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Pregabalin as a Treatment for Painful Diabetic Peripheral Neuropathy: A Meta-Analysis

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Background and Objectives: Painful diabetic peripheral neuropathy (DPN) is an increasingly prevalent disorder that is best managed through a multimodal approach. We examined the effects of pregabalin on pain control, sleep disturbance, and the patient's global impression of change (PGIC) for the treatment of this disorder.

Methods: Studies were identified using the National Library of Medicine's PubMed and EMBase databases (1966 to July 15, 2007). Inclusion criteria were randomized trials comparing pregabalin to placebo in the treatment of DPN for adult patients. A total of 13 abstracts were identified of which 3 met inclusion criteria. Data were collected from each article and results were recorded. Primary outcome was pain at the conclusion of the study. Secondary outcomes included number of patients with 50% reduction in mean pain score, PGIC ratings at endpoint, and adverse events. A random-effects model was used.

Results: The 3 studies yielded 728 total subjects from 5 centers, of which 476 received pregabalin (dose range 75 to 600 mg/day) and 252 received placebo. Pregabalin treatment was associated with a significant decrease in pain scores (weighted mean difference, 1.15), higher likelihood to achieve at least a 50% reduction in mean pain score (relative risk [RR], 4.05), and improved PGIC ratings (RR = 1.45). Pregabalin was associated with an increased risk of somnolence, dizziness, and edema.

Conclusions: Pregabalin has significant effects on the pain associated with DPN as well as secondary endpoints that affect patients' quality of life. *Reg Anesth Pain Med 2008;33:389-394.*

Key Words: Pregabalin, Diabetes, Pain, Neuropathy, Meta-analysis, Analgesia.

Diabetes mellitus is an increasingly prevalent multiple organ system disorder with numerous devastating systemic effects. While several manifestations of this disease, including retinopathy and nephropathy, are often considered the most deleterious health effects related to this disease, the pain associated with diabetic peripheral neuropathy (DPN) has a dramatic negative effect on the patients' daily quality of life and function. Diabetic peripheral neuropathy classically presents with bilateral lower extremity "burning" pain and can also be associated with sensory loss, paresthesias, and allodynia.[1] Neuropathic pain is a diverse designation that covers a variety of conditions, but the largest subset is DPN. Neuropathic pain can be described as a malfunction of the sensory pathways of the central and peripheral nervous systems.[2]

While there are multimodal and multidisciplinary approaches to the treatment of painful DPN, the primary treatment pathway is pharmacologically based. The pathophysiology of neuropathic pain provides several treatment targets including abnormal peripheral nerve activity, decreased inhibition of central nervous system pathways, and heightened response to normal afferent input.[3] The treatment of painful DPN includes addressing the etiol-

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Accepted for publication February 15, 2008.

Grant Support: Department of Anesthesiology and Critical Care Medicine; The Johns Hopkins University; Baltimore, Maryland and NIH grant #MH075884 (R.W.H.) and the IASP Trainee Fellowship funded by the Scan/Design by Jens and Inger Bruun Foundation (R.W.H.). The authors have no conflicts of interest. This work was carried out at The Johns Hopkins Medical Institutes. Ms. Lesley and Dr. Adams contributed equally to this work.

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1098-7339/08/3305-0001$34.00/0
doi:10.1016/j.rapm.2008.02.012

ogy of the disorder and managing the symptoms.[4] This includes slowing of the metabolically-induced nerve damage through strict blood glucose control, and the treatment of the debilitating pain and associated sleep disturbances, respectively.[5]

Opioid therapy has been found to be effective for the treatment of neuropathic pain on a short term basis, but concerns about side effects and potential concern regarding addiction limit their use.[6-8] Neuromodulating medications, including tricyclic antidepressants and anticonvulsants, have become the mainstay of treatment for neuropathic pain. While these medications have been able to make excellent advances in pain control and improved quality of life, one of the primary factors limiting their widespread use is intractable adverse effects.[9,10] Pregabalin has been shown to have a similar mechanism to gabapentin, working via the $\alpha_2\delta$-1 protein accessory subunit of voltage-gated calcium channels, but with improved bioavailability, and dosing structure.[11,12] The administration of these anticonvulsants is associated with improved pain control for patients with neuropathic pain, specifically diabetic peripheral neuropathy and postherpetic neuralgia.[1,4,13] This meta-analysis examines the effects of pregabalin over placebo on not only pain control, but also quality of life issues including sleep disturbance and patient's global impression of change (PGIC).

