Pregabalin for painful HIV neuropathy

A randomized, double-blind, placebo-controlled trial

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ABSTRACT

Objective: Pregabalin is effective in several neuropathic pain syndromes. This trial evaluated its efficacy, safety, and tolerability for treatment of painful HIV-associated neuropathy.

Methods: This randomized, double-blind, placebo-controlled, parallel-group trial included a 2-week double-blind dose-adjustment (150–600 mg/day BID) phase, a 12-week double-blind maintenance phase, and an optional 3-month open label extension phase. The primary efficacy measure was the mean Numeric Pain Rating Scale (NPRS) score, an 11-point numeric rating scale. Secondary measures included Patient Global Impression of Change (PGIC) and sleep measurements.

Results: Baseline mean NPRS score was 6.93 for patients randomized to pregabalin (n = 151) and 6.72 for those to placebo (n = 151). Pregabalin average daily dosage (SD) was 385.7 (160.3) mg/d. At endpoint, pregabalin and placebo showed substantial reductions in mean NPRS score from baseline: -2.88 vs -2.63, $p = 0.3941$. Pregabalin had greater improvements in NPRS score relative to placebo at weeks 1 (-1.14 vs -0.69, $p = 0.0131$) and 2 (-1.92 vs -1.43, $p = 0.0393$), and at weeks 7 (-3.22 vs -2.53 $p = 0.0307$) and 8 (-3.33 vs -2.53, $p = 0.0156$). At all other time points, differences between groups were not significant. Sleep measurements and 7-item PGIC did not differ among treatment groups; however, collapsed PGIC scores showed 82.8% of pregabalin and 66.7% of placebo patients rated themselves in 1 of the 3 "improved" categories ($p = 0.0077$). Somnolence and dizziness were the most common adverse events with pregabalin.

Conclusions: Pregabalin was well-tolerated, but not superior to placebo in the treatment of painful HIV neuropathy. Factors predicting analgesic response in HIV neuropathy warrant additional research.

Classification of Evidence: This Class II trial showed that pregabalin is not more effective than placebo in treatment of painful HIV neuropathy. *Neurology*® 2010;74:413–420

GLOSSARY

AE = adverse events; **ANCOVA** = analysis of covariance; **ARF** = activity region finder; **ARV** = antiretroviral; **GPS** = Gracely Pain Scale; **HADS** = Hospital Anxiety and Depression Scale; **HIV-DSP** = HIV-associated distal sensory polyneuropathy; **LOCF** = last observation carried forward; **mBPI-sf** = modified Brief Pain Inventory–short form; **NPRS** = Numeric Pain Rating Scale; **NPSI** = Neuropathic Pain Symptom Inventory; **NRS** = Numeric Rating Scale; **PGIC** = Patient Global Impression of Change; **VAS** = visual analog scale.

HIV-associated distal sensory polyneuropathy (HIV-DSP) is the most common neurologic complication of HIV infection and a major cause of morbidity in patients with HIV and AIDS.[1-5] Symptoms of HIV-DSP appear more commonly in the advanced stages of HIV infection.[4-6] Clinical benefit from numerous agents evaluated to date has been inconsistent.[7-10]

Anticonvulsants such as gabapentin and pregabalin exert an analgesic effect by binding to the α_2-δ subunit of voltage-gated calcium channels on primary afferent nerves and

