Pregabalin Beneficial Effects on Sleep Quality or Health-Related Quality of Life Are Poorly Correlated With Reduction on Pain Intensity After an 8-Week Treatment Course

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Background: Pregabalin (PGB) has been shown to improve sleep quality and health-related quality of life (HRQoL) as well as pain intensity in patients with neuropathic pain.

Objective: The objective of the study was to explore the magnitude of the correlations between changes in pain intensity, sleep quality, and HRQoL after PGB treatment.

Methods: One hundred thirty-eight patients with neuropathic pain of any origin and without an adequate response to analgesics received an 8-week treatment course of PGB in an open-label fashion. Pain intensity, sleep quality, and HRQoL outcomes were evaluated at baseline and at week 8 by means of an 11-point (0-10) numerical rating scale (NRS), the Pittsburgh Sleep Quality Index (PSQI), and the EuroQol health-state visuoanalogic scale (EQ-5D VAS) score, respectively.

Results: At week 8, mean PGB dose was 166.7 ± 7.8 mg/d. Pain intensity NRS score, PSQI total score, and EQ-5D VAS score were improved by 66.5% ± 1.9%, 40.0% ± 3.6%, and 26.4% ± 4.7% (all $P < 0.01$), respectively. Correlations between percent change from baseline in pain NRS score and PSQI total score or EQ-5D VAS scores were $r = 0.36$ ($P < 0.01$, $R^2 = 0.11$) and $r = -0.20$ ($P < 0.02$, $R^2 = 0.05$), respectively. A multivariate logistic regression analysis disclosed that PSQI score change below the median (ie, a better outcome) was related to higher EQ-5D VAS score change (odds ratio, 2.15; 95% confidence interval, 1.09–4.25), whereas pain intensity NRS score change below the median was not (odds ratio, 1.58; 95% confidence interval,0.78–3.23).

Conclusions: In our study, PGB-related improvements in sleep quality and HRQoL were marginally related to reductions in pain intensity in patients with neuropathic pain. Improvement in sleep quality was a significant predictor of better HRQoL, whereas pain intensity reduction was not.

Key Words: pain, sleep quality, health-related quality of life, pregabalin

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Pregabalin (PGB) is an anticonvulsant drug that binds to α2-δ subunit of the N-type voltage-dependent calcium channel.[1,2] Voltage-dependent calcium channel–containing subunits appear to be involved in presynaptic regulation of neurotransmitter release. It has been shown that PGB is capable of inhibiting glutamate, noradrenaline, acetylcholine, and substance P release at several different central nervous system locations including the neocortex, the amygdala, the hippocampus, the striatum, the spinal cord, the cerebellum, and the habenula.[3–5] Pregabalin is approved by the US Food and Drug Administration for the treatment of painful diabetic peripheral neuropathy, fibromyalgia, and postherpetic neuralgia and as adjunctive therapy in adults with partial-onset seizure disorder.[6] In Europe, PGB is also approved for neuropathic pain and generalized anxiety disorder.[6]

Pregabalin effects on sleep quality and health-related quality of life (HRQoL) have been studied in many clinical trials. For example, a recent meta-analysis has shown that PGB 150 to 600 mg/d significantly improved pain-related sleep interference in patients with neuropathic pain.[7] Health-related quality of life was also improved by PGB.[8,9] It has been suggested that improvements on sleep or HRQoL may be correlated to PGB analgesic effects,[10] but the magnitude of such correlation remains unknown. Therefore, we conducted the present study aiming at further exploring the correlation between changes in pain intensity, sleep quality, and HRQoL after a PGB 8-week treatment course.

METHODS

Study Sample

Eligible patients were men and women 18 years or older with a diagnosis of neuropathic pain of any origin and without an adequate response to analgesics. Female patients were required to be nonpregnant, nonlactating, postmenopausal, or surgically sterilized; women at risk of pregnancy were required to be using an appropriate method of contraception. Patients with pain lasting less than 3 months or with severe diseases or renal insufficiency were excluded. Patients were required to be on a stable analgesic regimen for the previous month and during the trial. Inadequate response to those analgesics was defined as a daily pain intensity less than 4 on an 11-point numerical rating scale (NRS).[11]

Patients were recruited in the neurological or endocrinologic departments of the Mutual Health Institute, Central Hospital, or Santa Clara Medical Center, Asunción, Paraguay, between August 2008 and June 2010. Neuropathic pain diagnoses were established in all cases by study physicians.

