studies was limited by the low quality of reporting, and by the large number and heterogeneity of outcome measures and tests used in the studies.

The following is a description of the main conclusions and the implications from practice that could be derived from the available evidence to address the initial questions:

- **Diagnosis, assessment, and natural history.** There are no discriminative or evaluative measurement instruments that have been adequately investigated with respect to psychometric measurement properties in this context. Despite the serious limitations of most of the individual studies, most estimates of the prevalence of chronic pain after TSCI vary from 40 to 75 percent of patients. Pain

is moderate to severe in 25 to 60 percent of these persons, is often associated with psychologic and psychiatric conditions, and is severe enough to impair or prevent optimal physical function and daily living.

- **Pharmacologic interventions.** There is a dearth of research in this area, which includes most of the interventions that are regarded as the core for the management of other types of neuropathic pain. The few studies available have such small sample sizes, poor methodology, and incomplete reports, that it was not possible to judge the value of any individual intervention or group of interventions. Although it appears that local anesthetics, opioids, and clonidine given spinally may be effective to relieve CNP following TSCI, better research is needed. While the needed evidence is gathered from methodologically rigorous studies, clinicians interested in using pharmacologic interventions will have to rely on research on these interventions in other patient populations.
- **Spinal cord and deep brain stimulation techniques.** The studies had similar deficiencies to those described above. The limited evidence available suggests that spinal cord stimulation has a variable rate of early success and a low rate of long-term effectiveness. Deep brain stimulation has a low rate of early success and an even lower long-term success coupled with important adverse events. These findings make it difficult to justify the use of either procedure as a method of treating CNP after TSCI. Transcutaneous electrical nerve stimulation (TENS) may reduce the sensation of “pain unpleasantness,” if patients have positive expectations of treatment effectiveness.
- **Dorsal root entry zone (DREZ) lesions and other surgical interventions.** All studies on DREZ showed high rates of success but had poorly defined or lacked inclusion and exclusion criteria, included no control groups, and did not report adequately the severity of the adverse effects experienced by patients. Even recognizing the problems regarding the validity and generalizability of the studies, some may look to DREZ lesioning or other spinal surgeries as a last resort when other palliative efforts have failed. Given that the studies did not adequately report the severity of the adverse effects experienced by patients, it is unknown whether DREZ lesioning and other spinal surgeries pose unwarranted risks to patients.

Future Research

Research on the management of central CNP following TSCI is in its infancy. The following are some suggestions for future research:

- Multicenter collaboration to set a research agenda. The Consortium for Spinal Cord Medicine may be well positioned to facilitate this level of collaboration or alternative strategies may be needed to foster pragmatic working relationships, even among groups that do not have a tradition of cooperation. Such collaborative groups could study the research problems and provide training in clinical research to young investigators.
- Given the prevalence and severity of CNP following TSCI and the dearth of research to support any therapeutic strategy, it is imperative to develop effective strategies to improve the number, validity, precision, and relevance of future studies.
- Larger studies with more rigorous design, more comprehensive reports, and longer-term followup are needed to establish the effectiveness and adverse effects of most of the interventions available. Special emphasis should be made to gather evidence on the effect of different interventions in women and adolescents.
- Research groups should make efforts to select a core set of validated and clinically relevant outcomes to be measured in all the studies in addition to any other outcomes of interest to the specific groups of researchers.
- More rigorous studies, ideally, large double-blind multicenter RCTs, are clearly needed to establish the relative effectiveness and safety of different pharmacologic interventions. Priority should be given to interventions with established roles for the management of other types of neuropathic pain, such as tricyclic antidepressants, anticonvulsants, local anesthetics, and opioids. Studies designed to judge the added value of these interventions given in combination, through invasive routes (e.g., epidural and intrathecal infusions of opioids and local anesthetics), or using different formulations (e.g., sustained release preparations) should also be a priority.
- Since CNP is associated with psychosocial difficulties, other noninvasive approaches such as multidisciplinary or self-management approaches should be developed for those with TSCI and evaluated.
- More definitive studies are needed to determine the effectiveness and safety of non-pharmacologic interventions. Based on the evidence available, the most promising interventions are spinal cord stimulation and DREZ lesions. These interventions are also invasive and potentially harmful. The studies that are needed,

however, will require complex controlled designs with close attention to safety issues, substantial resources, and efficient collaboration among research groups.

- Studies are also needed to determine whether the response to treatment is influenced by the level and cause of the TSCI, as well as by the duration, distribution, and characteristics of the pain and comorbid factors (e.g., anxiety and depressive disorders).
- There is a great opportunity for consumer groups to call for and support more research activities, given the number of important questions that remain unanswered.
- Funding and conducting the research that is required will not be easy, given the complexity of the disorder, the frequent presence of comorbidity, and the variety of interventions and outcomes available. Future research efforts will require commitment among different groups of stakeholders, some of which do not have a tradition of collaboration.

In summary, this report includes the first set of systematic reviews on the management of chronic CNP following TSCI. They incorporate state-of-the-art methodology and are ready for incorporation into evidence-based clinical practice guidelines or performance measures. The report also provides a

detailed description of the many limitations of the evidence available and provides recommendations to fill existing knowledge gaps through rigorous research. Filling such gaps will not be easy and will require highly innovative efforts and collaboration among different groups of decisionmakers. If this field continues to produce few, small, incompletely reported studies with heterogeneous designs, instead of the high quality collaborative efforts required, research in this area will continue to be of little value to guide important clinical and policy decisions.

Availability of Full Report

The full evidence report from which this summary was taken was prepared for AHRQ by the McMaster University's Evidence-based Practice Center under contract number 290-97-0017. It is expected to be available in early 2002. At that time, printed copies may be obtained free of charge from the AHRQ Publications Clearinghouse by calling 800-358-9295. Requestors should ask for Evidence Report/Technology Assessment No. 45, *Management of Chronic Central Neuropathic Pain Following Traumatic Spinal Cord Injury*. When available, Internet users will be able to access the report online through AHRQ's Web site at: www.ahrq.gov.



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