Supplemental data at www.neurology.org

Figure 1   Subject flow through the trial
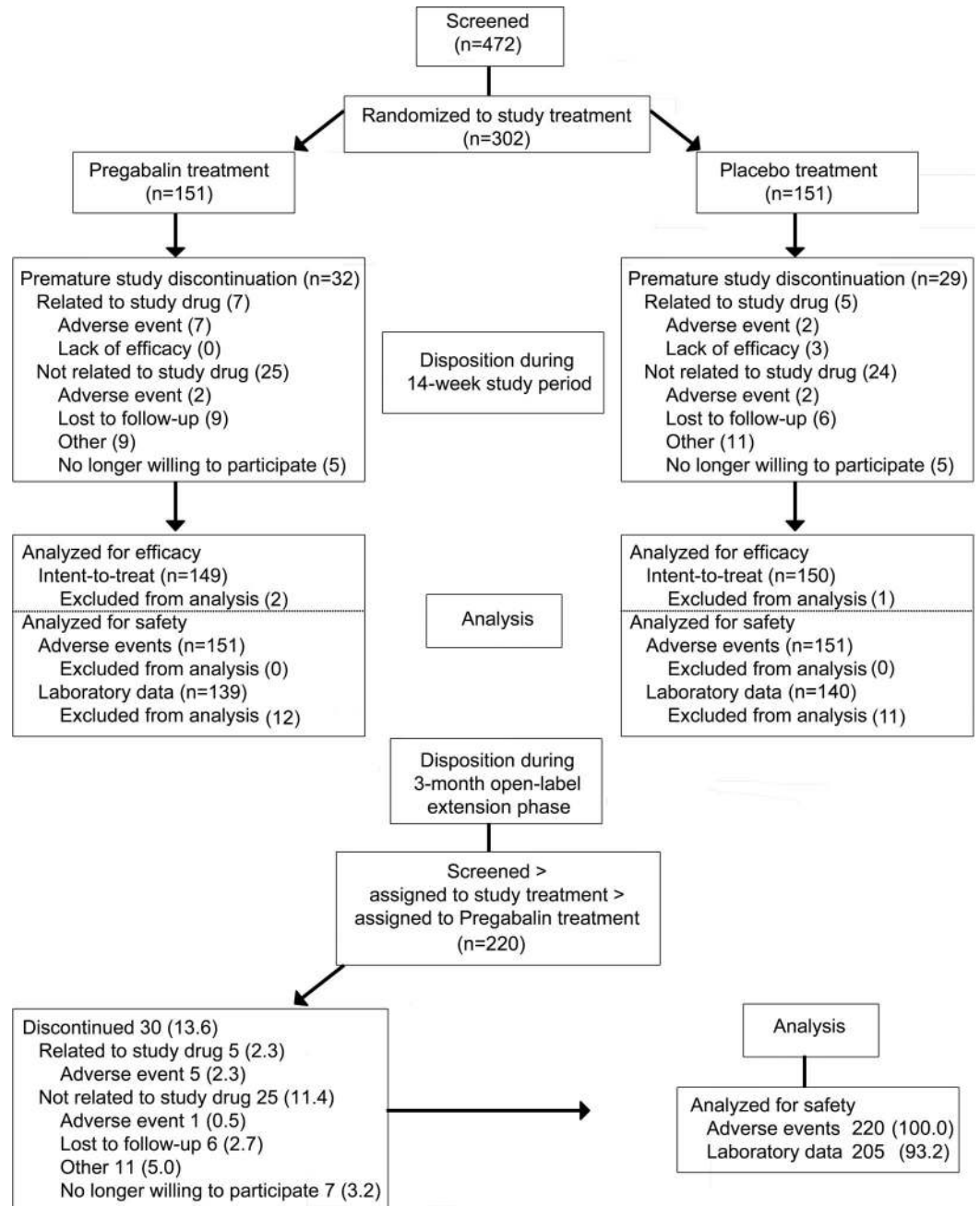
suppressing the release of neurotransmitters from central terminals.[11] In one small placebo-controlled trial, gabapentin was effective in reducing pain related to HIV-DSP.[12] Pregabalin, which has an improved pharmacokinetic profile, has shown efficacy in relieving neuropathic pain associated with diabetic peripheral neuropathy,[13-17] postherpetic neuralgia,[18-20] and spinal cord injury,[21,22] and pain associated with fibromyalgia.[23-25] The current controlled

study evaluates the efficacy and safety of pregabalin in painful HIV-DSP.

METHODS This randomized, placebo-controlled, double-blind, multicenter study evaluated the efficacy, safety, and tolerability of pregabalin for the treatment of pain associated with HIV-DSP (evidence level: Class II). Following trial completion, subjects had the option of enrolling in a 3-month, open-label extension trial (figure 1).