The study was approved by the institutional review board at each center. It was conducted according to the Declaration of Helsinki. All the subjects gave their informed consent previous to participation in the study.

TABLE 1. Sample Characteristics

Variable	Value
Sample size	138
Male sex	86 (62)
Age, mean (SD), y	56.6 (1.2)
Body mass index, mean (SD), kg/m^2	27.7 (0.5)
Pain etiology, n (%)	
Diabetic neuropathy	85 (61)
Post-herpetic neuralgia	38 (28)
Other neuropathies*	15 (11)
Pain duration, mean (SD), mo	24.5 (2.3)
Pain medication, n (%)	
NSAIDs	66 (47)
Opioids	18 (13)
Antidepressants	22 (16)
Vitamin B_6 (adjuvant)	14 (10)
Benzodiazepines	11 (8)
Gabapentin	9 (6)
Antiepileptics	9 (6)
Corticosteroids	4 (3)
At week 8	
Pregabalin dose, mean (SD), mg/d	166.7 (7.8)
75 mg, n (%)	48 (35)
150–225 mg, n (%)	57 (41)
300–450 mg, n (%)	34 (24)
Compliance with therapy, n (%)	
Every day	85 (61)
Almost every day	46 (33)
Sometimes	8 (6)
Never	0 (0)

*Including polyneuropathy, chronic radiculopathy, and others.

Study Design, Treatments, and Outcomes

This was an open-label, uncontrolled study. Patients were evaluated at baseline and after 8 weeks of PGB treatment. Pregabalin titration followed a semirigid scheme. Patients began with 75 mg/d and were up-titrated up to 300 mg/d at week 4. Afterward, dose could be changed according to tolerability or efficacy.

Pain, sleep, and HRQoL outcomes were evaluated at baseline and at week 8. Pain was evaluated by means of an 11-point (0–10) NRS.[11] Scores for minimal, average, or maximal pain intensity during the previous week or average intensity during the previous day were recorded. A single pain intensity NRS measure was then obtained by averaging individual pain intensity measures. Sleep was evaluated by the Pittsburgh Sleep Quality Index (PSQI).[12] Finally, HRQoL was evaluated by the EuroQol 5D scale (EQ-5D).[13] The health-state visuoanalogic scale (VAS) was used as the HRQoL outcome. Higher PSQI or pain intensity NRS scores represent a worse outcome, whereas higher EQ-5D VAS values represent a better one.

The primary outcome of the study was the correlation between pain intensity NRS score and PSQI total score and EQ-5D VAS score.

Statistical Analysis

Sample size was calculated with the primary outcome in mind. It was determined that 130 subjects would be needed to detect a correlation coefficient between pain intensity score and PSQI or EQ-5D scores of at least 0.25 (maximal allowed β error = 0.2, α error = 0.025). This sample size would be enough for detecting odds ratios (ORs) of 2.3 or greater when searching for independent predictors of improved HRQoL after PGB treatment. Thirteen additional subjects were also recruited to compensate for dropouts.

Correlations between PSQI, EQ-5D VAS, and pain intensity NRS scores were explored by parametric Pearson coefficient (r). R^2 determination coefficients (ie, the proportion of variability in one of the variables that can be explained by variations in the other) were calculated as $r * r$.

Significance of week 8-to-baseline changes in the explored outcomes was tested by paired t test. Such differences are expressed as a percentage of change. Between-group t tests were used for other comparisons. Finally, independent contribution of week 8-to-baseline changes in PSQI or pain scores to change in EQ-5D score was explored by logistic regression analysis. For this analysis, all outcomes were dichotomized to their medians.

RESULTS

Ninety-seven percent of recruited subjects (138/143) completed the study. Characteristics of the final sample are shown in Table 1. Of the 5 dropouts, 2 were related to adverse events

