Randomized Trial

Effect of Concomitant Pain Medications on Response to Pregabalin in Patients with Postherpetic Neuralgia or Spinal Cord Injury-Related Neuropathic Pain

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Background: Patients with neuropathic pain (NeP) often receive combination therapy with multiple agents in the hopes of improving both pain and any comorbidities that may be present. While pregabalin is often recommended as a first-line treatment of NeP, few studies have examined the effects of concomitant medications on the efficacy of pregabalin.

Objective: To examine the effects of concomitant medications on the efficacy and safety of pregabalin for the treatment of NeP.

Study Design: Data were derived from 7 randomized placebo-controlled trials of pregabalin (150, 300, 600, and flexible 150 – 600 mg/d) for the treatment of postherpetic neuralgia (PHN) and 2 randomized placebo-controlled trials for the treatment of NeP due to spinal cord injury (SCI-NeP). On each day, patients rated the severity of their pain and pain-related sleep interference (PRSI) over the previous 24 hours on a scale from 0 to 10, with higher scores indicating greater severity. Patients were also continually monitored for the occurrence of adverse events.

Setting: A pooled retrospective analyses of data from randomized clinical trials.

Methods: Changes from baseline in mean weekly pain and PRSI scores were compared between patients who received concomitant NeP medications and patients who did not receive concomitant NeP medications. Results of these comparisons are presented separately for the PHN (through 4, 8, and 12 weeks) and SCI-NeP (through 12 weeks) cohorts. Common adverse events are also presented for each treatment group.

Results: Pregabalin significantly improved both pain and PRSI scores relative to placebo at most dose levels and time points examined. Notably, little difference was observed in the extent of therapeutic response to pregabalin between patients who received concomitant NeP medications and patients who did not receive concomitant NeP medications. Additionally, the profile of treatment-emergent adverse events appeared to be largely unaffected by the use of concomitant NeP medications in the pooled patient population.

Limitations: Our analysis is limited in that the original trials of pregabalin were not powered to examine the effects of concomitant NeP medications.

Conclusions: The data presented here demonstrate that therapeutic response to pregabalin and the occurrence of adverse events in patients with NeP are generally unaffected by the concurrent use of other NeP medications.

Trial Registration numbers: NCT00159666; NCT00301223; NCT00407745

Key words: Pregabalin, neuropathic pain, pain-related sleep interference, concomitant medications, postherpetic neuralgia, spinal cord injury, efficacy, safety

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Neuropathic pain (NeP) is a specific type of pain resulting from a lesion or disease of the somatosensory nervous system (1,2). A variety of treatment options exist for the management of NeP, including antiepileptic drugs, tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, opioids, and tramadol (2-4). Despite the variety of agents available, NeP is difficult to manage. This is due in part to the severe and chronic nature of NeP and to the fact that patients with NeP often present with one or more comorbidities. For example, patients with NeP often experience disturbed sleep, anxiety, depression, and report low overall health-related quality of life (5-9). As a result, patients often receive combination therapy with multiple agents in the hopes of improving both pain and any comorbidities that may be present (10).

Pregabalin is recommended as a first-line treatment for certain types of NeP (4,11-13). It is approved in the United States for the treatment of painful diabetic peripheral neuropathy (pDPN), postherpetic neuralgia (PHN), neuropathic pain due to spinal cord injury (SCI-NeP), fibromyalgia, and as adjunct therapy for partial onset seizures (14). The analgesic, anxiolytic, and anticonvulsant properties of pregabalin are thought to be attributed to its binding to the $\alpha 2\delta$ subunit of voltage gated neuronal calcium channels and the resulting modulation of excitatory neurotransmitter release (15,16). The potential for pregabalin to interact with other drugs is low due to its lack of plasma protein binding, bypassing hepatic metabolism, and being excreted unchanged in the urine (17). While this may make pregabalin a candidate agent for use in concert with other agents, few studies have been conducted of pregabalin-based combination therapy (18). Specifically, it is unknown whether the concomitant use of other NeP agents augments or potentially diminishes the effects of pregabalin. The purpose of the current study therefore was to examine the effect of concomitant NeP medications on therapeutic response to pregabalin in patients with NeP.

Methods

Study Design

Data were derived from 9 randomized placebo-controlled trials of pregabalin for the treatment of PHN or SCI-NeP. Patients with pDPN were not included in the current analysis because clinical trials of pregabalin for the treatment of pDPN, unlike trials for PHN or SCI-NeP, did not allow the concomitant use of other NeP medications. Data from 7 PHN trials were pooled to comprise the PHN cohort, whereas data from 2 SCI trials were pooled to comprise the SCI-NeP cohort (Table 1). Individual trials within the PHN and SCI-NeP cohorts shared similar inclusion and exclusion criteria (19-27). All patients were ≥ 18 years of age and were required to have a pain severity score ≥ 4 on a scale from 0 to 10 at randomization.

All patients provided informed consent before participation, and all studies were conducted in compliance with the ethics principles originating in or derived from the Declaration of Helsinki, internal review board requirements, and Good Clinical Practices guidelines.

