Examining the Time to Therapeutic Effect of Pregabalin in Spinal Cord Injury Patients With Neuropathic Pain

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ABSTRACT

Purpose: In 2 large-scale, placebo-controlled trials, pregabalin improved both pain and pain-related sleep interference in patients with neuropathic pain due to spinal cord injury (SCI). In both trials, pregabalin found statistically significant improvement compared with placebo after 1 week of treatment. However, the effects of pregabalin in the days immediately after initiation of treatment are unknown. The purpose of the present analysis was to determine timing of pregabalin's therapeutic effect in the days after initiation of treatment.

Methods: Data were derived from 2 trials of pregabalin in patients with SCI-related neuropathic pain. Each day patients rated severity of pain and pain-related sleep interference over the past 24 hours on a scale from 0 to 10, with higher scores indicating greater severity. To quantify timing of therapeutic effect, we compared (pregabalin [vs] placebo) daily average pain and pain-related sleep interference scores over the first 14 days of treatment. Significant improvement was defined as the first day, of ≥2 consecutive days, that pregabalin significantly ($P < 0.05$) reduced mean scores compared with placebo. To further quantify timing of therapeutic effect, each treatment group was examined to determine the time required to achieve a ≥1-point improvement in pain and pain-related sleep interference score among patients with a clinically meaningful and sustained response (≥30% improvement from baseline to end point) by using a time-to-event analysis method. Kaplan–Meier analyses were used to estimate the median (or 25th quartile) time (in days) required to achieve a ≥1-point improvement, among these responders, in pain and pain-related sleep interference scores. Comparisons between pregabalin and placebo were made with a log-rank test.

Findings: In both trials, significant improvement of pain and pain-related sleep interference occurred within 2 days of initiating treatment with pregabalin. Among patients reporting a clinically meaningful and sustained response to treatment (patients with ≥30% improvement from baseline to end point), the time to a ≥1-point improvement of pain and pain-related sleep interference occurred significantly earlier among pregabalin-treated patients than among placebo-treated patients. Finally, the timing of pregabalin's effect on pain and pain-related sleep interference was unaffected by the use of concomitant medications that were allowed for treatment of neuropathic pain in both trials.

Implications: Treatment with pregabalin results in rapid time to significant improvement in both pain and pain-related sleep interference in patients with neuropathic pain due to SCI. These findings should only be used as a guide to physicians and patients as to when clinical response to pregabalin may be expected. (*Clin Ther.* 2015;37:1081–1090)

Key words: neuropathic pain, pregabalin, sleep interference, spinal cord injury.

INTRODUCTION

Although ~65% of patients with spinal cord injury (SCI) experience chronic pain, several distinct types of pain, diverse in their cause, severity, and duration, may occur after SCI.[1–5] Neuropathic pain that results from damage to the sensory system itself may present spontaneously, either as continuous or intermittent pain, or may be evoked by a stimulus.[3,4] Such pain is often severe, chronic, and refractory to treatments, which may include anticonvulsants, antidepressants, and analgesics.[1,3,4,6] This may be reflected in the observation that

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up to 40% of patients with SCI experience neuropathic pain 5 years after injury.[1] Overall, SCI-related neuropathic pain has significant negative effects on patient function and quality of life.[7–10]

In patients with SCI, as in many chronic pain conditions, sleep is often negatively affected. Nearly 40% of patients with SCI frequently experience difficulty falling asleep or staying asleep because of pain.[10] This is not unexpected because pain and sleep exhibit a bidirectional relation, with changes in one (positive or negative) reciprocally affecting the other.[11–14] Because of this complex relation, current guidelines for the treatment of chronic painful conditions recommend a treatment strategy targeted at both pain and sleep disturbance to improve overall patient quality of life.[14]

Pregabalin, an $\alpha_2\delta$ ligand, is the only US Food and Drug Administration-approved treatment for SCI-related neuropathic pain in the United States. Efficacy of pregabalin was reported in two 12 to 16 week, large-scale, randomized, placebo-controlled trials in patients with SCI with neuropathic pain.[15,16] In these trials, treatment with 150 to 600 mg/d flexible-dose pregabalin was associated with statistically significant improvements in both pain and pain-related sleep interference at end of study compared with placebo.[15,16] Notably, statistically significant improvements over placebo were evident for pregabalin after 1 week of treatment and were sustained throughout the remainder of the trials.[15,16] In these trials, however, week 1 was the first time point evaluated, and weekly scores were defined as the average score over the previous 7 days. Therefore, the effects of pregabalin in the days immediately after initiation of treatment are unknown.

In this retrospective analysis, we examined patient data over the first 14 days of treatment in the 2 randomized, placebo-controlled trials of pregabalin in patients with SCI with neuropathic pain to better understand the timing of therapeutic effect in this patient population.

METHODS

Data Sources

Data for this retrospective analysis were derived from 2 randomized, placebo-controlled trials of flexible-dose pregabalin (150–600 mg/d) for the treatment of neuropathic pain associated with SCI. The study reported by Siddall et al[15] was conducted in Australia, whereas the study reported by Cardenas et al[16] was conducted in Chile, China, Colombia, the Czech Republic, Hong Kong, India, Japan, the Philippines, the Russian Federation, and the United States. Inclusion criteria was similar for both studies and included the following: aged $\geq$18 years; complete or incomplete SCI of $\geq$12 months' duration; below-level neuropathic pain that was continuous for $\geq$3 months or remitting/relapsing for $\geq$6 months; and an average pain score $\geq$4, on a scale from 0 (no pain) to 10 (worst possible pain), in the 7 days before randomization. Stable use of a variety of concomitant medications was allowed during both trials. Permitted medications that could, potentially, affect pain included tramadol, opioids, tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, and antiepileptic drugs.

Patients initially received 150 mg/d pregabalin or matching placebo. Dose adjustments, based on patient tolerability, were allowed during the first 3[15] or 4[16] treatment weeks. After the dose adjustment phase, patients received an optimized dose of pregabalin for the remainder of the study (150, 300, or 600 mg/d BID for 9 weeks;[15] or 150, 300, 450, or 600 mg/d BID for 12 weeks[16]).

Both studies used daily diaries in which patients rated pain (on a scale from 0 [no pain] to 10 [worst possible pain]) and pain-related sleep interference (on a scale from 0 [pain did not interfere with sleep] to 10 [pain completely interfered with sleep]) over the previous 24 hours. The primary efficacy measure for the studies reported by Siddall et al[15] (mean change in weekly pain score from baseline to end point) and Cardenas et al[16] (duration adjusted average change in pain) were based on patient pain diaries. Both studies examined mean change from baseline to end point in pain-related sleep interference score as a secondary efficacy measure.

Analysis of Change in Pain and Pain-Related Sleep Interference at Study End Point

Least squares mean change, from baseline to end point, in pain and pain-related sleep interference scores were compared between the pregabalin and placebo treatment groups by using analysis of covariance, with baseline score as a covariate and with pooled center and treatment as fixed cofactors. Missing patient data were imputed with a last-observation-carried-forward approach. Significance was declared if the 2-tailed test for the difference between treatment groups was significant at the 0.05 level.