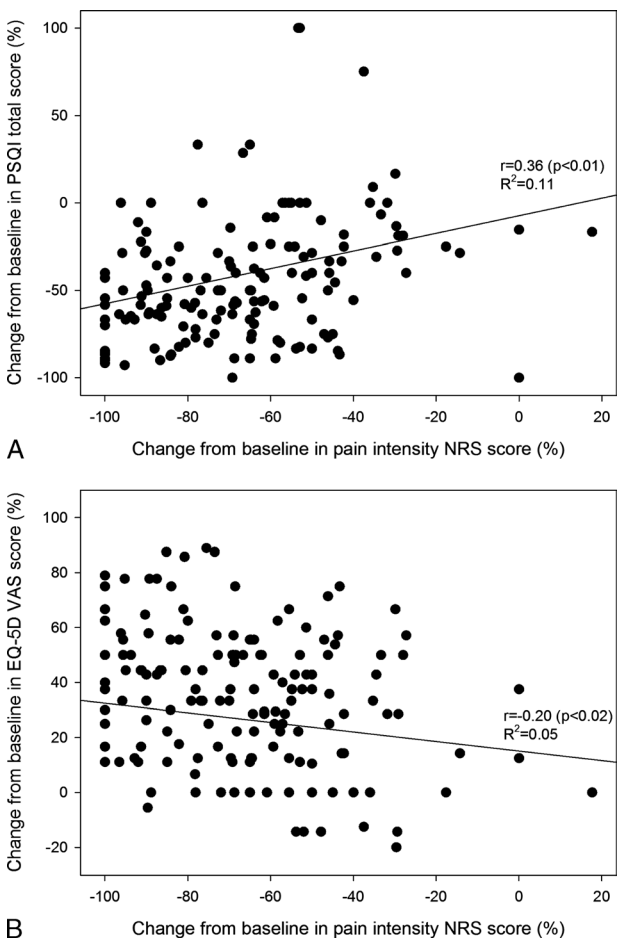

FIGURE 1. Correlation between percent change from baseline in pain intensity NRS score with change in PSQI total score (upper panel) or EQ-5D VAS score (lower panel).

(severe dizziness or somnolence), whereas the other 3 withdrew their consent. As can be seen, at week 8, most subjects were on moderate PGB doses. Compliance with treatment was good to excellent in 94% of patients. Most frequently reported comorbidities were cardiovascular (44%, hypertension), endocrine (30%, diabetes, obesity, hypothyroidism), or rheumatic (23%, arthrosis or arthritis).

Significant week 8-to-baseline differences in all explored outcomes were identified. Pain intensity NRS score was 5.7 ± 0.2 (mean ± SEM) at baseline and 2.0 ± 0.1 at week 8 (change = −66.5% ± 1.9%; $P < 0.01$, paired t test). Pittsburgh Sleep Quality Index score was 10.4 ± 0.3 at baseline and 5.4 ± 0.3 at week 8 (change = −40.0% ± 3.6%; $P < 0.01$). Finally, EQ-5D VAS score was 50.7 ± 1.8 at baseline and 76.7 ± 1.4 at week 8 (change = 26.4 ± 4.7%; $P < 0.01$).

Correlations between percent change from baseline in pain NRS score and PSQI total score or EQ-5D VAS were poor, as can be seen in Figure 1. Percent change from baseline in all explored outcomes was comparable in subjects manifesting nighttime pain complaints at baseline (PSQI question 5.h) or not (Fig. 2).

Median values for change from baseline in pain intensity NRS, PSQI total, or EQ-5D VAS scores were −68%, −49%, or 34%, respectively. A multivariate logistic regression analysis showed that improvement in PSQI total score was significantly related to improvement in EQ-5D VAS score (OR, 2.15; 95% confidence interval [CI], 1.09–4.25]; $P = 0.03$), whereas this was not the case for improvement of pain intensity NRS score (1.58 [0.78–3.23]; $P = 0.21$) as shown in Figure 3. Sleep quality–by–pain intensity interaction was not significant.

Fifty percent of patients reported an adverse event. Most frequent adverse events were somnolence (14 cases, mild = 8, moderate = 2, severe = 2) and dizziness (14 cases, mild = 8, moderate = 5, severe = 1). There were no serious adverse events.

DISCUSSION

In this study, significant but poor correlations between improvements in pain, sleep quality and HRQoL after an 8-week PGB treatment course were found. Correlations coefficients never surpassed 0.36 or $R^2 = 0.11$, meaning that only 11% changes in PSQI total scores or in EQ-5D VAS scores are expected following variations in pain intensity after PGB treatment. Therefore, PGB effects on sleep quality or HRQoL are only marginally related to improvements in pain in patients with neuropathic pain.

