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REVIEW ARTICLE (META-ANALYSIS)

Gabapentinoids Are Effective in Decreasing Neuropathic Pain and Other Secondary Outcomes After Spinal Cord Injury: A Meta-Analysis

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Abstract

Objective: To examine the effectiveness of gabapentin and pregabalin in diminishing neuropathic pain and other secondary conditions in individuals with spinal cord injury (SCI).

Data Sources: A systematic search was conducted using multiple databases for relevant articles published from 1980 to June 2013.

Study Selection: Controlled and uncontrolled trials involving gabapentin and pregabalin for treatment of neuropathic pain, with ≥3 subjects and ≥50% of study population with SCI, were included.

Data Extraction: Two independent reviewers selected studies based on inclusion criteria and then extracted data. Pooled analysis using Cohen's *d* to calculate standardized mean difference (SMD), SE, and 95% confidence interval (CI) for primary (pain) and secondary outcomes (anxiety, depression, sleep interference) was conducted.

Data Synthesis: Eight studies met inclusion criteria. There was a significant reduction in the intensity of neuropathic pain at <3 months (SMD=.96±.11; 95% CI, .74−1.19; $P<.001$) and between 3 and 6 months (SMD=2.80±.18; 95% CI, 2.44−3.16; $P<.001$). A subanalysis found a significant decrease in pain with gabapentin (SMD=1.20±.16; 95% CI, .88−1.52; $P<.001$) and with pregabalin (SMD=1.71±.13; 95% CI, 1.458−1.965; $P<.001$). A significant reduction in other SCI secondary conditions, including sleep interference (SMD=1.46±.12; 95% CI, 1.22−1.71; $P<.001$), anxiety (SMD=1.05±.12; 95% CI, .81−1.29; $P<.001$), and depression (SMD=1.22±.13; 95% CI, .967−1.481; $P<.001$) symptoms, was shown. A significantly higher risk of dizziness (risk ratio [RR]=2.02, $P=.02$), edema (RR=6.140, $P=.04$), and somnolence (RR=1.75, $P=.01$) was observed.

Conclusions: Gabapentin and pregabalin appear useful for treating pain and other secondary conditions after SCI. Effectiveness comparative to other analgesics has not been studied. Patients need to be monitored closely for side effects.

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Spinal cord injury (SCI) can result from traumatic damage (direct physical impact, eg, due to a fall or violence) or nontraumatic damage.[1] Lee et al[2] found the global incidence rate of SCI to be 179,312 cases per annum in 2007. There are many complications after an SCI, but perhaps one of the most frequent and debilitating is pain. The International Association for the Study of Pain Task Force on Taxonomy[3] has produced a pain taxonomy (including pain terms and the classification of pain syndromes) and frequently updates it as new research becomes available. The International Association for the Study of Pain Task Force characterizes pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage."[3] Neuropathic pain is defined as "pain caused by a lesion or disease of the somatosensory nervous system."[3] Studies[4-7] examining pain prevalence among individuals with various types of pain have suggested that as many as 40% to 50% of patients with SCI experience neuropathic pain. Pain contributes to poor physical,

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cognitive, and psychosocial health.[8,9] It can adversely affect recreational activities and work.[10] It has been shown that patients with neuropathic pain within the first few months post-SCI (subacute period) may continue to have pain, which can worsen in the following 3 to 5 years.[6]

The management of neuropathic pain has proven to be difficult. Nonsteroidal anti-inflammatory drugs and similar analgesics often are not effective. Pharmacologic management for SCI neuropathic pain includes the use of antidepressants, antiepileptics, and opioids.[11,12] Gabapentin and pregabalin are 2 newer anticonvulsant medications used to treat neuropathic pain in people with SCI, in addition to their use for migraines, bipolar illness, and epilepsy.[13] Gabapentin and pregabalin are very similar to gamma-aminobutyric acid, the primary inhibitory neurotransmitter in the brain. Both drugs increase inhibitory neurons by blocking calcium influx, thereby reducing nociceptive neuron signaling and consequent pain sensation.[14]

Gabapentin and pregabalin are now considered to be first-line treatment for post-SCI neuropathic pain.[15] Initial studies of the effects of gabapentin and pregabalin on non-SCI pain have been promising, showing that pain relief was experienced in patients with a variety of neuropathic pain syndromes such as diabetic neuropathy, nonspecific neuropathies, trigeminal neuralgia, central pain after stroke, and postherpetic neuralgia.[16] In a recent review of pharmacologic interventions for post-SCI neuropathic pain, Snedecor et al[17] found that pregabalin and gabapentin were effective in decreasing pain based on the numeric rating scale.

