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REVIEW ARTICLE (META-ANALYSIS)

Systematic Review of Pharmacologic Treatments of Pain After Spinal Cord Injury: An Update

Swati Mehta, MA,[a,b,c] Amanda McIntyre, RN, MSc,[a,b] Shannon Janzen, MSc,[a,b] Eldon Loh, MD, FRCPC,[a,b,c] Robert Teasell, MD, FRCPC,[a,b,c] Spinal Cord Injury Rehabilitation Evidence Team[a,b,c,d]

From the [a]Lawson Health Research Institute, London, ON; [b]Parkwood Institute, London, ON; [c]Western University, London, ON; and [d]University of British Columbia, Vancouver, BC, Canada.

Abstract

Objective: To update a systematic review of published research on pharmacotherapy for pain post-spinal cord injury (SCI).

Data Sources: PubMed/MEDLINE, CINAHL, Embase, and PsycINFO databases were searched for articles from 2009 to September 2015 examining treatment of pain post-SCI.

Study Selection: Studies were included for analysis if they met the following 4 a priori criteria: (1) written in the English language; (2) ≥50% of subjects had an SCI, unless results were stratified by population type; (3) participants included ≥3 subjects with an SCI; and (4) any intervention involving pharmacologic treatment for the improvement of pain.

Data Extraction: Randomized controlled trials were assessed for methodologic quality using the Physiotherapy Evidence Database scoring system. All research designs were given a level of evidence according to a modified Sackett Scale.

Data Synthesis: Seven new studies met our inclusion criteria. The new studies fell into the following categories: analgesics (n=1), anticonvulsants (n=2), antidepressants (n=2), antispastics (n=1), and cannabinoids (n=1). There was evidence for 5 new pharmacotherapies among the SCI population; these included the following: oxycodone, duloxetine, venlafaxine, phenol block, and dronabinol. Levels of evidence for all therapy modalities were updated based on the new evidence.

Conclusions: Anticonvulsants remain the most studied and supported pharmacotherapy for neuropathic pain post-SCI. Antidepressants showed reduction in pain only among those with comorbid depression. Botulinum toxin and phenol blocks were supported for the reduction of mixed pain post-SCI.

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In 2014, there were an estimated 276,000 individuals with spinal cord injury (SCI) living in the United States, with approximately 12,500 new SCI cases occurring annually.[1] Among this population, prevalence rates of pain are reported to range from 25% to 96%.[2] This large discrepancy is because of variability in study methodology (eg, data collection methods, pain definitions[2,3]) and heterogeneity in the SCI population.[2] Regardless, pain is a significant complication post-SCI that is often managed pharmacologically.

In 2010, our research group conducted a comprehensive systematic review on pharmacologic treatments for pain among individuals with SCI.[4] In total, 28 studies met inclusion, 21 of which were randomized controlled trials (RCTs). The findings demonstrated that analgesics was the treatment most studied, with strong evidence for reducing neuropathic pain found for many of the drugs (ie, intravenous ketamine or alfentanil, intravenous morphine alone or in combination with clonidine, tramadol). Anticonvulsants (eg, gabapentin, pregabalin) were shown to have the strongest evidence for efficacy. Among antidepressants, amitriptyline was the only one shown to be effective, and this was among individuals with both SCI and depression. Finally, the evidence was weak for cannabinoids and antispasticity medications.[4]

Since the publication by Teasell et al,[4] additional reviews and meta-analyses have been conducted that focus on specific types of medications[5,6] and on specific types of pain.[7] Moreover,

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medications that have shown benefit in other populations have since been examined in an SCI population (eg, venlafaxine,[8] dronabinol,[9] oxycodone[10]).

In addition to these research advancements, ongoing efforts have been made for the development of both SCI pain guidelines and a pain taxonomy. The International Spinal Cord Injury Pain Classification developed a 3-tier format for defining pain.[11] The first tier corresponds to the type of pain: nociceptive, neuropathic, other, and unknown. The second and third tiers describe the pain subtype (nociceptive pain: musculoskeletal, visceral, and other; neuropathic pain: at level SCI pain, below level SCI pain, and other) and the primary source of pain, respectively.[11] As consensus is reached on pain definitions, guideline development has also been prioritized. Current Canadian guidelines, the Can-Pain Rehabilitation Clinical Practice Guideline for Management of Neuropathic Pain after Spinal Cord Injury,[12] is underway. Given the continued scientific progress and the importance of pain management among this unique population, an update of the previous review[4] was warranted. Therefore, it was our objective to conduct a systematic review of published studies to examine the effectiveness of pharmacologic treatment for pain after SCI.