Treatment Groups

Treatments arms included placebo, 150 mg/d fixed-dose pregabalin, 300 mg/d fixed-dose pregabalin, 600 mg/d fixed-dose pregabalin, and 150 – 600 mg/d flexible dose pregabalin in the PHN trials, while treatment arms included placebo and 150 – 600 mg/d flexible dose pregabalin in the SCI-NeP trials. Within each treatment arm, patients were classified into 2 groups based on their use of concomitant NeP medications. Patients receiving opioids, antiepileptic drugs, tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, or tramadol were included in the + concomitant NeP medications groups, whereas all other patients were included in the - concomitant NeP medications group.

Efficacy Analyses

Each day, patients rated the severity of their pain and pain-related sleep interference (PRSI) over the previous 24 hours on a scale from 0 to 10, with higher scores indicating greater severity. Changes in pain and PRSI scores were analyzed through 4, 8, and 12 weeks for the PHN cohort and through 12 weeks for the SCI cohort. First, changes in pain and PRSI scores were compared between placebo and each pregabalin treatment arm in the - concomitant NeP medications group. Then changes in pain and PRSI scores were compared between placebo and each pregabalin treatment arm in the + concomitant NeP medications group.

Finally, changes in pain and PRSI scores were compared between the - concomitant NeP medications group and the + concomitant medications group within each treatment arm, including placebo.

All efficacy analyses of pain and PRSI utilized a mixed-model repeated measures (MMRM) model with

change from baseline in pain and PRSI as dependent variables (separate models for each); treatment, study, patients, week, and group as covariates; and interaction terms such as treatment by group and treatment by group by week. MMRM is a likelihood-based analysis that, in contrast to last-observation or baseline-observation carried forward approaches, uses all observed values from individual patients to compensate for missing values without explicitly imputing any data. The advantage of this approach is that all data are used to fit the model assumed for the response and, under a missing at random assumption, the true treatment effect is likely not to be either under- or over-estimated.

To support these primary efficacy analyses, additional sensitivity analyses were done that took into account the duration of concomitant NeP medication use. For these sensitivity analyses patients were only included in the + concomitant NeP medication group if they received concurrent NeP medication for ≥ 7 days. Patients who did not receive concurrent NeP medications or who received them for < 7 days were included in the - concomitant NeP medications group. Treatment groups were then compared as described for the primary analyses.

Safety

The combined PHN and SCI-NeP data set was analyzed for the incidence of adverse events (AEs). Weighted incidence rates were calculated for each event and those occurring in ≥ 5% of patients, in either the placebo or pregabalin (all doses combined) treatment arms, were reported for the - and + concomitant NeP medications groups. A Cochran-Mantel-Haenszel test was then used to analyze the risk difference (95% CI) between pregabalin and placebo treatment arms in the - and + concomitant NeP medications groups. Risk difference is calculated by subtracting the absolute risk with placebo from the absolute risk with pregabalin to determine the level of risk that can be attributed to treatment.

Results

Efficacy in PHN Studies

Overall, 1,401 patients were included in the PHN analysis and the percentage of patients who received concomitant NeP medications ranged from 15% – 40% across all treatment arms. Patient demographics were similar between the - and + concomitant NeP medications groups in each treatment arm (Table 2).

The analgesic effects of pregabalin were first examined in patients who did not receive concomitant NeP medications. As expected, all doses of pregabalin significantly improved mean pain scores compared with placebo through 4, 8, and 12 weeks of treatment (Fig. 1A-C). Similar results were evident when the analgesic effects of pregabalin were examined in patients who received concomitant NeP medications (Fig. 1D-F). The lone exception occurred with the 150 mg/d dose of pregabalin through 12 weeks, where improvements over placebo appeared evident but did not reach the

Table 1. *Studies included in the 2 pooled analyses.*

Study	Treatment period	Treatment arm
PHN[a]		
Study 1008-030 (19)	5-week treatment	PBO PGB 150 mg/d[b]
Sabatowski et al (21)	1-week dose escalation 7-week dose maintenance	PBO PGB 150 mg/d PGB 300 mg/d
Dworkin et al (20)	1-week dose escalation 7-week dose maintenance	PBO PGB 600 mg/d[c]
Freynhagen et al (22)	4-week dose escalation 8-week dose maintenance	PBO PGB 600 mg/d PGB 150 – 600 mg/d[d]
van Seventer et al (24)	1-week dose escalation 12-week dose maintenance	PBO PGB 150 mg/d PGB 300 mg/d PGB 600 mg/d
Stacey et al (25)	4-week treatment	PBO PGB 300 mg/d PGB 150 – 600 mg/d[d]
Guan et al (26)	4-week dose optimization 4-week dose maintenance	PBO PGB 150 – 600 mg/d[d]
SCI-NeP		
Siddal et al (23)	3-week dose optimization 9-week dose maintenance	PBO PGB 150 – 600 mg/d[d]
Cardenas et al (27)	4-week dose optimization 12-week dose maintenance	PBO PGB 150 – 600 mg/d[d]

[a] The studies by Freynhagen et al and Guan et al also enrolled patients with painful diabetic peripheral neuropathy who were excluded from the current analysis.
[b] This study also utilized a pregabalin 75 mg/d treatment arm that was not included in the current analysis, since it is below the recommended starting dose for postherpetic neuralgia patients.
[c] Patients received 600 or 300 mg/d based on creatinine clearance, resulting in their receiving comparable doses.
[d] Indicates flexible dosing.
PBO = placebo; PGB = pregabalin.

