Pregabalin relieves symptoms of painful diabetic neuropathy
A randomized controlled trial

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Abstract—Objective: Pregabalin, an alpha_2-delta ligand with analgesic, anxiolytic, and anticonvulsant activity, has been evaluated for treatment of neuropathic pain. The authors assessed the efficacy and tolerability of pregabalin (75, 300, 600 mg/day) vs placebo in patients with diabetic peripheral neuropathy (DPN). Methods: Patients with a 1- to 5-year history of DPN and average weekly pain score of ≥4 on an 11-point numeric pain-rating scale were enrolled in a 5-week, double-blind, multicenter, placebo-controlled study. Patients (n = 338) were randomized to receive one of three doses of pregabalin or placebo TID. Pregabalin 600 mg/day was titrated over 6 days; lower doses were initiated on day 1. Results: Patients in the 300- and 600-mg/day pregabalin groups showed improvements in endpoint mean pain score (primary efficacy measure) vs placebo (Φ = 0.0001). Improvements were also seen in weekly pain score, sleep interference score, patient global impression of change, clinical global impression of change, SF-McGill Pain Questionnaire, and multiple domains of the SF-36 Health Survey. Improvements in pain and sleep were seen as early as week 1 and were sustained throughout the 5 weeks. Responders (patients with ≥50% reduction in pain compared to baseline) were 46% (300 mg/day), 48% (600 mg/day), and 18% (placebo). Pregabalin was well tolerated with a low discontinuation rate. The most common adverse events were dizziness and somnolence. Conclusions: In patients with diabetic peripheral neuropathy, pregabalin demonstrated early and sustained improvement in pain and a beneficial effect on sleep, which were confirmed by positive patient global impression. Pregabalin was well tolerated at all doses.

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Pregabalin\(^1\) has demonstrated efficacy in treating neuropathic pain (NeP) and sleep interference associated with diabetic peripheral neuropathy (DPN) and postherpetic neuralgia (PHN).\(^2,3\) Studies with laboratory animals show pregabalin selectively binds to the \(\alpha_2-\delta\) subunit protein of voltage-gated calcium channels in various regions of brain\(^4\) and in the superficial dorsal horn of the spinal cord (F. Bian et al., R. Williams et al., personal communications). In vitro, pregabalin acts as a presynaptic inhibitor of the release of excitatory neurotransmitters in stimulated neurons.\(^4,5\) It reduces influx of calcium into isolated synaptic endings,\(^6\) thereby reducing release of synaptic vesicles by exocytosis. This has been measured in vitro with several excitatory neurotransmitters, including glutamate,\(^5\) substance P, and calcitonin gene-related peptide,\(^7\) which are particularly relevant for potential analgesic action. Pregabalin’s effect of inhibiting neurotransmitter release is enhanced by prolonged depolarization or prior inflammation.\(^8,9\) Pregabalin has no activity at GABA\(_A\), GABA\(_B\), or benzodiazepine receptors,\(^10\) and there are no known pharmacokinetic drug-drug interactions with pregabalin.

Gabapentin is widely used to treat NeP, in part, because it has fewer troublesome side effects than tricyclics and almost no drug interactions.\(^11-13\) Yet, it shows nonlinear bioavailability and requires titration to the higher doses (i.e., ≥1,800 mg/day) at which response rates have been greatest.\(^13,14,16\) Though structurally related to gabapentin, pregabalin exhibits linear pharmacokinetics across its therapeutic dose range, with low intersubject variability, unlike the less-than-proportional pharmacokinetics observed with increasing doses of gabapentin.\(^17\) This study evaluated the effectiveness of pregabalin vs placebo in relieving NeP associated with DPN. Attention was given to the impact of diabetic NeP on sleep and health-related quality of life, as these are documented, relevant comorbidities of DPN.\(^18\)

Methods. This was a randomized, double-blind, placebo-controlled, parallel-group, multicenter study conducted in accordance with the Declaration of Helsinki and in compliance with ICH Good Clinical Practice Guidelines. The protocol and a copy of the informed consent document were reviewed and approved by the institutional review board at each of the 45 study centers, all located in the United States. Each patient or legal guardian read and signed informed consent before initiating any study procedures.