Eligibility and enrollment. Eligible subjects had painful HIV-DSP for ≥3 months, confirmed by a neurologist at screening, using established diagnostic criteria,[2] and a Karnofsky Per-

Figure 2   Study design and dosing schedule

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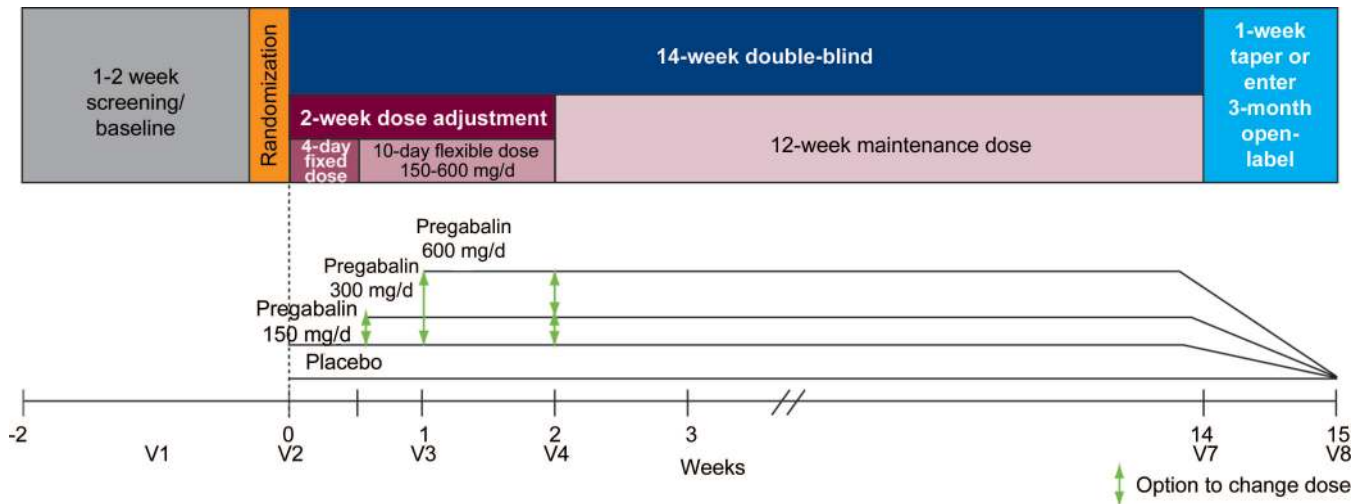
formance Score of ≥60 at screening. Patients receiving neurotoxic antiretroviral (ARV) drugs known to cause sensory neuropathy clinically similar to HIV-DSP must have been on stable doses for ≥3 months before screening. Doses of other pain medications had to be stable for ≥1 month before treatment and throughout the study. Subjects receiving serotonin-norepinephrine reuptake inhibitors or antiepileptics were excluded. Nonpharmacologic therapies (e.g., physical therapy, acupuncture) had to be stable for ≥30 days before screening and throughout the study. Patients were excluded for significant pain unrelated to HIV-DSP; a confounding condition associated with neuropathy (e.g., diabetes mellitus, B12 deficiency, alcoholism); or abnormalities in major organ function.

Standard protocol approvals, registrations, and patient consents. The study was conducted in accordance with the ethics principles of the Declaration of Helsinki, was consistent with Good Clinical Practice guidelines, and was approved by all Institutional Review Boards. Written informed consent was obtained from all participating patients. The trials were registered at the NIH Web site (ClinicalTrials.gov: NCT00232141 and NCT00264875).

Randomization scheme and treatment. The studies were conducted at 40 centers in the United States and Puerto Rico from October 2005 to November 2007. Subjects who completed at least 4 daily pain diary entries during the last 7 days of a 2-week screening period (no study drug administration) with an average score of ≥4 on the Numeric Pain Rating Scale (NPRS) were randomized in a 1:1 ratio to pregabalin or placebo. Randomization assignments were controlled by a central computerized telerandomization system, such that investigators remained blinded to treatment assignments during the study. Study drug and placebo were identical in appearance in order to preserve blinding. The randomized subjects entered a 2-week dosage-adjustment phase and initially received either pregabalin 150 mg/day or placebo BID taken with or without food (figure 2). On day 3, subjects were contacted to assess pain response and tolerability. Based on these factors, the dose was increased to 300 mg/day (150 mg BID) or maintained at 150 mg/day (75 mg BID). During office visits at the end of weeks 1 and 2, the dose was adjusted up to a maximum of 600 mg/day (300 mg BID) or down to a minimum of 150 mg/day (75 mg BID) or maintained

based on individual response and tolerability. After week 2, doses could no longer be adjusted, and subjects entered the 12-week maintenance phase. Subjects remained on the maintenance regimen until the end of week 14; subjects unable to tolerate their maintenance regimen were discontinued.