Table 2. *Patient demographics and baseline characteristics in the 7 PHN trials.*

	PBO (N = 485)		PGB 150 (N = 251)		PGB 300 (N = 318)		PGB 600 (N = 159)		PGB FLEX (N = 188)	
Characteristic	- NeP conmeds	+ NeP conmeds	- NeP conmeds	+ NeP conmeds	- NeP conmeds	+ NeP conmeds	- NeP conmeds	+ NeP conmeds	- NeP conmeds	+ NeP conmeds
n (%)	344 (70.9)	141 (29.1)	150 (59.8)	101 (40.2)	208 (65.4)	110 (34.6)	114 (71.7)	45 (28.3)	160 (85.1)	28 (14.9)
Gender, n Male Female	 190 154	 59 82	 70 80	 47 54	 99 109	 53 57	 53 61	 23 22	 85 75	 15 13
Mean age, years	69.7	70.2	70.5	71.1	71.3	72.1	68.0	68.3	67.2	67.6
Baseline pain, mean (SD)	6.5 (1.5)	6.9 (1.6)	6.5 (1.6)	6.7 (1.8)	6.7 (1.5)	6.6 (1.5)	6.6 (1.6)	6.5 (1.5)	6.5 (1.6)	7.0 (1.4)
Baseline PRSI, mean (SD)	4.5 (2.6)	4.9 (2.5)	4.6 (2.6)	4.5 (2.5)	4.7 (2.6)	4.7 (2.3)	4.8 (2.4)	4.9 (2.4)	4.6 (2.5)	5.0 (2.4)

conmeds = concomitant medications; FLEX = flexible dosing; NeP = neuropathic pain; PBO = placebo; PGB = pregabalin; PRSI = pain-related sleep interference; SD = standard deviation.

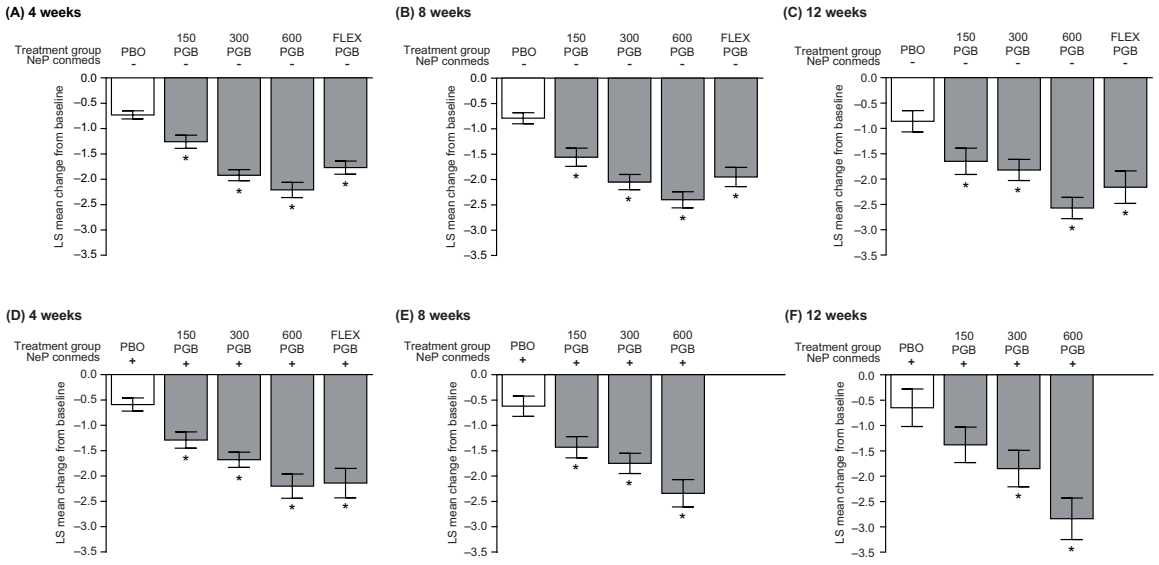

Fig. 1. *Pregabalin-mediated pain relief compared with placebo among PHN patients who did not receive concomitant neuropathic pain medications (A-C) and patients who received concomitant neuropathic pain medications (D-F). Scores range from 0 = no pain to 10 = worst possible pain. Data shown are least squares mean ± standard error. Conmeds = concomitant medications; FLEX = flexible dose 150 – 600 mg/d; LS = least squares; NeP = neuropathic pain; PBO = placebo; PGB = pregabalin. *All P < 0.001 (A), all P < 0.001 (B), all P < 0.013 (C), all P < 0.001 (D), all P < 0.004 (E), and all P < 0.017 (F) versus placebo. There were insufficient numbers of patients receiving concomitant neuropathic pain medications to analyze the pregabalin FLEX group at weeks 8 (n = 4) and 12 (n = 3).*

level of statistical significance (Fig. 1F). Notably, no significant differences were noted in the extent of pain when comparing patients in the - and + concomitant NeP medications groups. This was true for all treatment arms through 4, 8, and 12 weeks (Table 3).