The study consisted of a 1-week baseline phase and a 5-week double-blind treatment phase that included a 1-week titration and 4-week fixed-dose period. Following week 5 of the double-blind
phase, patients had the option of entering an open-label follow-on study. During the baseline and double-blind phases, patients recorded a daily pain score in a pain diary. At the end of the baseline phase, eligible patients were randomized to receive placebo, 75, 300, or 600 mg/day of pregabalin during the double-blind period. Pregabalin or matching placebo capsules were administered orally, three times a day for a period of 5 weeks. Patients randomized to the 600 mg/day arm titrated to the full dose over the 6-day titration period, while patients randomized to receive pregabalin 75 mg/day and 300 mg/day began at the full dose without titration.

The randomization code was generated with a block size of eight and was maintained by the Clinical Pharmacy Operations department, with no access by other individuals or departments. Medication was shipped to the sites in blocks in unit-dose trays; each box contained three capsules (active medication or placebo) in both the 25 mg and 100 mg pregabalin strength. Each patient was assigned the next sequential random number at the site and took one small and two larger capsules, with the proper mix of active medication and placebo, for each dose to achieve double-blinding. The first dose of study medication was taken on August 21, 1998, and the last observation was recorded on June 24, 1999. The blind was maintained until all decisions regarding data evaluability were made.

Eligible patients were men and women 18 years of age or older with a diagnosis of type 1 or type 2 diabetes mellitus and distal symmetric sensorimotor polyneuropathy for 1 to 5 years. Female patients were required to be nonpregnant, nonlactating, postmenopausal, surgically sterilized, or using effective contraception. Each patient's anti-diabetic medication was to be stabilized prior to initiation of the study and held constant throughout the study, provided adequate glucose control was maintained to ensure patient safety. Patients must have completed at least four daily pain diaries during the baseline phase, and had to have an average baseline daily pain score of \( \leq 4 \) (on a 0 to 10 scale). Patients were also required to have a score of \( \geq 0.40 \) mm on the visual analog scale (VAS) of the Short-Form McGill Pain Questionnaire (SF-MPQ) at baseline and randomization visits.

Patients with hemoglobin A1c levels of \( >11\% \) were excluded, as were patients with clinically significant or unstable hepatic, respiratory, or hematologic illnesses, unstable cardiovascular disease, or symptomatic peripheral vascular disease. Since pregabalin is renally excreted, patients with an estimated creatinine clearance of \( \leq 60 \) ml/minute based on serum creatinine levels were excluded. Patients with any conditions that might confound pain assessment (for example, other severe pain or a skin condition in an area affected by neuropathy) were excluded as well. Patients who had failed to respond to previous treatment with gabapentin at doses \( \geq 1,200 \) mg/day for treatment of pain associated with diabetic neuropathy. Patients were allowed to take up to 3 g of acetaminophen daily and to continue stable treatment with selective serotonin reuptake inhibitors (SSRIs). All other NeP medications were prohibited during the course of the study.

The primary efficacy measure was pain, as recorded by the patient in a daily diary; rating was based on an 11-point numerical scale that ranged from 0 (no pain) to 10 (worst possible pain). Each day on awakening, patients circled the number on the scale that best described their average pain over the previous 24 hours. Mean pain scores were computed at endpoint (the last seven scores while on study drug) and for each week in the study. Secondary efficacy measures were the daily sleep interference diary, SF-MPQ (including the pain descriptors total score, the VAS, and present pain intensity [PPI]) completed by the patient at each clinic visit, and the Clinical Global Impression of Change (CGIC) and Patient Global Impression of Change (PGIC) administered at the completion visit. Additionally, the SF-36 Health Survey (SF-36) to assess quality of life and the Profile of Mood States (POMS) questionnaire to determine mood stability were administered at study randomization and completion. For the SF-36, scores for eight HRQoL domains—physical functioning, role limitations due to physical problems, social functioning, bodily pain, mental health, role limitations due to emotional problems, vitality, and general health perceptions—were calculated, with higher scores indicating a better HRQoL. The POMS measured and provided scores for total mood disturbance as well as six mood scales—tension-anxiety, depression-dejection, anger-hostility, vigor-activity, fatigue-inertia, and confusion-bewilderment—based on patient assessments of 65 mood descriptors.

