Linking Changes in Pain Severity to Changes in Other Outcomes in Patients With Posttraumatic Peripheral Neuropathic Pain Treated With Pregabalin

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BACKGROUND

- Chronic pain impacts many aspects of patients' lives, including daily functioning, sleep, and mood[1]
- Numerous patient-reported outcome (PRO) measures have been developed to assess pain severity and other outcomes in clinical trials of chronic pain
- Assessment of daily function and mood is recommended in clinical trials of chronic pain[2]; while assessment of sleep is not specifically recommended, it is justified by strong evidence for an adverse effect of pain on sleep[3]
- Understanding the relationship between changes in pain severity and impact on daily function, mood, and sleep disturbance may help inform treatment decisions and set patient expectations for impact of analgesic therapy

OBJECTIVE

- To evaluate the relationship between changes in pain severity and changes in patient-reported sleep disturbance, pain interference with daily function, and anxiety and depression in patients with posttraumatic peripheral neuropathic pain

METHODS

Study Design

- This is a secondary analysis of data derived from a randomized, double-blind, placebo-controlled, 8-week clinical study of flexible-dose pregabalin in patients with posttraumatic peripheral neuropathic pain[4]

Patients

- All patients with data from the clinical trial were included in this analysis regardless of treatment allocation or effects

Assessments

- Average weekly score on the numeric rating scale (NRS; 0 = no pain to 10 = worst possible pain) recorded daily by patients
- Pain Severity Index (average of the 4 scores from worst pain, least pain, average pain, and pain now) and Pain Interference Index (composite of 7 interference items rated 0 [does not interfere] to 10 [completely interferes]) from the modified Brief Pain Inventory[5]
- Hospital Anxiety and Depression Scale anxiety (HADS-A) and depression (HADS-D) subscales based on 1-week recall[6]
- Medical Outcomes Study–Sleep Scale (MOS-SS) 9-item Sleep Problems Index and 4-item sleep disturbance subscale based on 1-week recall[7]
- Daily Sleep Interference Scale (0 = no interference to 10 = completely interferes) based on 24-hour recall

Analyses

- Changes from baseline to end of treatment at week 8 in PRO scores were evaluated as a function of the change in pain NRS score over the same period
- Linear regression models were used to evaluate the relationship between change in pain and PROs
- Mean changes in PROs were estimated for a 2-point improvement in pain severity, a clinically meaningful improvement[8]
- Four sensitivity analyses were performed
  - Patients with ≥30% pain response
  - Patients with ≥50% pain response
  - Patients treated with pregabalin
  - Patients treated with placebo
- Analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, North Carolina, USA)
- *P*<0.05 was considered statistically significant

RESULTS

- Main study results have been reported elsewhere[4]
- Patients (N=254) had a mean age of 51.7 years and 50.8% were female (**Table 1**)

Table 1. Patient Demographic and Clinical Characteristics

	Placebo (n=127)	Pregabalin (n=127)
Women, n (%)	52 (40.9)	77 (60.6)
Mean age (SD), y	51 (13)	52 (14)
Age 65–80 years, n (%)	25 (19.7)	29 (22.8)
White, n (%)	120 (94.5)	124 (97.6)
Mean weight (SD), kg	81 (17)	78 (15)
Mean duration of neuropathic pain (range)	4.4 (0.2–29.0)	4.3 (0.3–26.0)
Primary neuropathic pain diagnosis,[a] n (%)		
Trauma	59 (46.5)	62 (48.8)
Surgical	41 (32.3)	44 (34.6)
Amputation	6 (4.7)	3 (2.4)
Nerve injury	12 (9.4)	8 (6.3)
Other	9 (7.1)	10 (7.9)
Concomitant pain medications,[b] n (%)	101 (79.5)	102 (80.3)
NSAIDs/COX-2	46 (36.2)	57 (44.9)
TCAs	39 (30.7)	41 (32.3)
SNRI	7 (5.5)	2 (1.6)
Opioids	15 (11.8)	20 (15.8)
Tramadol	41 (32.3)	42 (33.1)
Anticonvulsants[c]	46 (36.2)	41 (32.3)

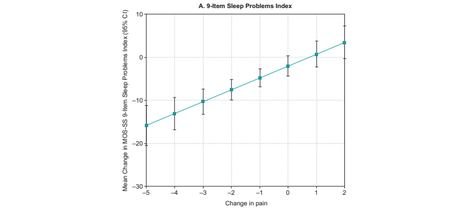
SD, standard deviation; NSAIDs, nonsteroidal anti-inflammatory drugs; COX-2, cyclooxygenase 2; TCAs, tricyclic antidepressants; SNRI, serotonin-norepinephrine reuptake inhibitor

[a] As reported by investigator

[b] Medications may not have been specifically prescribed for neuropathic pain

[c] Antiepileptic drugs other than gabapentin were allowed

Figure 1. Relationship Between Change in Pain Severity and Sleep Disruption



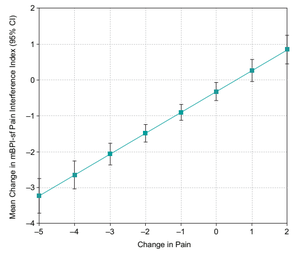
N=254

P<0.001 for the overall relationship in each figure

MOS-SS, Medical Outcomes Study–Sleep Scale; CI, confidence interval

- Linear relationships were observed between change in patient-reported sleep disruption (**Figure 1**), pain interference on daily function (**Figure 2**), and anxiety and depression symptoms (**Figure 3**) as a function of changes in pain severity on the NRS
- The derived plots can be interpreted as showing, at the individual patient level, the mean change in PRO score (y axis) that can be expected with the various incremental changes in pain severity (x axis)
- For example, a 2-point decrease in pain corresponded to an estimated 7.6-point decrease (improvement) in the MOS-SS 9-Item Sleep Problems Index, 11.9-point decrease in MOS-SS sleep disturbance, and 1.6-point decrease in sleep interference (**Figure 1**)
- A 2-point decrease in pain was associated with an estimated 1.5-point decrease in pain interference on daily function (**Figure 2**)