Patients who completed the final visit of the double-blind study could continue into a 3-month, open-label study extension. Open-label pregabalin treatment was initiated at 150 mg/day (75 mg BID); adjustments within the 150 to 600 mg/day dose range were made throughout the study to optimize pain control and tolerability. Subjects were not aware of which treatment they had received during the double-blind trial.

Assessments. The primary efficacy measure was change from baseline in mean NPRS score at endpoint at 14 weeks (last observation carried forward [LOCF]). Subjects rated pain experienced during the previous 24 hours on an 11-point NPRS ranging from 0 (no pain) to 10 (worst possible pain). A rating of 1 to 3 was considered mild pain; 4 to 6, moderate pain; and 7 to 10, severe pain.[26]

Secondary efficacy measures included change from baseline to week 14 in Numeric Rating Scale (NRS) Sleep Interference Score, Medical Outcomes Study Sleep Scale, Hospital Anxiety and Depression Scale (HADS), and Patient Global Impression of Change (PGIC). Pain was assessed with the modified Brief Pain Inventory–short form (mBPI-sf), Neuropathic Pain Symptom Inventory (NPSI), and Gracely Pain Scale (GPS). Safety assessments included adverse events (AEs), clinical laboratory tests, vital signs, and physical examination. Neurologic examination including mental status, cranial nerve function, motor function, reflexes, and coordination was performed at screening and last visit.

Static mechanical allodynia was evoked by applying the plastic base of a von Frey hair in the area of maximum pain for 10 seconds with sufficient pressure to indent the skin. Dynamic mechanical allodynia was evoked by gently stroking the area of maximum pain with a foam brush. Punctate hyperalgesia was evoked by pinprick over the area of maximum pain with a supplied safety pin. Temporal summation was evoked by repeatedly tapping the area of maximum pain with a 300 g (6.65) Von Frey hair at a rate of approximately 2 Hz (2 taps per second) for 60 seconds. Cold allodynia was evoked by applying a standardized

cool (15°C ± 2°C) metal rod. Cold hyperalgesia was evoked by applying a cold (4°C) metal rod. Patients were asked to rate the pain produced by the applied stimuli on an 11-point NRS. All assessments were performed once at baseline and at endpoint.

During the open-label extension study, efficacy and safety assessments were done at months 1, 2, and 3. Pain was measured on a 100-mm visual analog scale (VAS), where 0 corresponded to no pain and 100 corresponded to worst possible pain. The VAS was completed at entry and at each monthly visit. Safety assessments included AEs, edema, weight, and vital signs.

Statistical analysis. The study was designed to provide 90% power to detect a difference of at least 1.1 (a clinically meaningful difference) in the NPRS change from baseline in weekly mean pain score between pregabalin-treated subjects and placebo at an alpha level of 0.05, a tolerance for type II error set at beta = 0.10, and a common SD of 2.2.[26]

Efficacy and safety measures were assessed for all patients who received study medication based on intention to treat. Comparison of the pregabalin and placebo groups on the change from baseline in mean NPRS scores at endpoint using the LOCF was conducted using an analysis of covariance (ANCOVA) model with treatment and pooled site as fixed effects, and baseline pain score as a covariate.

Secondary analyses included examination of responder rates based on ≥30% and ≥50% reduction in mean weekly pain score using Cochran-Mantel-Haenszel tests. The PGIC was compared between treatment groups using a Cochran-Mantel-

Haenszel test. Descriptive statistics were reported for the open-label study.

Evoked pain measures and CD4, CD8, or HIV plasma viral loads were compared within and between treatment groups at baseline, endpoint assessments, and also for change from baseline values.

A post hoc, hypothesis-generating exploratory analysis of evoked pain measures was done to identify patient subgroups with greatly differing treatment effects. Activity region finder (ARF), a data mining technique that uses a recursive partitioning procedure, identified subgroups with a high mean response or a high proportion of respondents.[27] Following subgroup identification, pregabalin and placebo groups were compared on the change from baseline in mean NPRS scores at endpoint LOCF, using an ANCOVA model with treatment and pooled site as fixed effects and baseline pain score, the ARF-identified subgroup as a covariate, and an additional term for the interaction of this subgroup with treatment. Least squares estimates of treatment differences from this interaction term were obtained from the ANCOVA model.