Figure 1. Summary of participant flow during the study. *One patient randomized to the 300 mg/day group withdrew before taking study medication because of concern over baseline abnormal ECG. ITT = intention to treat.
Table 1 Summary of patient characteristics: intent-to-treat population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo, n = 97</th>
<th>Pregabalin 75 mg/day, n = 77</th>
<th>Pregabalin 300 mg/day, n = 81</th>
<th>Pregabalin 600 mg/day, n = 82</th>
<th>All patients, n = 337</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>59 (60.8)</td>
<td>43 (55.8)</td>
<td>48 (59.3)</td>
<td>52 (63.4)</td>
<td>202 (59.9)</td>
</tr>
<tr>
<td>Women</td>
<td>38 (39.2)</td>
<td>34 (44.2)</td>
<td>33 (40.7)</td>
<td>30 (36.6)</td>
<td>135 (40.1)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>91 (93.8)</td>
<td>74 (96.1)</td>
<td>76 (93.8)</td>
<td>77 (93.9)</td>
<td>318 (94.4)</td>
</tr>
<tr>
<td>Black</td>
<td>5 (5.2)</td>
<td>1 (1.3)</td>
<td>3 (3.7)</td>
<td>3 (3.7)</td>
<td>12 (3.6)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (1.0)</td>
<td>2 (2.6)</td>
<td>2 (2.5)</td>
<td>2 (2.4)</td>
<td>7 (2.1)</td>
</tr>
<tr>
<td>Age, y Mean (SD)</td>
<td>57.8 (11.6)</td>
<td>61.3 (10.5)</td>
<td>59.0 (9.2)</td>
<td>62.0 (9.7)</td>
<td>59.9 (10.5)</td>
</tr>
<tr>
<td>Baseline pain score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>6.6 (1.5)</td>
<td>6.7 (1.3)</td>
<td>6.2 (1.4)</td>
<td>6.2 (1.5)</td>
<td>6.4 (1.4)</td>
</tr>
<tr>
<td>Median</td>
<td>6.7</td>
<td>6.6</td>
<td>6</td>
<td>6.3</td>
<td>6.4</td>
</tr>
<tr>
<td>Min, max</td>
<td>2.9, 9.6</td>
<td>3.7, 10.0</td>
<td>3.9, 10.0</td>
<td>3.7, 10.0</td>
<td>2.9, 10.0</td>
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<tr>
<td>Antidiabetic medication, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td>47 (48.5)</td>
<td>30 (39.0)</td>
<td>33 (40.7)</td>
<td>32 (39.0)</td>
<td>142 (42.1)</td>
</tr>
<tr>
<td>Oral</td>
<td>67 (69.1)</td>
<td>55 (71.4)</td>
<td>65 (80.2)</td>
<td>60 (73.2)</td>
<td>247 (73.3)</td>
</tr>
</tbody>
</table>

modified ridit scores, adjusting for center. As specified by the protocol, patients who experienced a 50% or greater decrease in pain from baseline to endpoint were considered responders. The proportion of responders was analyzed using the CMH test with table scores, adjusting for center.

Results. A total of 578 patients were screened and 338 were randomized to treatment. Of the 240 patients not randomized, 238 did not meet the eligibility criteria or withdrew because of administrative reasons and 2 had severe adverse events prior to taking medication. One patient who was randomized withdrew before taking study medication and was not included in the ITT population (figure 1). The characteristics of the 337 ITT patients are summarized in table 1. The treatment groups were well balanced with respect to demographic and disease characteristics. Most patients (306 patients, 91%) were diagnosed with type 2 diabetes, and most (319 patients, 95%) were receiving medications for their diabetes, either insulin (various forms) or oral antidiabetic agents such as metformin hydrochloride, glibenclamide, glipizide, and troglitazone. Pain scores at baseline were similar across treatment groups. A total of 69 patients received concurrent NeP medications; 46 (14%) used acetaminophen, the only pain medication allowed during the study. Twenty-five patients took protocol-prohibited analgesics during the study or with inadequate washout periods prior to study start.

