A systematic review of pharmacologic treatments of pain after spinal cord injury

CRD summary
This review concluded that anticonvulsant and analgesic medications demonstrated the strongest evidence for treating pain after spinal cord injury. Some caution should be exercised in interpreting the conclusions as evidence was limited, some studies included mixed populations and not all all details of the review process were reported.

Authors' objectives
To assess the efficacy of pharmacological management of pain in individuals with spinal cord injury.

Searching
MEDLINE, CINAHL, EMBASE and PsycINFO were searched from 1980 to June 2009 for studies published in English; search terms were reported. References of retrieved articles were screened.

Study selection
Any study in which the pharmacological intervention for pain management was clearly defined and at least 50% of the participants had a spinal cord injury (minimum of three participants with spinal cord injury required) was eligible for inclusion in the review. All types of pain after spinal cord injury (such as nociceptive, neuropathic and mixed) were examined. Inclusion criteria were based on the previously established spinal Cord Injury Rehabilitation Evidence (SCIRE) methodology.

Most of the included studies were randomised controlled trials (RCTs). Other designs included case series, before and after studies, a prospective controlled study and an observational study. Included studies examined anticonvulsants, antidepressants, analgesics, cannabinoids and antispastic medications for treatment of pain after spinal cord injury. Most studies included participants with neuropathic pain after spinal cord injury. Many studies did not distinguish between neuropathic and musculoskeletal pain. A variety of pain-assessment tools was used; the two most common were visual analogue scale (VAS) and McGill Pain Questionnaire. Studies were conducted in USA, Europe and Asia.

The authors did not state how the papers were selected for inclusion in the review.

Assessment of study quality
Study quality was assessed using the PEDro scoring system for RCTs or the Downs and Black tool for non-randomised studies (maximum score of 28). PEDro assessment consisted of 11 questions with a maximum score of 10; a study with a PEDro score of 5 or lower was deemed poor quality. The included studies were also categorised according to level of evidence, using a modified Sackett scale.

Two reviewers independently assessed methodological quality. Any disagreements were resolved by a blinded third reviewer.

Data extraction
The authors did not state how data were extracted for the review.

A summary of intervention outcomes, type of pain, pain scale and results was extracted. The authors stated whether findings were statistically significant or not. P-values were reported.

Methods of synthesis
The authors conducted a narrative synthesis. Studies were grouped by intervention.

Results of the review
Twenty-eight studies were included in the review: 21 RCTs; one prospective controlled study; one observational study; three case series; and three before-and-after studies. PEDro scores ranged from 4 to 10. Nineteen RCTs were considered to be of excellent or good quality. Downs and Black scores ranged from 4 to 18.

**Anticonvulsants**: Pregabalin (two RCTs) and gabapentin (three RCTs, one case series, one before-and-after study) were found to improve neuropathic pain after spinal cord injury, although one RCT found no significant between group differences when gabapentin was compared with an active control. No statistically significant difference in pain was found for levetiracetam (one RCT), valproic acid (one RCT) and lamotrigine (one RCT), although a subgroup of patients with incomplete spinal cord injury reported a significant improvement in neuropathic pain.

**Antidepressants**: Compared with placebo, amitriptyline (a tricyclic antidepressant) was found to reduce post spinal cord injury pain in depressed persons (two RCTs). No significant difference in post spinal cord injury neuropathic pain was found between trazodone (a tricyclic antidepressant) and placebo (one RCT).

**Analgesics**: Intravenous lidocaine, intravenous ketamine and alfentanil, tramadol (one RCT) and intrathecal morphine and/or clonidine (one RCT, one prospective controlled study) were found to improve neuropathic pain. This association was largely of short-term benefits when associated with intravenous lidocaine. Intravenous morphine was found to improve dynamic mechanical allodynia pain after spinal cord injury (one RCT). A reduction in pain was reported following administration of topical lidocaine, capsaicin (one case study). No significant between-group difference in neuropathic pain was found when mexilitine was compared with placebo (one RCT).

**Cannabinoids**: Conflicting evidence was found for use of tetrahydrocannabinol in the reduction of spastic pain. A significant reduction was found in post spinal cord injury pain after 10mg oral tetrahydrocannabinol at day one compared with baseline measures (one before-and-after study). However, no significant improvement in pain was found compared with placebo on day eight and day 43 in a subset of these participants, as well as no difference in measures of mood or attention (one RCT).

**Anti-spasticity medications**: Intrathecal baclofen reduced musculoskeletal pain (one before-and-after study) associated with spasticity. There was conflicting evidence for neuropathic pain (one RCT, one before-and-after study). Botulinum toxin was found to reduce post spinal cord injury pain associated with spasticity (one case series).

**Authors' conclusions**
The authors concluded that there was strong evidence that gabapentin and pregabalin as well as intravenous analgesics such as lidocaine, ketamine, and morphine were effective in reducing post spinal cord injury neuropathic pain. Tricyclic antidepressants showed a benefit for neuropathic pain in depressed patients. Intrathecal baclofen reduced musculoskeletal pain associated with spasticity, but there was conflicting evidence for neuropathic pain. Cannabinoids showed conflicting evidence in improving spasticity-related pain and when given together clonidine and morphine were found to improve neuropathic pain. Most studies did not specify participants' types of pain, which made it difficult to identify the type of pain being targeted by the treatment.

**CRD commentary**
The review question was supported by broad inclusion criteria. A number of electronic databases were searched. The search was restricted to English-language studies and no specific attempts were made to locate unpublished studies, which may have led to relevant papers being missed. Publication bias was not formally assessed. The authors did not report the methods used in the review process for study selection or data extraction, so reviewer error and bias could not be ruled out. Study quality was assessed with appropriate criteria and summary scores were presented. Given the differences between studies, a narrative synthesis was appropriate. It appeared that a number of studies included patients other than spinal cord injury, which complicated any interpretation of the results. Studies did not specify participants' types of pain, which made it difficult to identify the type of pain being targeted by the treatment. Given this and the lack of reporting of all details of the review process the authors conclusions should be interpreted with some caution.

**Implications of the review for practice and research**
**Practice**: The authors did not state any implications for practice.
Research: The authors stated that future studies should consider the response of specific pain subtypes in spinal cord injured populations using larger sample sizes and spinal cord specific pain assessment tools. A multimodal approach to treating pain after spinal cord injury was suggested and this included non-pharmacological and behavioural interventions.

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