Methods

The National Library of Medicine's PubMed database and EMBase were searched for the time period 1966 to July 15, 2007. These databases were searched for all articles containing text words "pregabalin" or "Lyrica" (387 articles) and pain (356,874 articles). These 2 searches were then combined using the Boolean term "and" (168 articles). The results were limited to randomized controlled trials to yield 13 abstracts. The reference lists of these articles were reviewed for additional studies not found on the initial search. No additional articles were found. The full article of each abstract was then reviewed by one of the authors (C.L.W.) for inclusion into the meta-analysis. No minimum sample sizes were invoked for inclusion of studies in the analysis. Two reviewers, in a blinded fashion to minimize bias, analyzed the articles independently (M.R.L., M.C.B.A.). Any disputes were resolved by agreement of at least 2 authors (R.W.H., C.M.B.). The primary outcome for assessment was measurement of pain at the conclusion of the study. For the purpose of this meta-analysis, only randomized trials comparing pregabalin vs. placebo for the treatment of painful diabetic peripheral neuropathy (DPN) were included. Other inclusion criteria were trials involving only adult patients. We excluded any studies where pain scores could not be obtained.

Data (including study characteristics, number, and mean age of study subjects, type of pain, and outcome data) were collected from each article and results were recorded. In addition to the primary outcome measure of pain at the conclusion of the study, secondary measures extracted from included studies, when available, were the number of participants who had a 50% reduction in mean pain scores during the trial, PGIC ratings at endpoint, and adverse events as defined by the study. Data were estimated and extrapolated from figures and tables as needed.

A random effects model was used. All statistical analyses including assessment for heterogeneity were performed with RevMan 4.2.7 (The Cochrane Collaboration, 2004; www.cochrane.org). After the data compilation was complete, we performed an analysis of the file drawer problem to provide an estimate of the number of unpublished studies or subjects showing no difference between treatment regimens that would be needed to be "discovered" in someone's file drawer to invalidate our results as described by Rosenthal.[14] The level of significance for all tests was set at an alpha level of 0.05.

Results

Our search resulted in 13 abstracts of which 3 met inclusion criteria. A total of 10 articles were rejected because they did not evaluate the efficacy of pregabalin in DPN patients. There were 728 total subjects in the 3 randomized trials used for this meta-analysis, of which 476 received pregabalin

Table 1. Studies Included in the Meta-Analysis

Study	Study Population (Sex)	Subjects (n)	Dose (mg/d)	Length of Study	Effect on Endpoint Mean Pain Score
Lesser (2004)[15]	M/F	239 P/97 p	75, 300, 600 TID	5 weeks	Decreased
Rosenstock (2004)[16]	M/F	76 P/70 p	300 TID	8 weeks	Decreased
Richter (2005)[17]	M/F	161 P/85 p	150, 600 TID	6 weeks	Decreased

NOTE. Data from Lesser,[15] Rosenstock,[16] and Richter.[17]
Abbreviations: P, pregabalin group; p, placebo group; TID, 3 times a day.

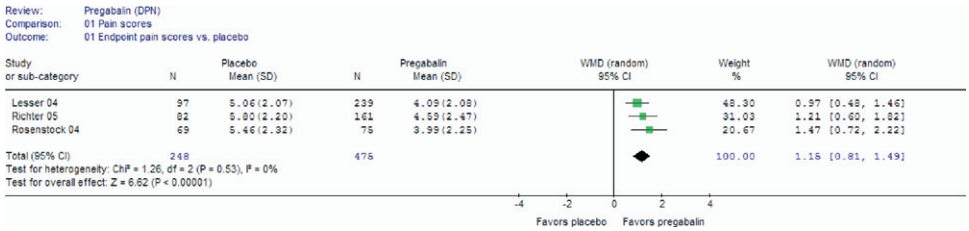

Fig 1. Pregabalin vs. placebo: pain scores. The weighted (pooled) estimate for the effect of oral pregabalin on DPN as measured by endpoint mean pain scores. "N" represents the number of subjects in each experimental group. The entire diamond (pooled estimate) lies to the right of the weighted mean difference (WMD) = 0 (which represents "no difference"), suggesting that pregabalin administration is associated with lower pain scores (WMD = 1.15 [95% CI, 0.81 to 1.49]). DPN, diabetic peripheral neuropathy. Data from Lesser,[15] Richter,[17] and Rosenstock.[16]

and 252 received placebo. Doses ranged from 75 to 600 mg/day.