More than 85% of patients in each treatment group completed the study (see figure 1). During the 5-week double-blind treatment phase, 35 patients withdrew prior to completing the study; 18 of these were due to AEs. More patients receiving pregabalin 600 mg/day withdrew due to AEs (12.2% [10/82]) as compared with the other treatment groups (75 mg/day, 2.6% [2/77]; 300 mg/day, 3.7% [3/81]; placebo, 3.1% [3/97]). A very high percentage of completers chose to enter the open-label phase of the trial (93% of the 75 mg group [62/67], 92% of the 300 mg group [70/76], 97% of the 600 mg group [68/70], and 97% of the placebo group [86/89]). An additional 5 patients in the 75-mg/day group, 2 in the 600-mg/day group, and 2 in the placebo group entered open label without completing the study.

The primary efficacy measure, endpoint mean pain score, was significantly improved by pregabalin 300 and 600 mg/day when compared to placebo (table 2). The efficacy of pregabalin 75 mg/day, as anticipated, was not different from placebo.

Both pregabalin 300 and 600 mg/day significantly reduced pain compared to placebo as early as week 1 following treatment initiation, the first time point for which a
Table 2  Endpoint* mean pain scores: results of analysis of covariance

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>Least squares mean</th>
<th>SE</th>
<th>Difference from placebo</th>
<th>95% CI</th>
<th>Adjusted† p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>97</td>
<td>5.06</td>
<td>0.21</td>
<td>-0.15</td>
<td>(-0.76, 0.46)</td>
<td>0.6267</td>
</tr>
<tr>
<td>Pregabalin 75 mg/day</td>
<td>77</td>
<td>4.91</td>
<td>0.24</td>
<td>-0.15</td>
<td>(-0.76, 0.46)</td>
<td>0.6267</td>
</tr>
<tr>
<td>Pregabalin 300 mg/day</td>
<td>81</td>
<td>3.90</td>
<td>0.23</td>
<td>-1.26</td>
<td>(-1.96, -0.56)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Pregabalin 600 mg/day</td>
<td>81</td>
<td>3.60</td>
<td>0.23</td>
<td>-1.45</td>
<td>(-2.06, -0.85)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

* Endpoint = Last seven available scores while on study medication.
† Adjustment based on Hochberg's procedure applies to pregabalin 300 mg/day and 600 mg/day only, per protocol.

weekly mean could be computed (figure 2). These effects were significant at each week of the study and persisted through endpoint. There was a significantly higher proportion of responders (patients with ≥50% reduction in pain) in the 300-mg/day pregabalin group (37/81, 46%) and 600-mg/day pregabalin group (39/81 patients, 48%) compared with placebo (17/97, 18%). Further, a greater proportion of patients in the 600-mg/day group achieved higher levels of response, such as ≥60%, ≥70%, and ≥80% reduction in pain. For example, the proportion of patients achieving a ≥70% reduction in pain was significantly higher in the 600-mg/day group (22/81, 27%) than the 300 mg/day group (13/81, 16%) or the placebo group (6/97, 6%) (figure 3). Using the clinically important improvement rate of 30%, 26% response rates were similar in the 300-mg/day (50/81, 62%) and 600-mg/day (53/81, 65%) groups and lower with placebo (32/97, 33%).

Similarly, the mean sleep interference score was improved by both pregabalin 300 and 600 mg/day compared with placebo by week 1 (figure 4). The sleep interference scores for the 300- and 600 mg/day pregabalin groups were lower than the sleep interference scores of the placebo group at each week during the double-blind phase and differed by 1.3 and 1.6 (p = 0.0001) for the two doses at endpoint.

Other secondary efficacy measures demonstrated a similar pattern of findings. For the SF-MPQ, treatment with pregabalin 300 and 600 mg/day significantly reduced total score (comprised of sensory and affective scores, both of which improved with pregabalin 300 and 600 mg), PPI, and VAS compared with placebo (table 3). The PGIC and CGIC scores were likewise better for both of these pregabalin doses compared with the placebo group (p = 0.001 for each comparison) (figure 5). For the top two categories, "much improved" and "very much improved," on PGIC, pregabalin rates were 55.7% (44/79) for 300 mg/day and 69.2% (54/78) for 600 mg/day, while the placebo rate was 24.2% (23/95). For these categories on CGIC, pregabalin rates were 58.2% (46/79) for 300 mg/day and 64.1% (50/78) for 600 mg/day, while the placebo rate was 26.3% (25/95).