Methods

Literature search strategy

This systematic review is an update of the Teasell[4] article; as such, an updated literature search was conducted to locate all studies published from 2009 to September 2015 in several scientific databases: PubMed/MEDLINE, CINAHL, Embase, and PsycINFO. The following keywords were used to retrieve articles: *spinal cord injuries*, *pain*, *pain treatment*, *pharmacology*, *pain management*, *anticonvulsants*, *cannabinoids*, *antidepressants*, *anesthetic*, and *analgesic*. A detailed search strategy can be found in supplemental appendix S1 (available online only at http://www.archives-pmr.org/). Among studies included for review, references were scanned to identify additional relevant articles missed in the original search.

Study selection

Studies were included for analysis if they met the following 4 a priori criteria: (1) written in the English language; (2) ≥50% of subjects had an SCI, unless results were stratified by population type; (3) participants included ≥3 subjects with an SCI; and (4) any intervention which involved pharmacologic treatment for the improvement of pain. Studies assessing concomitant therapies were included for review. Studies were not excluded based on study design, the type of pain post-SCI (ie, nociceptive, neuropathic, mixed), or specific etiology. There were no specified criteria in terms of the timing or intensity of therapy. Studies were excluded if information on patient demographics, research design, intervention, and/or results could not accurately be extracted from the article. The titles and abstracts of articles were reviewed by 2 independent reviewers (S.M. and A.M.). A third reviewer (S.J.) resolved any conflicts regarding inclusion or exclusion of articles. Full articles were retrieved of eligible studies. Figure 1 provides an outline of the retrieval and selection of studies.

List of abbreviations:

PEDro	**Physiotherapy Evidence Database**
RCT	**randomized controlled trial**
SCI	**spinal cord injury**
VAS	**visual analog scale**

Data extraction

Two independent reviewers (S.M. and A.M.) assessed RCTs for methodologic quality using the Physiotherapy Evidence Database (PEDro) scoring system.[13] Discrepancies were resolved by a third, blinded reviewer (S.J.). The tool assesses 11 items on study quality that are answered using a yes (score = 1) or no (score = 0) question. Because the first item is a measure of external validity, it is not used in calculating the final score (maximum total score = 10). To descriptively assess the methodologic quality of RCTs, total PEDro scores were categorized as poor (<4), fair (4–5), good (6–8), or excellent (9–10) (table 1).[14] Additionally, all research designs were given a level of evidence according to a modified Sackett Scale[15] (table 2).

Data were extracted from the studies using an electrical abstraction sheet which included author(s), year, treatment characteristics, study design, intervention/control protocol, outcome measure pre- and posttreatment scores, and adverse effects. Investigations involving similar interventions were grouped and tabulated. When assessment of a specific pain type was not conducted, inclusion of mixed pain was assumed. Data from studies assessed in the previous systematic review are presented in table 3; however, descriptive results were only provided for new studies found in the updated search. Conclusions statements drew on evidence from both previous studies and new studies.

Results

The study selection process is outlined in figure 1. Seven new studies, including 5 RCTs and 2 non-RCTs met our inclusion criteria. Therefore, a total of 35 studies, including the previously reported 28 from the systematic review published by Teasell,[4] were used to inform conclusion statements. Table 3 provides information on study characteristics and outcomes for all treatment types. Table 4 provides conclusion statements for each treatment.

Analgesics

One new study examined the effect of oxycodone on neuropathic pain post-SCI.[10] This resulted in a total of 12 studies examining the effectiveness of analgesics in reducing pain after SCI, as shown in table 2.[10,16-26] Barrera-Chacon et al[10] recruited patients with SCI with anticonvulsant-refractory neuropathic pain. Most patients remained on combination oxycodone and anticonvulsants (ie, gabapentin, pregabalin), similar to baseline (83%). A significant decrease in pain intensity based on the visual analog scale (VAS) was reported at 1 month, from a mean score of 7.1 to 4.3; scores continued to decrease at 3-month follow up ($P<.001$). Over 81% of participants reported improved physical activity, and 60% reported better sleep by 3-month follow-up. However, no significant improvement in quality of life was reported at 3-month follow-up. Side effects were uncommon but included headache, dry mouth, constipation, and nausea.

Anticonvulsants

A total of 13 studies examined the effect of anticonvulsants in reducing pain post-SCI.[27-39] Two new studies examined the effect