Figure 2. Relationship Between Change in Pain Severity and Change in Pain Interference on Daily Function



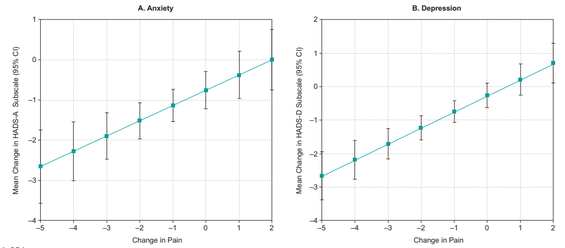
N=254

P<0.001 for the overall relationship

mBPI-sf, modified Brief Pain Inventory short-form; CI, confidence interval

- A 2-point decrease in pain was associated with an estimated 1.5-point decrease in HADS-A and a 1.2-point decrease in HADS-D (**Figure 3**)

Figure 3. Relationship Between Change in Pain Severity and Mood



N=254

P<0.001 for the overall relationship for each figure

HADS-A, Hospital Anxiety and Depression Scale–anxiety subscale; CI, confidence interval; HADS-D, Hospital Anxiety and Depression Scale–depression subscale

- Significant associations between change in pain severity and change in each PRO were observed (**Figures 1–3**; *P*<0.001)
- The mean improvements in sleep, pain interference on daily function, and mood outcome scores that correspond to a 2-point improvement in pain severity score (a clinically important improvement) are shown in **Table 2**
- In general, these sensitivity analyses tended to support the results of the main analysis of the total sample, with some exceptions; for example, 50% responders on the Pain Interference Index scale and the placebo group for HADS-D subscale and for the MOS-SS 9-item Sleep Problems Index (**Table 2**)

Table 2. Mean (95% CI) Improvement in PROs That Corresponded to a 2-Point Improvement in Pain

	MOS-SS Sleep Disturbance	MOS-SS 9-Item Sleep Problems Index	Sleep Interference	HADS-A	HADS-D	Pain Interference Index
All subjects (N=254)	−11.87 (−14.83, −8.91)	−7.59 (−9.91, −5.27)	−1.64 (−1.86, −1.43)	−1.52 (−1.97, −1.07)	−1.23 (−1.58, −0.88)	−1.48 (−1.72, −1.25)
Subgroups						
≥30% responders (n=82)[a]	−11.57 (−19.17, −3.98)	−7.41 (−13.31, −1.50)	−1.54 (−2.05, −1.03)	−1.57 (−2.61, −0.53)	−1.39 (−2.13, −0.65)	−1.68 (−2.22, −1.14)
≥50% responders (n=48)[a]	−13.12 (−25.04, −1.19)	−8.37 (−18.07, −1.32)	−1.70 (−2.7, −0.70)	−2.04 (−3.88, −0.21)	−1.25 (−2.5, 0)	−2.21 (−3.13,−1.28)
Pregabalin-treated patients (n=127)	−15.79 (19.76, −11.83)	−9.85 (−13.14, −6.57)	−1.67 (−1.96, −1.38)	−1.64 (−2.25, −1.03)	−1.56 (−2.00, −1.12)	−1.71 (−2.05, −1.38)
Placebo-treated patients (n=127)	−7.09 (−11.51, −2.68)	−4.93 (−8.22, −1.65)	−1.62 (−1.95, −1.29)	−1.41 (−2.09, −0.74)	−0.83 (−1.39, −0.27)	−1.18 (−1.51, −0.85)

CI, confidence interval; PRO, patient-reported outcome; MOS-SS, Medical Outcomes Study–Sleep Scale; HADS-A, Hospital Anxiety and Depression Scale–anxiety subscale; HADS-D, Hospital Anxiety and Depression Scale–depression subscale

[a] ≥30% and ≥50% responders are those patients who achieved at least a 30% and 50% reduction in pain, respectively, in the clinical trial on which this analysis was based

Reductions in scores on pain and other PROs represent improvements

- For some of the PROs, there was a change in score even with no change in pain severity. For example, individuals with no change in pain severity still showed almost a 4.3-point improvement on the MOS-SS sleep disturbance subscale
- This can be taken to suggest that there may exist effects of treatment that are independent of the effects on pain, which, in this case, can be specific effects on sleep
- Further support for this comes from a sensitivity analyses, for which pregabalin-treated patients with no change in pain improved (decreased) by 7.50 points on MOS-SS sleep disturbance subscale, whereas placebo-treated patients with no change in pain improved only by 1.35 points on sleep disturbance subscale

CONCLUSIONS

- A clear relationship is observed between improvements in pain and improvements in patient-reported daily function, sleep, anxiety, and depression in patients with chronic posttraumatic neuropathic pain
- To our knowledge, this is the first study that demonstrates this set of relationships in patients with posttraumatic peripheral neuropathic pain
- Specifically, these results provide a direct quantitative relationship between an incremental change in pain severity and the expected magnitude of change of a given PRO for an individual patient with posttraumatic peripheral neuropathic pain
- The results of this analysis may be helpful in setting patient expectation for the benefit of analgesic treatment

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