Pregabalin treatment also led to improvements in specific patient-reported outcomes of health status as measured by the social function, bodily pain, and vitality domains of the SF-36. Both the 300 and 600 mg/day pregabalin groups were better than placebo in the social functioning domain (p < 0.05 and p < 0.01) and in the bodily pain domain (p < 0.005 and p < 0.0005). Additionally, the 75 and 300 mg/day pregabalin groups were better than placebo in the vitality domain (p < 0.05 and p < 0.01). Further, the 300 mg/day pregabalin group had better re-
results than the placebo group on the tension-anxiety mood scale of the POMS ($p < 0.05$).

Pregabalin was generally well tolerated. No age- or sex-related differences were noted in the frequency of AEs. Among patients receiving the 300 and 600 mg/day doses, the most frequently occurring AEs were CNS-related and usually mild or moderate in intensity (table 4). Dizziness, somnolence, and peripheral edema were the most common AEs reported. To determine, post hoc, whether CNS AEs may have unblinded patients to their treatment assignment, the primary efficacy analysis was repeated after exclusion of patients reporting dizziness or somnolence. The primary results remained significant following this analysis, with the difference from placebo on endpoint mean pain scores being $-0.89$ for pregabalin 300 mg/day ($p < 0.05$) and $-1.38$ for 600 mg/day ($p < 0.005$). Thus, it does not appear that the presence of dizziness or somnolence had an impact on the primary result. A total of eight patients experienced serious AEs during the study—one in the 75-mg/day pregabalin group, four in the 600-mg/day pregabalin group, and three in the placebo group. Of these serious AEs, only one led to discontinuation from the study (a patient receiving placebo who withdrew due to an allergic reaction). No deaths were reported during the study.

The number of patients who experienced deterioration based on the neurologic examinations of gait, muscle strength, or reflexes was similar across treatment groups. A total of seven patients, three in the placebo group, three in the 75 mg/day group, and one in the 300 mg/day group, experienced weight gain $\geq 7\%$ between baseline and study completion. However, none of these was reported as an adverse event. No other clinically significant changes were noted in physical examinations, including vital signs and orthostatic hypotension. No unusual clinical laboratory values were noted during the study.

**Discussion.** In this double-blind, placebo-controlled trial, pregabalin at 300 and 600 mg/day was safe and effective for the treatment of NeP associated with DPN. The effect was measurable and significant by the end of the first week and sustained throughout the 5 weeks of the study.

The improvement demonstrated on the primary efficacy measure (i.e., reduction in endpoint mean

### Table 3 Short-Form McGill Pain Questionnaire (SF-MPQ): total score, VAS, and PPI at endpoint*: results of analysis of covariance

<table>
<thead>
<tr>
<th>Treatment (mg/day)</th>
<th>N</th>
<th>Least squares mean</th>
<th>SE</th>
<th>Difference from placebo</th>
<th>95% CI</th>
<th>Adjusted† p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SF-MPQ total score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Placebo</td>
<td>97</td>
<td>15.06</td>
<td>0.84</td>
<td>0.01</td>
<td>(-2.43, 2.44)</td>
<td>0.9966</td>
</tr>
<tr>
<td>Pregabalin 75</td>
<td>77</td>
<td>15.06</td>
<td>0.94</td>
<td>-4.89</td>
<td>(-7.29, -2.48)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Pregabalin 300</td>
<td>81</td>
<td>10.17</td>
<td>0.92</td>
<td>-5.18</td>
<td>(-7.58, -2.79)</td>
<td>0.0001</td>
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<tr>
<td>Pregabalin 600</td>
<td>81</td>
<td>9.88</td>
<td>0.91</td>
<td></td>
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<td></td>
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<tr>
<td>VAS score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>97</td>
<td>53.49</td>
<td>2.46</td>
<td>-3.79</td>
<td>(-10.90, 3.32)</td>
<td>0.2947</td>
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<tr>
<td>Pregabalin 75</td>
<td>77</td>
<td>49.70</td>
<td>2.74</td>
<td>-16.09</td>
<td>(-23.11, -9.08)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Pregabalin 300</td>
<td>81</td>
<td>37.40</td>
<td>2.69</td>
<td>-19.01</td>
<td>(-26.00, -12.01)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Pregabalin 600</td>
<td>81</td>
<td>34.48</td>
<td>2.65</td>
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<td></td>
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<tr>
<td>PPI score</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>97</td>
<td>1.79</td>
<td>0.10</td>
<td>-0.12</td>
<td>(-0.41, 0.18)</td>
<td>0.4286</td>
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<td>Pregabalin 75</td>
<td>77</td>
<td>1.67</td>
<td>0.11</td>
<td>-0.59</td>
<td>(-0.88, -0.30)</td>
<td>0.0001</td>
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<td>Pregabalin 300</td>
<td>81</td>
<td>1.20</td>
<td>0.11</td>
<td>-0.61</td>
<td>(-0.90, -0.32)</td>
<td>0.0001</td>
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<tr>
<td>Pregabalin 600</td>
<td>81</td>
<td>1.18</td>
<td>0.11</td>
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</tbody>
</table>

