Relationship Between Pain Relief and Improvements in Patient Function/Quality of Life in Patients With Painful Diabetic Peripheral Neuropathy or Postherpetic Neuralgia Treated With Pregabalin

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ABSTRACT

Background: In patients with chronic pain due to diabetic peripheral neuropathy (DPN) or postherpetic neuralgia (PHN), pregabalin treatment results in pain relief and improved patient function/quality of life (QoL). Few studies, however, have examined the exact relationship between pain relief and improvements in patient function/QoL. It is unclear, for example, whether pregabalin has a direct independent effect on patient function/QoL or whether improvements in function/QoL are an indirect consequent of pain relief.

Objectives: To determine whether improvements in function/QoL in response to pregabalin treatment are related to the extent of pain relief in patients with neuropathic pain due to DPN or PHN and to determine whether pregabalin has a direct independent effect on patient function/QoL that is distinct from its effects on pain.

Methods: Data from 11 randomized, double-blind, placebo-controlled trials of pregabalin for the treatment of DPN or PHN were pooled for this analysis. Changes in patient function/QoL scores were plotted according to the extent of pain relief to assess whether greater levels of pain relief were associated with greater improvement in function/QoL. A novel mediation analysis was used to asses to what extent the effects of pregabalin on function/QoL scores are a direct treatment effect as opposed to an indirect effect mediated through improvements in pain or sleep.

Results: Moderate-to-substantial pain relief (a ≥30% decrease in pain) in response to pregabalin treatment was associated with significant ($P < 0.05$) improvements in 36-Item Short Form Health Survey (SF-36) scores (used to assess patient function/QoL). In many patients, greatest improvement in SF-36 scores was reported by patients achieving ≥50% decrease in pain. Analysis of Patient Global Impression of Change scores revealed a similar trend, where >80% of patients who achieved substantial pain relief also reported their status as much or very much improved. A substantial direct pregabalin treatment effect was evident for many SF-36 domains that could not be explained by pain relief or improvement in sleep.

Conclusions: In patients with chronic pain due to DPN or PHN, improvements in patient function/QoL in response to pregabalin treatment are correlated with the extent of pain relief. However, such improvements in function/QoL are not mediated entirely through pain relief but are the result of a combination of pregabalin's effects on pain and sleep disturbance and a direct effect on patient function itself. (*Clin Ther.* 2013;35:612–623)

Key words: diabetic peripheral neuropathy, postherpetic neuralgia, pregabalin, quality of life.

INTRODUCTION

Neuropathic pain results from damage to the nervous system and may be characterized as central or peripheral, depending on the site of the lesion.[1] This pain is often chronic and difficult to manage, resulting in substantial physical, social, and economic consequences. For example, patients with chronic neuropathic pain frequently experience anxiety, depression, and sleep disturbance.[2–4] Chronic pain also affects regular activ-

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ities of daily living[5–8] and is a major cause of health care utilization, work absenteeism, and unemployment.[9–12] Approximately 43% of patients with neuropathic pain have had their employment status affected in some manner,[4] and excess health care costs range from $1600 to $7000 per year.[13] Overall, patients with neuropathic pain report substantially low levels of health-related quality of life (QoL), and pain severity is a primary predictor of negative health impact.[14]

Pregabalin, an $\alpha_2\delta$ ligand, has shown efficacy for a variety of chronic neuropathic pain conditions.[15–17] It is approved for the treatment of central neuropathic pain due to spinal cord injury and peripheral neuropathic pain due to diabetic peripheral neuropathy (DPN) or postherpetic neuralgia (PHN) in the United States[18] and for the treatment of peripheral and central neuropathic pain in the European Union.[19] Several clinical trials of neuropathic pain have demonstrated that treatment with pregabalin results in improved patient-reported outcomes related to function and overall QoL. Few studies, however, have examined the nature of the relationship between pregabalin-mediated pain relief and improvements in overall patient function/QoL. It is also unclear whether pregabalin has a direct independent effect on patient function/QoL or whether function/QoL improvements are an indirect consequent of pregabalin-mediated pain relief.

The objectives of this study, therefore, were to determine whether improvements in function/QoL are related to the extent of pregabalin-mediated pain relief in patients with neuropathic pain due to DPN or PHN and to determine whether pregabalin has a direct independent effect on patient function/QoL that is distinct from its analgesic effects.

PATIENTS AND METHODS

Data

Data from 11 randomized, double-blind, placebo-controlled trials of pregabalin for the treatment of DPN (Pfizer Inc, data on file, study number 040),[20–24] PHN (Pfizer Inc, data on file, study number 030),[25–27] and DPN/PHN[28] were pooled for this analysis. In each trial, patients received fixed-dose (150, 300, or 600 mg/d) or flexible-dose (150–600 mg/d) pregabalin for 8 to 13 weeks. All the studies shared inclusion criteria that included a primary diagnosis of painful DPN (type 1 or 2 diabetes mellitus with a hemoglobin A_{1c} level ≤11% and painful, distal, symmetrical, sensorimotor polyneuropathy for ≥6 months) or PHN (pain present for ≥3 months after healing of the herpes zoster skin rash); age ≥18 years; an average pain score >4 (on an 11-point numeric rating scale [NRS] from 0 = no pain to 10 = worst possible pain) over a 7-day baseline period; and a score ≥40 mm on the 0- to 100-mm visual analog scale of the Short-Form McGill Pain Questionnaire at screening and randomization. Patients with low creatinine clearance were excluded.

Each study was approved by the institutional review board or independent ethics committee at each participating investigational center, and all the patients provided written informed consent before entering the study. Each study was conducted in compliance with the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice Guidelines.

Efficacy Measures

The primary efficacy measure in each study was end point mean pain score (on the 11-point NRS) derived from daily patient pain diaries. End point pain improvement was characterized as substantial (≥50% decrease), moderate (≥30% to <50%), minimal (≥15% to <30%), marginal (>0% to <15%), or none (0%). These ranges were based on the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) guidelines, which define pain improvement thresholds as substantial (≥50% decrease), moderate (≥30%), and minimal (≥15%).[29]

Each study also included 36-Item Short Form Health Survey (SF-36), Patient Global Impression of Change (PGIC), and Daily Sleep Interference Scale (DSIS) scores as secondary efficacy measures. The SF-36 includes 8 health status domains (physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health) used to measure patient function/QoL.[30] Domain scores range from 0 to 100, with higher scores indicating greater health. The PGIC reports overall patient health status/QoL on a 7-point scale from 1 = very much worse to 7 = very much improved.[31] The DSIS is a patient-reported measure that rates sleep on an 11-point NRS. Scores range from 0 = pain did not interfere with sleep to 10 = pain completely interfered with sleep.

Statistical Analysis

In this post hoc analysis, we explored 2 sets of hypotheses: (1) that higher pain relief in response to pre-