Changes in PRSI scores were also examined in patients in the - and + concomitant NeP medications groups. Again, all doses of pregabalin significantly im-

Table 3. *Effect of concomitant NeP medications on pregabalin-mediated pain relief in patients with PHN.*[a]

Treatment	- NeP conmeds, n	+ NeP conmeds, n	- NeP conmeds vs + NeP conmeds		
			LS mean difference (SE)	95% CI	*P*-value
4 weeks					
PBO	339	138	0.14 (0.15)	(-0.16, 0.44)	0.36
PGB 150 mg/d	149	101	-0.03 (0.19)	(-0.41, 0.34)	0.87
PGB 300 mg/d	203	108	0.24 (0.18)	(-0.11, 0.59)	0.18
PGB 600 mg/d	112	42	0.01 (0.27)	(-0.53, 0.55)	0.97
PGB flexible[b]	158	28	-0.37 (0.31)	(-0.98, 0.24)	0.23
8 weeks[c]					
PBO	223	83	0.17 (0.22)	(-0.27, 0.60)	0.46
PGB 150 mg/d	93	75	0.13 (0.26)	(-0.37, 0.64)	0.60
PGB 300 mg/d	143	87	0.30 (0.23)	(-0.16, 0.75)	0.20
PGB 600 mg/d	112	42	0.06 (0.31)	(-0.55, 0.67)	0.85
12 weeks[c]					
PBO	76	33	0.21 (0.41)	(-0.59, 1.01)	0.61
PGB 150 mg/d	53	34	0.27 (0.41)	(-0.55, 1.08)	0.52
PGB 300 mg/d	88	36	-0.03 (0.39)	(-0.80, 0.75)	0.95
PGB 600 mg/d	70	26	-0.27 (0.46)	(-1.17, 0.64)	0.56

[a] Change from baseline; scores range from 0 = no pain to 10 = worst possible pain.
[b] Indicates flexible dosing of 150 – 600 mg/d.
[c] Analysis of FLEX dosing arm was not performed due to a low number of patients in the + NeP conmeds group at weeks 8 (n = 4) and 12 (n = 3).
Conmeds = concomitant medications; FLEX = flexible; LS = least squares; NeP = neuropathic pain; PBO = placebo; PGB = pregabalin; PHN = postherpetic neuralgia; SE = standard error.