Table 1 provides a detailed overview of studies included in the analysis. All of the studies were conducted in the U.S. and were performed in more than 5 centers. Figure 1 shows the pooled estimate (meta-analysis) demonstrating the effect of oral pregabalin on the primary endpoint "mean pain scores." Pregabalin treatment was associated with a significant decrease in pain score (weighted mean difference, 1.15; 95% confidence interval [CI]: 0.81 to 1.49). Patients who received pregabalin treatment were significantly more likely to achieve at least a 50% reduction in mean pain score (relative risk [RR], 4.05; 95% CI: 3.01 to 5.46) (Fig 2). Patients treated with pregabalin were significantly more likely using a PGIC scale to rate their overall condition as improved (RR, 1.45; 95% CI: 1.26 to 1.67) (Fig 3). Finally, pregabalin was associated with a significantly increased risk of somnolence (RR, 0.21; 95% CI: 0.11 to 0.42) (Fig 4), dizziness (RR, 0.22; 95% CI: 0.12 to 0.41) (Fig 5), and edema (RR, 0.31; 95% CI: 0.14 to 0.69) (Fig 6). Heterogeneity was not statistically significant in any of the pooled analyses (Figs 1-6). The file drawer analysis revealed it would require 11,027 subjects with negative findings to invalidate the results of this meta-analysis.

Discussion

Compared with placebo, pregabalin demonstrated improved pain control in patients with diabetic peripheral neuropathy. Baseline and posttreatment pain scores were used to determine the change in patients' neuropathic pain. Most responders reported a significant decrease in pain early in the treatment regimen. Secondary endpoints assessed sleep interference and the patients' PGIC. These outcomes demonstrated significant improvement throughout the treatment groups. However, patients were found to be at risk for increased side effects relative to the placebo group including dizziness, increased somnolence, and edema.[15-17]

In addition to the effects upon neuropathic pain, pregabalin has anxiolytic and anticonvulsant properties.[18] While the mechanism of pregabalin-in-

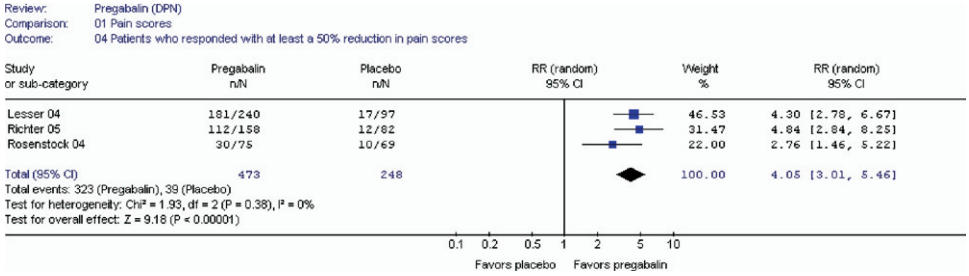

Fig 2. Pregabalin vs. placebo: ≥50% reduction in pain scores. The weighted (pooled) estimate for the effect of oral pregabalin on DPN as measured by the number of patients with a 50% reduction in mean pain scores from baseline at endpoint. "N" represents the number of subjects in each experimental group. "n" represents the number of patients with a 50% reduction in mean pain scores. The entire diamond (pooled estimate) lies to the right of relative risk (RR) = 1 (which represents "no difference"), suggesting that patients treated with pregabalin are more likely to achieve a 50% reduction in pain (RR, 4.05; 95% CI: 3.01 to 5.46). DPN, diabetic peripheral neuropathy. Data from Lesser,[15] Richter,[17] and Rosenstock.[16]

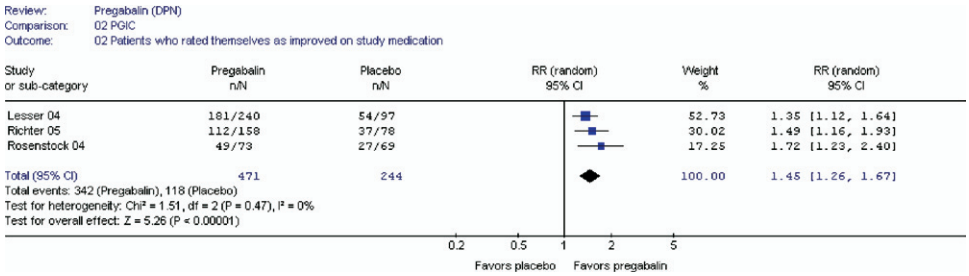

Fig 3. Pregabalin vs. placebo: patient global impression of change (PGIC). The weighted (pooled) estimate for the effect of oral pregabalin on DPN as measured by the number of patients who rated their overall status as improved at endpoint on the PGIC questionnaire. "N" represents the number of subjects in each experimental group. "n" represents the number of patients who rated themselves as improved. The entire diamond (pooled estimate) lies to the right of relative risk (RR) = 1 (which represents "no difference"), suggesting that patients treated with pregabalin are more likely to rate their overall status as improved (RR, 1.45 [95% CI: 1.26 to 1.67]). DPN, diabetic peripheral neuropathy. Data from Lesser,[15] Richter,[17] and Rosenstock.[16]