RESULTS Patient characteristics. A total of 302 patients (151 pregabalin, 151 placebo; figure 2) were randomized with treatment groups balanced for baseline NPRS score (mean 6.93 pregabalin [SD 1.5], 6.72 placebo [SD 1.5]), duration of neuropathic pain, analgesic treatment, and neurotoxic ARV treatment (table 1). No significant differences between pregabalin and placebo treatment groups were identified at baseline and endpoint assessments with respect to CD4, CD8, or HIV plasma viral load, and likewise, no differences within a treatment group (using change from baseline values) with respect to CD4, CD8, and viral load counts at the endpoint assessments.

Overall, 241 patients (80%) completed the 14-week study; 32 pregabalin subjects (21%) and 29 placebo subjects (19%) terminated early (figure 1). Of 151 patients receiving pregabalin, 17 subjects (11.3%) achieved a maximum dose of 150 mg/day, 53 (35.1%) achieved 300 mg/day, and 91 (53.6%) achieved 600 mg/day. The average daily pregabalin dosage (SD) was 385.7 (160.3) mg/day. A total of 220 subjects elected to enter the open-label extension study, and 169 completed the study. During the open-label study, the average dose was 312.9 mg/day.

Efficacy. Pain reduction at the 14-week endpoint was similar in placebo and pregabalin groups. NPRS scores at endpoint LOCF relative to baseline for pregabalin showed an average decrease of 2.88 compared with an average decrease of 2.63 for placebo (difference −0.25, $p = 0.3914$). Weekly pain scores were lower for pregabalin at weeks 1 and 2 (figure 3), with subjects in the pregabalin group experiencing an average decrease of 1.14 in NPRS scores compared with an average decrease of 0.69 for the placebo group at week 1 ($p = 0.0131$). The mean change

Table 1	Demographic and baseline characteristics	
	Placebo	Pregabalin
Mean age, y (SD)	46.8 (7.5)	48.2 (8.1)
Sex, n (%)		
Women	31 (21)	26 (17)
Men	120 (80)	125 (83)
Race, n (%)		
White	87 (58)	84 (56)
Black	47 (31)	58 (38)
Asian	1 (1)	0
Other	16 (11)	9 (6)
Mean Numeric Pain Rating Scale pain score (SD)	6.7 (1.5)	6.9 (1.5)
Mean disease duration, y		
HIV diagnosis	12.6	13.9
Polyneuropathy diagnosis	5.0	5.4
Neuropathic pain symptoms	6.0	6.2
Mean HIV viral load (SD)	14,547 (58,296)	8762.7 (34,316)
Mean CD4 count (SD)	437.35 (255.17)	483.44 (273.53)
Pain medications prior to initiation of treatment, n (%)		
Antiepileptics	31 (21)	30 (20)
Tricyclic antidepressants	9 (6)	8 (5)
Opioids	45 (30)	50 (33)
Nonsteroidal anti-inflammatory drugs	38 (25)	37 (25)
Other	26 (17)	18 (12)

Figure 3 Mean change from baseline in Numeric Pain Rating Scale score
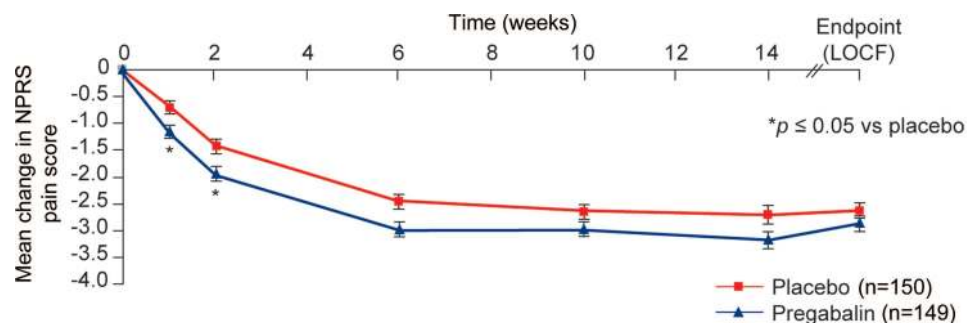
from baseline in NPRS scores also differed between the 2 treatment groups at weeks 2 (-1.92 vs -1.43, $p = 0.0393$), 7 (-3.22 vs -2.53, $p = 0.0307$), and 8 (-3.33 vs -2.53, $p = 0.0156$). No difference was observed at weeks 6, 10, and 14 ($p = 0.0879$, $p = 0.3060$, and $p = 0.1856$). Final achieved dosage did not correlate with pain response.