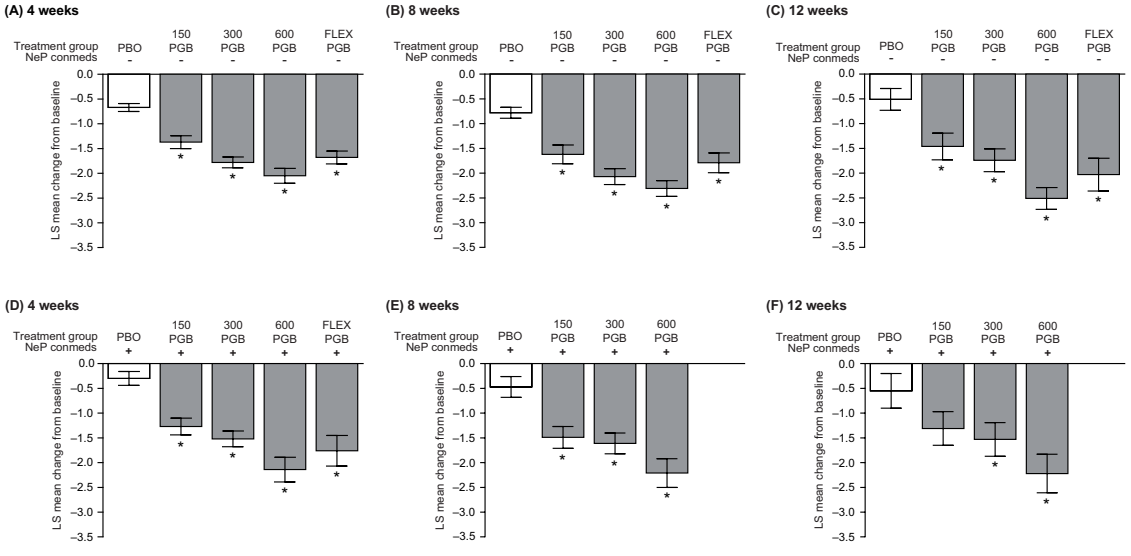

Fig. 2. *Pregabalin-mediated improvements in PRSI compared with placebo among PHN patients who did not receive concomitant neuropathic pain medications (A-C) and patients who received concomitant neuropathic pain medications (D-F). Scores range from 0 = pain did not interfere with sleep to 10 = pain completely interfered with sleep. Data shown are least squares mean ± standard error. Conmeds = concomitant medications; FLEX = flexible dose 150 – 600 mg/d; LS = least squares; NeP = neuropathic pain; PBO = placebo; PGB = pregabalin. *All P < 0.001 (A), all P < 0.001 (B), all P < 0.004 (C), all P < 0.001 (D), all P < 0.001 (E), and all P < 0.035 (F) versus placebo. Insufficient numbers of patients received concomitant neuropathic pain medications to analyze the pregabalin FLEX group at weeks 8 (n = 4) and 12 (n = 3).*

Table 4. *Effect of concomitant NeP medications on pregabalin-mediated improvements in PRSI in patients with PHN.*[a]

Treatment	- NeP conmeds, n	+ NeP conmeds, n	- NeP conmeds vs + NeP conmeds		
			LS mean difference (SE)[b]	95% CI	*P*-value
4 weeks					
PBO	340	137	0.37 (0.16)	(0. 06, 0.68)	0.02
PGB 150 mg/d	149	101	0.10 (0.20)	(-0.29, 0.49)	0.60
PGB 300 mg/d	203	108	0.26 (0.19)	(-0.11, 0.62)	0.17
PGB 600 mg/d	112	42	-0.08 (0.29)	(-0.65, 0.48)	0.77
PGB FLEX[b]	158	28	-0.07 (0.33)	(-0.71, 0.57)	0.83
8 weeks[c]					
PBO	223	83	0.31 (0.23)	(-0.15, 0.76)	0.19
PGB 150 mg/d	93	75	0.13 (0.27)	(-0.39, 0.65)	0.63
PGB 300 mg/d	143	87	0.46 (0.24)	(-0.01, 0.93)	0.06
PGB 600 mg/d	112	42	0.09 (0.32)	(-0.54, 0.73)	0.77
12 weeks[c]					
PBO	76	33	-0.04 (0.39)	(-0.81, 0.72)	0.91
PGB 150 mg/d	53	34	0.15 (0.40)	(-0.63, 0.93)	0.71
PGB 300 mg/d	88	36	0.21 (0.37)	(-0.52, 0.94)	0.57
PGB 600 mg/d	70	26	0.29 (0.45)	(-0.59, 1.17)	0.51

[a] Change from baseline; scores range from 0 = pain did not interfere with sleep to 10 = pain completely interfered with sleep.
[b] Indicates flexible dosing of 150 -600 mg/d.
[c] Analysis of FLEX dosing arm was not performed due to small number of patients in the + NeP conmeds group at weeks 8 (n = 4) and 12 (n = 3).
conmeds = concomitant medications; FLEX = flexible; LS = least squares; NeP = neuropathic pain; PBO = placebo; PGB = pregabalin; PRSI = pain-related sleep interference; SE = standard error.

proved mean scores compared with placebo through 4, 8, and 12 weeks of treatment in the - concomitant NeP medications group (Fig. 2A-C). Similar results were evident in the + concomitant NeP medications groups through 4 and 8 weeks (Fig. 2D-E). However, only the pregabalin 300 mg/d and 600 mg/d doses significantly improved PRSI scores compared with placebo through 12 weeks (Fig. 2F). The 150 mg/d dose trended toward improvement but did not reach the level of significance due to the large standard deviation associated with the data. The extent of pregabalin-mediated improvements in PRSI scores were not significantly different between the - and + concomitant NeP medications groups (Table 4).

Results of the pain and PRSI sensitivity analyses, taking into account the duration of concomitant NeP medication treatment, were similar to those of the primary analyses (data not shown). Slight differences were observed in the magnitude of treatment effects between groups due to a few patients being re-classified (from the + concomitant NeP medications group to the - concomitant NeP medications group) as a result of their having received concomitant treatment for < 7 days (see Methods for details). The number of patients changing classification from the + concomitant NeP medications group to the - concomitant NeP medications group was 30 for placebo and 24, 32, 5, and 10 for 150 mg/d-, 300 mg/d-, 600 mg/d-, and flexible pregabalin, respectively. Despite these minor differences, the overall direction and statistical significance of the comparisons were the same as the primary analyses with the following exception. In the PRSI sensitivity analyses, comparisons between the - and + concomitant NeP medications groups were no longer significant among patients receiving placebo through 4 weeks (*P* = 0.0871).

Efficacy in SCI-NeP Studies

Overall, 347 patients were included in the SCI-NeP analysis and the percentage of patients who received concomitant NeP medications was 43% in the placebo treatment arm and 40% in the pregabalin arm. Patient demographics were similar between the - and + concomitant NeP medications groups in each treatment arm (Table 5).