duced pain reduction has not been fully elucidated, the primary effects on neuropathic pain appear to be mediated by activity on voltage-gated calcium channels, similar to the mechanism of gabapentin. Pregabalin has an affinity for the $\alpha_2\delta$-1 accessory subunit of these channels; the binding of pregabalin to this subunit results in net neuronal inhibition, and decreased neurotransmitter release and postsynaptic excitability.[19,20]

Decreased quality of life is a secondary effect of the neuropathic pain. While the mechanism of sleep disturbance is not completely understood,[21] the impact on patient quality of life can be significant. Pain reduction alone can improve mood and quality of life.[22] Animal models suggest that pregabalin influences sleep patterns by increasing non-rapid eye movement sleep.[23] Pregabalin has demonstrated beneficial effects on mood and anxiety, contributing to the improved PGIC score.[24]

Adverse effects such as dizziness and peripheral edema are found to be more prevalent in higher dose regimens. When compared with pregabalin 150 mg/d, treatment with 600 mg/d was associated with higher rates of somnolence (22.0% vs. 5.1%), dizziness (37.8% vs. 10.1%), and edema (17.1% vs. 3.8%).[17] When compared with the more conventional therapy of 300 mg/d, treatment with 600 mg/d was associated with moderate increases in somnolence (26.8% vs. 23.5), dizziness (39% vs. 27.2%), and edema (13.4% vs. 7.4%).[15] Some patients receive a significant clinical effect on lower dose regimes, attenuating this risk.[13] Prior to the present meta-analysis, the correlation between pregabalin therapy and edema was not clear. The synthesis of data from the 3 studies selected (Fig 6) clearly favor placebo for reduction of adverse affects. Whereas the side effects associated with pregabalin are generally mild, physicians should monitor and counsel patients appropriately.

The pharmacokinetics of pregabalin allows a more rapid titration to the therapeutic dose and less frequent dosing than other anticonvulsants, including gabapentin. Similar to gabapentin, pregabalin has minimal interaction with other neuromodulat-

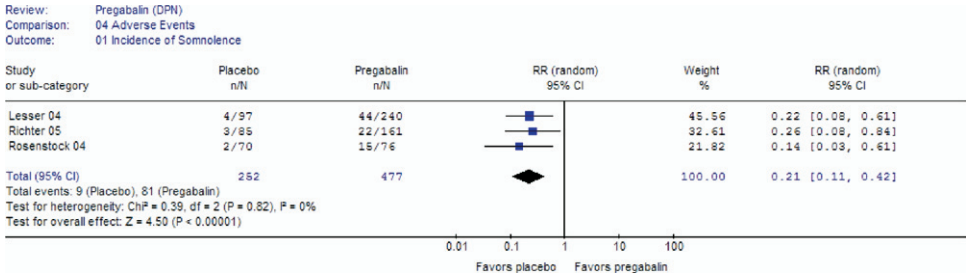

Fig 4. Pregabalin vs. placebo: the weighted (pooled) estimate for the effect of oral pregabalin on the incidence of somnolence. "N" represents the number of subjects in each experimental group. "n" represents the number of patients within an experimental group who reported somnolence. The entire diamond (pooled estimate) lies to the left of relative risk (RR) = 1 (which represents "no difference"), suggesting that pregabalin is associated with increased incidence of somnolence (RR, 0.21 [95% CI: 0.11 to 0.42]). DPN, diabetic peripheral neuropathy. Data from Lesser,[15] Richter,[17] and Rosenstock.[16]