No differences in 30% and 50% responder rates between the pregabalin and placebo groups were observed at any study visit or at endpoint. The endpoint LOCF 50% responder rate for pregabalin was 38.9% and 42.8% for placebo ($p = 0.5003$). The endpoint LOCF 30% responder rate for pregabalin was 56.3% and 55.9% for placebo ($p = 0.9061$).

The weekly sleep interference score was lower for pregabalin at time points up to week 6. At week 1, subjects receiving pregabalin had an average decrease of 1.04 in NRS-sleep interference scores compared with an average decrease of 0.68 in the placebo group ($p = 0.0469$). Differences between the 2 study groups also occurred at weeks 2 ($p = 0.0067$) and 6 ($p = 0.0452$), but not at weeks 10 ($p = 0.1053$) and 14 ($p = 0.0711$). At study endpoint, the pregabalin and placebo groups did not differ in NRS-sleep interference scores ($p = 0.4776$).

Pregabalin had a modest effect on the PGIC; 82.8% of subjects receiving pregabalin and 66.7% of subjects receiving placebo considered themselves to be "improved," 13.3% of subjects receiving pregabalin and 25.4% of subjects receiving placebo experienced "no change," and 3.9% of subjects receiving pregabalin and 7.9% of subjects receiving placebo felt that they had "worsened" by the end of the study ($p = 0.008$). However, when patient responses were analyzed by more specific categories (very much improved/much improved/minimally improved/no change/minimally worse/much worse/very much worse), the differences were not significant. The difference in the change in NPSI or HADS scores between pregabalin and placebo groups was not significant.

The pregabalin and the placebo groups experienced similar average decreases from baseline in GPS score of 2.70 and 2.76. p Values for correlations between the change from baseline at endpoint in the GPS and the change from baseline to endpoint in NPRS scores and mBPI-sf measures (including worst pain, average pain, Pain Severity Index, and Pain Interference Index at endpoint) were <0.0001 for all comparisons.

The mean baseline pain score was 38.61 on the 100-mm VAS at the start of the open-label study. The mean VAS score decreased to 30.75 after 4 weeks of treatment and was maintained at 29.39 at the 3-month endpoint.

The difference in the change from baseline to endpoint for any assessment of the evoked pain measures between the pregabalin and placebo groups was not significant. However, ARF analysis indicated that treatment effects differ greatly in subjects with the greatest sensitivity to pinprick at baseline (baseline punctate hyperalgesia score ≥8, n = 39). For these subjects, the change from baseline in mean NPRS scores at endpoint LOCF showed a 2.14-point greater improvement for pregabalin compared to placebo ($p = 0.0111$). For subjects with a low-to-moderate sensitivity to pinprick at baseline (a score ≤7 on assessment of punctate hyperalgesia), change from baseline difference was 0.06 points ($p = 0.8792$). No significant difference in pain score was found between groups when using the same criteria for other evoked pain assessments.

Safety and tolerability. Pregabalin treatment was generally well tolerated. A total of 123 pregabalin-treated subjects (81.5%) and 106 placebo-treated subjects (70.2%) reported AEs. The most commonly reported AEs were generally mild to moderate in intensity and included somnolence, dizziness, euphoric mood, headache, and peripheral edema (table 2).

Discontinuations due to AEs occurred in 9 subjects (6.0%) treated with pregabalin and 4 (2.6%) of

Table 2 Treatment-emergent adverse events (treatment-related) (≥5% in pregabalin group and > placebo)

Adverse event	Placebo (n = 151), %	Pregabalin (n = 151), %
Somnolence	8.6	23.2
Dizziness	10.6	19.2
Euphoric mood	0.7	9.9
Dry mouth	0.7	9.3
Peripheral edema	4.6	6.0

the subjects treated with placebo. The most common reasons for discontinuation due to pregabalin-related AEs were dizziness (4 subjects) and somnolence, confusional state, and disorientation (2 subjects each). The reasons for treatment-related discontinuations in the placebo group were hypoesthesia (1 subject), bladder pain (1 subject), nausea and vomiting (1 subject), and pain (1 subject). No treatment-related serious AEs occurred.