Pregabalin significantly reduced pain scores compared with placebo through 12 weeks in both the - concomitant NeP medications (Fig. 3A) and + concomitant NeP medications (Fig. 3B) groups. Pain scores were slightly less improved among pregabalin treated SCI-

Table 5. *Patient demographics and baseline characteristics in the 2 SCI-NeP trials.*

	Placebo (N = 173)		Pregabalin (N = 174)	
Characteristic	**- NeP conmeds**	**+ NeP conmeds**	**- NeP conmeds**	**+ NeP conmeds**
n (%)	98 (56.7)	75 (43.4)	105 (60.3)	69 (39.7)
Gender, n Male Female	 83 15	 61 14	 84 21	 54 15
Age, mean years	45.7	49.1	47.6	48.2
Baseline pain, mean (SD)	6.4 (1.4)	6.9 (1.4)	6.3 (1.3)	6.8 (1.4)
Baseline PRSI, mean (SD)	5.0 (2.4)	5.2 (2.3)	4.7 (2.5)	4.6 (2.6)

conmeds = concomitant medications (includes opioids, tramadol, antiepileptic drugs, tricyclic antidepressants, and serotonin-norepinephrine reuptake inhibitors; NeP = neuropathic pain; PRSI = pain-related sleep interference; SCI-spinal cord injury; SD = standard deviation.

NeP patients in the + concomitant NeP medications group compared to the - concomitant NeP medications group (P = 0.03) (Table 6). Pregabalin also significantly reduced PRSI scores compared with placebo through 12 weeks in both the - concomitant NeP medications (Fig. 4A) and + concomitant NeP medications (Fig. 4B) groups and the extent of pregabalin-mediated relief was unaffected by the use of concomitant NeP medications (Table 6).

Results of the sensitivity analyses, taking into account the duration of concomitant NeP medication treatment, were similar to those of the primary analyses. Only slight differences were observed in the magnitude of treatment effects between groups, but the overall direction and statistical significance of these effects were unchanged for both the pain and PRSI analyses (data not shown). The number of patients changing classification from the + concomitant NeP medications group to the - concomitant NeP medications group was 15 for placebo and 7 for flexible pregabalin, respectively.

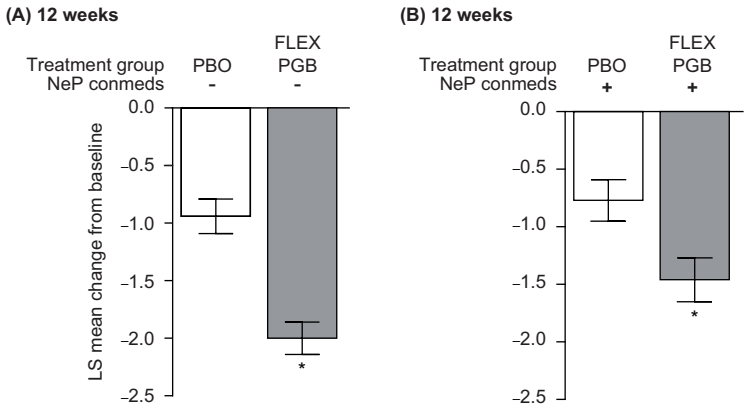

Fig. 3. *Pregabalin-mediated pain improvements compared with placebo among SCI patients who did not receive concomitant neuropathic pain medications (A) and patients who received neuropathic pain medications (B). Scores range from 0 = no pain to 10 = worst possible pain. Data shown are least squares mean ± standard error. Conmeds = concomitant medications; FLEX = flexible dose 150 – 600 mg/d; LS = least squares; NeP = neuropathic pain; PBO = placebo; PGB = pregabalin. *P < 0.001 (A) and P = 0.009 (B) versus placebo.*

Safety in the Combined PHN and SCI-NeP Studies

Nine types of treatment-emergent AEs (TEAEs) were reported with weighted incidence rate of ≥ 5% in either the placebo or pregabalin (all doses combined) treatment arms in the - concomitant NeP medications group (Table 7). Of these, 8 types (constipation, dizziness, dry mouth, fatigue, peripheral edema, somnolence, vision blurred, and weight increased) had a risk difference for pregabalin compared with placebo for which the lower limit of the 95% CI was > 0%. The AEs with the highest risk difference were dizziness (17.7%) and somnolence (15.5%).

The profile of TEAEs was similar in the + concomitant NeP medications group (Table 7). Four types of AEs (dizziness, dry mouth, peripheral edema, and somnolence), with weighted incidence rate of ≥ 5% in either the place-

bo or pregabalin treatment arms, had a risk difference for pregabalin compared with placebo for which the lower limit of the 95% CI was > 0%. The AEs with the highest risk difference were somnolence (12.1%), peripheral edema (7.2%), and dizziness (7.4%).

Discussion

The severity of pain and the presence of other comorbidities commonly results in a situation where patients with NeP receive multiple treatments simultaneously. However, some difficulties are associated with this approach. It may be difficult, for example, to assess the efficacy of a particular agent because the use of concomitant NeP treatments may mask the effects of the treatment of interest. Additionally, the potential for drug-drug interactions exists that may diminish the efficacy of one or more of the agents or result in serious adverse safety and tolerability issues.