The purpose of this study was to conduct a meta-analysis on the effectiveness of gabapentin and pregabalin in reducing neuropathic pain intensity, depression, anxiety, and sleep interference in individuals with SCI, and to investigate adverse events associated with this treatment.

Methods

Literature search strategy

A literature search for journal articles published from 1980 to June 2013 was conducted using the following databases: Medline, CINAHL, EMBASE, and PsycINFO. Keywords included spinal cord injuries, paraplegia, tetraplegia, quadriplegia, gabapentin, pregabalin, pain, neuropathic pain, and central pain. The reference lists of articles found were scanned for additional references.

Study selection

Journal articles were reviewed by 2 independent reviewers (S.M., A.M.) and included if they met the following criteria: (1) published in the English language; (2) examined the use of gabapentin or pregabalin in decreasing neuropathic pain as a primary outcome by using a comparison with placebo or another treatment; (3) had at least 3 study participants with SCI; (4) had a study sample with a minimum of 50% SCI participants; (5) included participants $\geq$18 years of age; and (6) reported pain intensity outcomes and/or pain interference in sleep, or effects on symptoms of depression and anxiety. Both controlled and uncontrolled studies were included. Excluded were single-subject designs and articles without sufficient data for analysis.

List of abbreviations:

CI	**confidence interval**
RCT	**randomized controlled trial**
RR	**risk ratio**
SCI	**spinal cord injury**
SMD	**standardized mean difference**

Study appraisal, data extraction, and data analysis

For each study, 2 reviewers independently extracted information on the study design, participant characteristics, gabapentin/pregabalin intervention, outcomes (pain intensity, sleep interference, anxiety, depression), and adverse events. Discrepancies were resolved through discussion. Follow-up times for study outcomes were divided into 2 groups: <3 months and 3 to 6 months.

A quality assessment was conducted for all randomized controlled trials (RCTs) by 2 blinded reviewers using the Physiotherapy Evidence Database scoring system.[18] Rare scoring discrepancies were resolved by a third blinded reviewer. The Physiotherapy Evidence Database tool consists of 10 items scored as 0 (absent) versus 1 (present), with a maximum score of 10. The following descriptors were used for the methodologic quality of a study: 9 or 10, excellent; 6 to 8, good; 4 or 5, fair; and <4, poor.[19]

Pooled analyses were conducted for each of the outcomes. In the case of RCTs, outcomes from the gabapentin or pregabalin treatment and placebo arms were extracted in order to calculate efficacy, whereas for non-RCTs, only pre-post data were used to calculate efficacy of treatment. Cohen's *d* was used to calculate the standardized mean difference (SMD) (±SE, 95% confidence interval [CI]) for the effect on pain intensity and on study secondary outcomes using the software package Comprehensive Meta-Analysis[a] (version 2). Effect sizes are commonly interpreted as small, >0.2; moderate, >0.5; and large, >0.8.[20] Pooled risk ratios (RRs) were calculated for adverse events. Heterogeneity between the studies was quantified using the I^2 statistic. An I^2 value >50% was used as the threshold to identify statistically significant heterogeneity. A fixed-effects model was used when the threshold for heterogeneity was not reached, and a random-effects model when it was exceeded.

Results

The search of the bibliographic databases and inspection of reference lists resulted in 135 initial references. Of these, 27 were duplicates; 68 articles were removed after examination of titles, 25 after examination of abstracts, and 15 after full text review. Reasons for exclusion included lack of an SCI population, epidemiologic studies, nonneuropathic pain population, and noninterventional studies. Only 8 articles met inclusion criteria and reported enough detail to be included in a meta-analysis.[21-28]

Study quality and design

Of the 8 studies, 6[22-26,28] were RCTs while 2[21,27] were non-RCTs. Of the 6 RCTs included in the study, 5[22-25,28] were of excellent quality and 1[26] was of good quality. Sample sizes ranged from 7 to 39. Three double-blinded RCTs[23,24,26] provided half their participants with gabapentin treatment post-SCI, while the remainder received placebo. The studies by Levendoglu[23] and Tai[26] and colleagues were crossover trials in which individuals received 4 weeks of gabapentin or placebo, and then a 2-week washout period was followed by the alternative treatment for another 4 weeks. Tai[26] provided dosages of up to 1800mg/d, while Levendoglu[23] and Rintala and colleagues[24] prescribed up to 3600mg/d. Only the study by Vranken