Treatment-related AEs were reported by 145 (65.9%) subjects in the open-label study. As during the double-blind study, AEs in the extension phase were generally mild to moderate in intensity. The most commonly reported AEs included somnolence, dizziness, peripheral edema, diarrhea, and fatigue. Discontinuations due to AEs occurred for 2.7% of subjects. No treatment-related serious AEs occurred.

DISCUSSION Symptomatic therapy for neuropathic pain remains an area in need of more effective therapies. While many neuropathic pain syndromes are clinically similar, the degree to which results derived from one human pain condition may apply to other neuropathic pain conditions caused by different underlying diseases is unclear. In this study we tested pregabalin, a medication demonstrated to be effective for diabetic peripheral neuropathic pain and postherpetic neuralgia, for efficacy in HIV. Control of pain due to peripheral neuropathy either associated with HIV infection or secondary to neurotoxicity of several antiretroviral treatments is a large unmet need. The results of this placebo-controlled, multicenter study show that pregabalin, at doses up to 600 mg/day, is safe and well-tolerated by HIV-infected individuals with DSP. The most common adverse experiences reported were generally of mild or moderate intensity and similar in frequency to those previously reported for pregabalin in studies that enrolled HIV-negative individuals.[13-25]

Based on the primary efficacy measure, change from baseline in mean NPRS score, the current study revealed no significant difference between placebo and pregabalin treatment arms. Similarly, there were no significant differences in the secondary pain measures, including responder rates based on ≥30% and ≥50% reduction in mean weekly pain score, mBPI-sf, NPSI, and GPS.

Evoked pain was assessed in all patients in this multicenter study. None of the evoked pain measures changed significantly in response to therapy. An exploratory analysis of the relationship between therapeutic response to pregabalin and evoked pain characteristics revealed that the presence of marked sensitivity to pinprick stimuli on punctate hyperalgesia assessment, but not mechanical allodynia, cold hyperalgesia, or cold allodynia, was associated with a significant and clinically meaningful response to pregabalin vs placebo. These data may provide insight into the mechanism of action of pregabalin in this and perhaps other patient populations with neuropathic pain. Punctate hyperalgesia in experimental pain models is a manifestation of central sensitization induced by C-fiber nociceptor activity.[28,29] These findings should be examined prospectively in future studies.

Individuals with HIV-associated DSP achieved NPRS treatment effect size similar to those in studies of diabetic peripheral neuropathy[13-17] and postherpetic neuralgia.[16,18-20] However, the placebo group in the current study had a much higher NPRS change than in the diabetic peripheral neuropathy or postherpetic neuralgia studies. Notably, there were no significant demographic, clinical, or laboratory differences at baseline between the placebo and pregabalin arms in our study (table 1).

Study design might affect placebo responses. We used a flexible-dose design rather than the fixed-dose schema used in most diabetic peripheral neuropathy and postherpetic neuralgia studies. It is unclear whether the difference in study design affected the outcome. We chose a flexible-dose design because this better approximates clinical practice, and there have been reports that this design may potentially decrease the placebo response, at least in trials for treatment of depression.[30,31] Furthermore, mild pain at baseline has also been suggested to increase the placebo response.[30] However, in this study, the average pain score was in the moderate range.

Dose did not correlate with response; however, this flexible-dose study was not randomized to different doses and not designed to detect dose response. Dose response has been demonstrated in fixed-dose studies of pregabalin.[14,15,17,19,20,23,24] In flexible-dose regimens, dose is adjusted for efficacy and tolerability. Direct comparison of dose groups introduces a selection bias (e.g., patients escalated to the highest dose may show less improvement than patients who

receive a lower dose, since less responsive patients would receive higher doses).

Notably, several other controlled symptomatic pain studies reported large placebo responses. This was true of a study of amitriptyline in which the substantial placebo response of 0.20 units on the GPS was sufficient to make the slightly greater amitriptyline response insignificant.[32] Similarly, large placebo response played a role in determination of efficacy for lamotrigine for HIV-associated neuropathy pain.[33] Future studies in HIV-DSP would benefit from study designs that minimize placebo response to allow identification of potentially active therapeutic agents.

AUTHOR CONTRIBUTIONS

DISCLOSURE

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