Our study examined the efficacy of pregabalin in the context of the use of concomitant NeP mediations. Therapeutic response to pregabalin was evident compared with placebo in patients who were receiving concomitant NeP medications. This shows that there was no "floor effect" present, whereby the use of other medications could potentially mask the effects of pregabalin. Not only was a therapeutic response to pregabalin evident in patients receiving concomitant NeP medications, but the magnitude of this response for both pain and PRSI was generally unaffected by the use of concomitant NeP medications. Pain scores were slightly less improved among pregabalin treated SCI-NeP patients in the + concomitant NeP medications group compared to the - concomitant NeP medications group, though this difference was small and not evident in analyses of PRSI scores in these patients. Further no effects of concomitant NeP medications were observed in the analyses of pain and

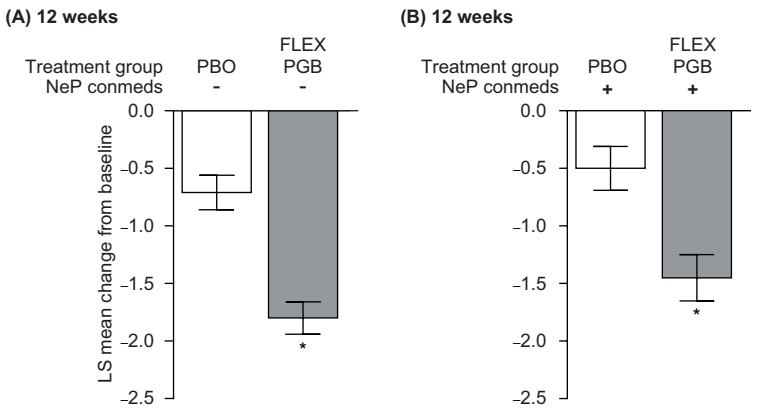

Fig. 4. *Pregabalin-mediated improvements compared with placebo in PRSI among SCI patients who did not receive concomitant neuropathic pain medications (A) and patients who received concomitant neuropathic pain medications (B). Scores range from 0 = pain did not interfere with sleep to 10 = pain completely interfered with sleep. Data shown are least squares mean ± standard error. Conmeds = concomitant medications; FLEX = flexible dose 150 – 600 mg/d; LS = least squares; NeP = neuropathic pain; PBO = placebo; PGB = pregabalin.* **P* < 0.001 (A) and *P* < 0.001 (B) versus placebo.

Table 6. *Effect of concomitant NeP medications on pregabalin-mediated improvements in pain and PRSI in SCI-NeP patients.*

Treatment	- NeP conmeds, n	+ NeP conmeds, n	- NeP conmeds vs + NeP conmeds		
			LS mean difference (SE)	95% CI	*P*-value
Pain[a]					
PBO	97	75	0.17 (0.24)	(-0.30, 0.63)	0.48
PGB FLEX[b]	105	69	0.54 (0.24)	(0.07, 1.00)	0.03
PRSI[c]					
PBO	96	74	0.20 (0.24)	(-0.27, 0.68)	0.40
PGB FLEX[b]	105	69	0.35 (0.24)	(-0.13, 0.83)	0.15

[a] Pain scores range from 0 = no pain to 10 = worst possible pain.
[b] Indicates flexible dosing of 150 – 600 mg/d.
[c] PRSI scores range from 0 = pain did not interfere with sleep to 10 = pain completely interfered with sleep.
conmeds = concomitant medications; FLEX = flexible; LS = least squares; NeP = neuropathic pain; PBO = placebo; PGB = pregabalin; PRSI = pain-related sleep interference; SCI = spinal cord injury; SE = standard error.

Table 7. *Occurrence (% of patients) of treatment-emergent adverse events.*[a]

	- NeP conmeds				+ NeP conmeds			
Adverse event	**Pregabalin**	**Placebo**	**Risk difference**	**95% CI**	**Pregabalin**	**Placebo**	**Risk difference**	**95% CI**
Constipation	5.3	3.0	**2.3**	(0.0, 4.6)	7.5	5.8	1.7	(-2.6, 6.0)
Diarrhea	-	-	-	-	5.6	3.0	2.6	(-0.8, 6.0)
Dizziness	24.9	7.2	**17.7**	(13.6, 21.8)	19.3	12.0	**7.4**	(1.2, 13.5)
Dry mouth	8.8	4.6	**4.2**	(1.3, 7.2)	6.8	1.9	**4.9**	(1.5, 8.2)
Fatigue	5.3	2.7	**2.6**	(0.3, 4.9)	6.1	5.8	0.2	(-3.9, 4.3)
Headache	6.7	5.4	1.3	(-1.5, 4.2)	6.3	6.3	0.1	(-4.2, 4.3)
Peripheral edema	7.9	2.6	**5.3**	(2.7, 7.8)	9.8	2.6	**7.2**	(3.3, 11.0)
Somnolence	19.2	3.8	**15.5**	(12.1, 18.9)	22.0	10.0	**12.1**	(6.1, 18.0)
Vision blurred	6.3	2.1	**4.2**	(1.9, 6.4)	-	-	-	-
Weight increased	5.9	1.5	**4.4**	(2.4, 6.5)	-	-	-	-
Urinary tract infection	-	-	-	-	4.0	5.2	-1.1	(-4.7, 2.5)

[a] Only events with weighted incidence rate of ≥ 5% of patients, in either the placebo or pregabalin (all doses combined) treatment arm, are shown.
conmeds = concomitant medication.
Risk differences with a lower 95% CI > 0% are in bold.