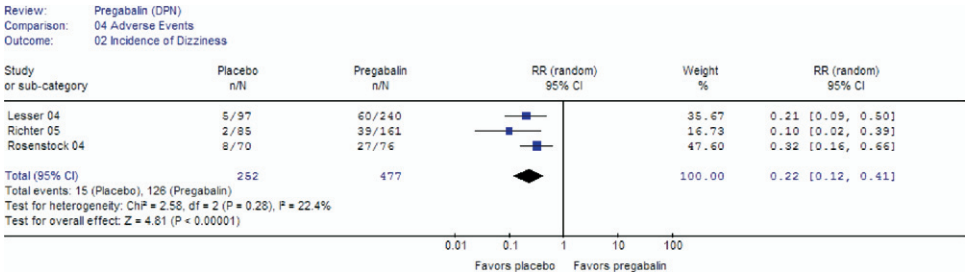

Fig 5. Pregabalin vs. placebo: the weighted (pooled) estimate for the effect of oral pregabalin on the incidence of dizziness. "N" represents the number of subjects in each experimental group. "n" represents the number of patients within an experimental group who reported dizziness. The entire diamond (pooled estimate) lies to the left of relative risk (RR) = 1 (which represents "no difference"), suggesting that pregabalin is associated with increased incidence of dizziness (RR, 0.22 [95% CI: 0.12 to 0.41]). DPN, diabetic peripheral neuropathy. Data from Lesser,[15] Richter,[17] and Rosenstock.[16]

ing medications, allowing the addition to the multidrug regimen necessary with many neuropathic pain patients.[18,19] Gabapentin and pregabalin have a similar mechanism of action, both believed to act upon the same accessory subunit of calcium channels, thus with effects on multiple neurotransmitters and receptor sites.[25] The subtle mechanistic difference in neuronal conductance between gabapentin and pregabalin results in a similar clinical effect but may account for the altered side effect profile.[26] While tricyclic antidepressants have demonstrated efficacy at treating painful DPN, their utility is limited by significant titration time and their side effect profile, including cardiac effects, dizziness, urinary retention, and drowsiness.[27-29] Opioid medications have also been used and found to be beneficial in short term treatment, but adverse effects such as somnolence, constipation, and addiction potential limit their efficacy as a primary therapeutic agent.[4,7]

Limitations of this study are those inherent to meta-analyses. The strength of a meta-analysis is dependent upon the composite papers being evaluated. The studies evaluated by this meta-analysis had a Cochrane Quality Score of 6 or higher and Jadad score of 5 to minimize study design weakness. Although the papers in this study had congruent data points to evaluate (pain scores, sleep scores, and PGIC), the data would be strengthened by a uniform dosing regimen. The advantage of this meta-analysis over the well-designed, composite, randomized controlled trials is that the aggregate study populations were able to be used to power an analysis that determined more significant differences.

The results of this meta-analysis demonstrate that pregabalin has significant effects on the pain associated with diabetic peripheral neuropathy as well as secondary endpoints that affect patient's quality of life. Extrapolations from this include using pregabalin as part of a multidrug regimen to decrease pain associated with DPN. This study demonstrates improved quality of life as assessed by sleep scores, and PGIC scores as the result of pregabalin therapy. While pregabalin clearly has a role as treatment for DPN and other neuropathic pain syndromes, what needs further delineation is whether the advantages of its side effect

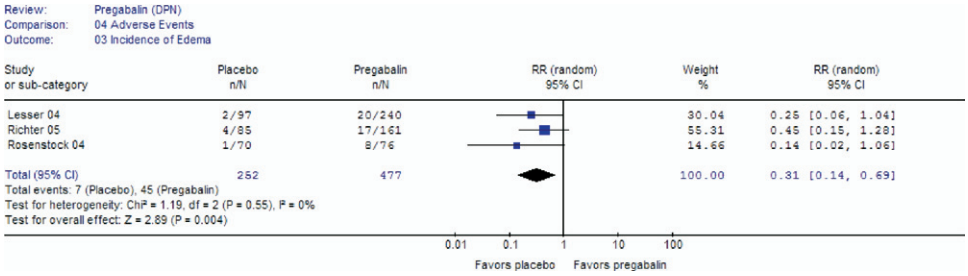

Fig 6. Pregabalin vs. placebo: the weighted (pooled) estimate for the effect of oral pregabalin on the incidence of edema. "N" represents the number of subjects in each experimental group. "n" represents the number of patients within an experimental group who experienced edema. The entire diamond (pooled estimate) lies to the left of relative risk (RR) = 1 (which represents "no difference"), suggesting that pregabalin is associated with increased incidence of edema (RR, 0.31 [95% CI: 0.14 to 0.69]). DPN, diabetic peripheral neuropathy. Data from Lesser,[15] Richter,[17] and Rosenstock.[16]

profile, titration, and impact upon quality of life make it a first line agent.

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