* Endpoint = Last observation after randomization while on study medication.
† Adjustment based on Hochberg's procedure applies to pregabalin 300 and 600 mg/day only, per protocol.

VAS = Visual Analogue Scale; PPI = present pain intensity.
Table 4 Summary of frequently occurring adverse events

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Placebo, n = 97</th>
<th>75 mg/day, n = 97</th>
<th>300 mg/day, n = 81</th>
<th>600 mg/day, n = 82</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness</td>
<td>5 (5.2)</td>
<td>6 (7.8)</td>
<td>22 (27.2)</td>
<td>32 (39.0)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>4 (4.1)</td>
<td>3 (3.9)</td>
<td>19 (23.5)</td>
<td>22 (26.6)</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>2 (2.1)</td>
<td>3 (3.9)</td>
<td>6 (7.4)</td>
<td>11 (13.4)</td>
</tr>
<tr>
<td>Headache</td>
<td>10 (10.3)</td>
<td>5 (6.5)</td>
<td>7 (8.6)</td>
<td>8 (9.8)</td>
</tr>
<tr>
<td>Amblyopia†</td>
<td>1 (1.0)</td>
<td>2 (2.6)</td>
<td>4 (4.9)</td>
<td>7 (8.5)</td>
</tr>
<tr>
<td>Ataxia</td>
<td>2 (2.1)</td>
<td>5 (6.5)</td>
<td>3 (3.7)</td>
<td>7 (8.5)</td>
</tr>
<tr>
<td>Confusion</td>
<td>2 (2.1)</td>
<td>0 (0.0)</td>
<td>4 (4.9)</td>
<td>7 (8.5)</td>
</tr>
<tr>
<td>Constipation</td>
<td>1 (1.0)</td>
<td>0 (0.0)</td>
<td>3 (3.7)</td>
<td>7 (8.5)</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>8 (8.2)</td>
<td>7 (9.1)</td>
<td>7 (8.6)</td>
<td>7 (8.5)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>3 (3.1)</td>
<td>3 (3.9)</td>
<td>4 (4.9)</td>
<td>6 (7.3)</td>
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<tr>
<td>Pain</td>
<td>5 (5.2)</td>
<td>4 (5.2)</td>
<td>4 (4.9)</td>
<td>6 (7.3)</td>
</tr>
<tr>
<td>Amnesia</td>
<td>1 (1.0)</td>
<td>2 (2.6)</td>
<td>0 (0.0)</td>
<td>5 (6.1)</td>
</tr>
<tr>
<td>Accidental injury</td>
<td>0 (0.0)</td>
<td>4 (5.2)</td>
<td>2 (2.5)</td>
<td>4 (4.9)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>0 (0.0)</td>
<td>2 (2.6)</td>
<td>6 (7.4)</td>
<td>4 (4.9)</td>
</tr>
<tr>
<td>Euphoria</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>5 (6.2)</td>
<td>4 (4.9)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>7 (7.2)</td>
<td>4 (5.2)</td>
<td>1 (1.2)</td>
<td>3 (3.7)</td>
</tr>
<tr>
<td>Infection</td>
<td>7 (7.2)</td>
<td>3 (3.9)</td>
<td>8 (9.9)</td>
<td>1 (1.2)</td>
</tr>
</tbody>
</table>

Values are n (%).