PRSI scores in patients with PHN. These analyses were based on a + concomitant NeP medications group that included all patients who had taken at least one dose of concomitant NeP medication regardless of duration. Sensitivity analyses, however, taking into account duration of concomitant NeP treatment, supported the primary analyses and further demonstrated that the use of concomitant NeP medications has little effect on therapeutic response to pregabalin.

Our study also examined the safety of pregabalin in the context of the use of concomitant NeP medications. For most common AEs, the risk difference (pregabalin versus placebo) was not increased among patients who received concomitant NeP medications compared with the risk difference among patients who did not receive concomitant NeP medications and was notably lower in some cases (e.g., dizziness). This may be, in part, because patients in the placebo + concomitant NeP medications group received medications with an intrinsic risk for AEs as opposed to patients in the placebo - concomitant NeP medications group. For example, the percentage of patients experiencing dizziness and somnolence was increased by 5% – 6% in the placebo + concomitant NeP medications group compared with the placebo - NeP concomitant medications group (Table 7). Overall, our data suggest that the use of concomitant NeP medications does not increase the risk of AEs commonly associated with pregabalin. An exception to this may be the risk of peripheral edema, which was somewhat higher in patients receiving concomitant NeP medications (7.2%) compared with those who did not receive concomitant NeP medications (5.3%).

Our findings have several practical implications. First, the data demonstrate that pregabalin may have a benefit in some patients who exhibit at least moderate levels of pain despite currently receiving other treatment for NeP. In both the PHN and SCI-NeP cohorts, patients were required to have a pain score of > 4 (on a scale from 0 to 10) to be eligible for inclusion in their respective clinical trial. Our findings also suggest that physicians may keep patients on their current NeP medications, if they so desire, when introducing pregabalin to the treatment regimen, since the response to pregabalin is not diminished by concomitant NeP medications. Since there was little difference in the magnitude of therapeutic response to pregabalin in the absence and presence of concomitant NeP medications, our findings add to the current uncertainty of the value of combination therapy in the treatment of NeP (10). For example, a trial comparing high-dose pregabalin (600 mg/d) and high-dose duloxetine (120 mg/d) to a combination of pregabalin 300 mg/d + duloxetine 60 mg/d in patients with pDPN demonstrated that this low-dose combination therapy, though well tolerated, was no more effective than either monotherapy (28).

The original trials of pregabalin were not powered to examine the effects of concomitant NeP medications. Indeed, our analysis was limited in that there were not enough PHN patients receiving concomitant NeP medications in the flexible-dose pregabalin arm to

analyze their effects through 8 and 12 weeks. Additionally, though the magnitude of therapeutic response of pregabalin was unaffected by the use of concomitant NeP medications, the current study did not address the possibility that these medications affect the timing of response to pregabalin. PHN patients were analyzed through 4, 8, and 12 weeks and SCI-NeP patients were analyzed through 12 weeks. The onset of response to pregabalin, however, can occur within 2 days of initiating treatment (28-32). One study in SCI-NeP patients demonstrated that concomitant NeP medications did not affect timing of response to pregabalin over the first 13 days of treatment (29).

Our findings were consistent in 2 different types of NeP: PHN, which is a classical peripheral NeP, and SCI-NeP, which is classified as central NeP. This is encouraging when attempting to extrapolate our findings to other NeP conditions such as pDPN. However, factors inherent to other NeP patient populations such as indication-specific comorbidities and other variables may confound such extrapolation, and care should be taken when attempting to do so. Despite these limitations the data presented here demonstrate that the therapeutic response to pregabalin for the treatment of NeP is largely unaffected by the concurrent use of other NeP medications.

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Author Contributions

All authors had full access to the data described herein, contributed to the interpretation of data, revised the work for important intellectual content, approved the final version of the manuscript, and agree to be accountable for all aspects of the manuscript. In addition, BP, MA, and EW designed and/or performed the statistical analyses.

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Conflict of Interest

BP, MA, and EW are full-time employees of and own stock in Pfizer Inc. The Anesthesiology Unit of the University of Western Australia, but not SAS personally, has received research and travel funding, and speaking and consulting honoraria, from bioCSL, Eli Lilly, Grunenthal, iXBiopharma, Janssen, Mundipharma, Pfizer, and Phosphagenics within the last 5 years. None of the authors received any reimbursement or honorarium with respect to development of this manuscript. The sponsor provided full access to data for all authors and did not play a role in the journal selection process.

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