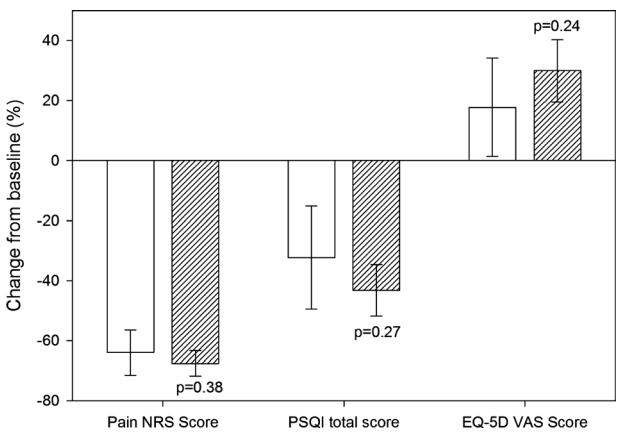

FIGURE 2. Change from baseline in PSQI scores, pain VAS scores, or EQ-5D VAS scores. ☐ Subjects without nighttime pain complaints. ▨ Subjects with nighttime pain complaints. Shown are means and 95% CIs. Reported P values were calculated by means of between-group t tests corrected for variance heterogeneity.

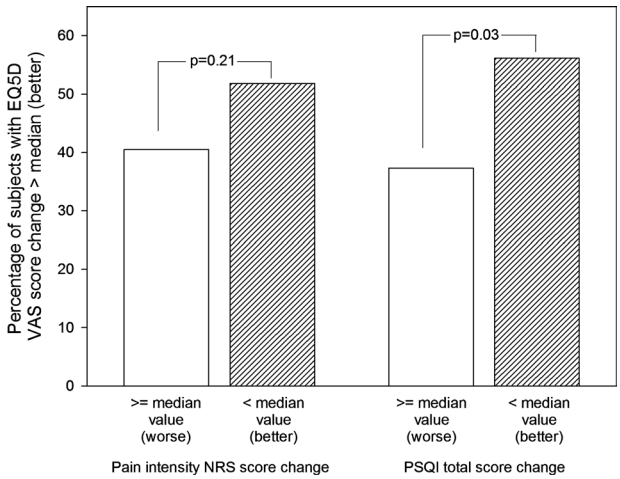

FIGURE 3. The EQ-5D VAS score change in subjects with PSQI score or pain VAS score changes above or below median values. A multivariate logistic regression analysis disclosed that PSQI score change below the median (ie, a better outcome) was related to higher EQ-5D VAS score change (OR, 2.15 [95% CI, 1.09–4.25]), whereas pain intensity NRS score change below the median was not (1.58 [95% CI, 0.78–3.23]).

The presence of a placebo effect constitutes a relative limitation to our study. Indeed, PGB effects on pain, sleep quality, and HRQoL are surely overestimated. Nonetheless, there is no reason to think that the placebo effect may have affected differently these measures, so the correlations between them are not biased. Confounding effects of nighttime pain or of pain origin were ruled out. Pregabalin effects on other domains, such as mood, which are known to be improved by the drug[14,15] were not explored; therefore, their effects on sleep quality and HRQoL could not be studied. Finally, fibromyalgia patients were not included in our study. Pregabalin is known to improve sleep quality and HRQoL in this group of patients.[16] Nonetheless, as fibromyalgia is physiopathologically different from neuropathic pain, our results may not be applicable to this group of patients.

The results of our study further suggest that PGB may improve sleep by other mechanisms not related to pain improvement in patients with neuropathic pain. Indeed, in rats, PGB increased the duration of non–rapid eye movement sleep and decreased rapid eye movement sleep after either a nighttime or daytime dose.[17] Similarly, in 24 healthy volunteers, PGB significantly increased slow-wave sleep both as a proportion of the total sleep period and the duration of stage 4 sleep as compared with placebo.[18] Pregabalin also reduced rapid eye movement sleep as a proportion of the total sleep period compared with placebo. Finally, PGB has been shown to be efficacious for restless-legs syndrome.[19] Our results further encourage the exploration of PGB efficacy on other sleep disorders, such as insomnia.

Previous studies have suggested that even patients showing a mild analgesic PGB effect can experience clinically important changes in function and health status.[10] Our results confirm that PGB-related improvement in HRQoL is not due entirely to its analgesic effects. Furthermore, our study showed that PGB-related improvement of sleep quality had a greater impact on HRQoL than pain improvement. Insomnia is associated with a number of adverse health outcomes such as poor physical health,

poor mental health including symptoms of anxiety and depression, and decreased quality of life.[20] Accordingly, improving sleep can lead in some cases to improvements in HRQoL,[20] such as may be the case with PGB.

In summary, our study showed that PGB-related improvements in sleep quality and HRQoL were marginally related to reductions in pain intensity. Pregabalin may show a sleep-promoting effect independent of the analgesic effect, which was in our study a major determinant of HRQoL improvement.

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