* Adverse events that occurred in ≥5% of patients in any pregabalin group.
† Reported by investigators as "blurred vision," "blurring of vision," or "blurry vision."

Pregabalin was well-tolerated at all evaluated doses. Even with no titration for the 300-mg/day dose and only 1 week of titration for the 600-mg/day dose, more than 85% of patients completed the study in each of these groups and almost all elected to continue in the open-label phase of the study. The most frequent AEs of dizziness, somnolence, and peripheral edema were generally graded as mild to moderate, and in most cases they did not lead to discontinuation from the study. Peripheral edema, the third most common dose-related adverse event, usually began within 2 to 3 weeks after initiation of therapy. Peripheral edema was not associated with changes in renal or liver function, serum sodium, serum albumin, or hematocrit. None of the following was reported in patients with peripheral edema: worsening congestive heart failure, pulmonary disease, deep vein thrombosis, hypoalbuminemia, azotemia, liver function abnormalities, excessive proteinuria, orthostatic hypotension, or hypertension. Peripheral edema also showed no correlation with weight gain.

Treatment with pregabalin was not associated with serious AEs such as orthostatic hypotension and other risks common in elderly patients and patients with cardiac arrhythmias as associated with some TCAs,27 or with gastrointestinal effects seen with nonsteroidal anti-inflammatory drug (NSAID) use.28 There are no known pharmacokinetic drug-drug interactions. The low rate of discontinuation secondary to AEs is particularly appealing and favors the potential use of pregabalin in the long-term treatment of DPN.

There is evidence of a dose-response relationship for pregabalin. The 75-mg/day dose was not effective, while the 300- and 600-mg/day doses were both effective compared with placebo. The threshold for benefit likely lies between 75 mg/day and 300 mg/day and may be better defined by studies of other doses, such as 150 mg.

While the proportion of responders was similar in the 300-mg/day and 600-mg/day groups, the higher dose was found to provide consistent advantages in mean pain score reduction in comparison to the 300-mg/day dose. For example, while 37/81 (46%) and 39/81 (48%) of patients in the 300- and 600-mg/day groups achieved a ≥50% reduction in mean score from study baseline to endpoint, 22/81 (27%) of patients in the 600-mg/day group achieved a ≥70% reduction in score compared with 13/81 (16%) in the
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300-mg/day group. This observation was supported by the
increased proportion of patients on the 600
mg/day dosage (54/78, 69%) who rated themselves on
the PGIC as much improved or very much improved
compared with patients receiving 300 mg/day (44/79,
56%). Although there was a higher incidence of AEAs at the
higher dose, there clearly were some patients in the
600-mg/day group whose pain relief was sub-
stantial enough to balance this, as shown by the high
rate of completion and continuation into open-label

This trial of 338 patients represents the largest
double-blind, placebo-controlled trial in the diabetic
NeP literature. The number of patients enrolled in
this study exceeds the combined number of patients
who participated in pivotal trials for amitriptyline
(n = 29),29 carbamazepine (n = 30),30 phenytoin (n = 40),31 and gabapentin (n = 165)13 (total n = 264). The
240 patients on active treatment nearly matches the
266 active patients in a review of 10 studies on tricy-
clic antidepressants for diabetic NeP.32

Direct comparisons of pregabalin with TCAs and
gabapentin have not been conducted. Although it is
structurally and mechanistically related to gabapen-
tin, pregabalin exhibits linear pharmacokinetics with
low intersubject variability as compared with gabapentin, which exhibits less-than-proportional
pharmacokinetics with increasing dose. These prop-
erties may make pregabalin easier to prescribe, with
a better-defined effective dose range and no need for
lengthy titrations generally required with gabapentin.

The efficacy profile for pregabalin was both statisti-
cally and clinically significant and is in the same
range as other drugs of first choice currently used to
treat the NeP associated with DPN. In this study,
65% (53/81) of patients receiving 600 mg/day of
gabapentin achieved a clinically important reduction in
pain score (≥30%)39 and 48% (39/81) achieved a
≥50% reduction in pain score. The results presented
here indicate that pregabalin is safe and effective as
treatment of neuropathic pain and other symptoms
associated with DPN.