Predictive Modeling of Response to Pregabalin for the Treatment of Neuropathic Pain Using 6-Week Observational Data: A Spectrum of Modern Analytics Applications

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ABSTRACT

Purpose: This post hoc analysis used 11 predictive models of data from a large observational study in Germany to evaluate potential predictors of achieving at least 50% pain reduction by week 6 after treatment initiation (50% pain response) with pregabalin (150–600 mg/d) in patients with neuropathic pain (NeP).

Methods: The potential predictors evaluated included baseline demographic and clinical characteristics, such as patient-reported pain severity (0 [no pain] to 10 [worst possible pain]) and pain-related sleep disturbance scores (0 [sleep not impaired] to 10 [severely impaired sleep]) that were collected during clinic visits (baseline and weeks 1, 3, and 6). Baseline characteristics were also evaluated combined with pain change at week 1 or weeks 1 and 3 as potential predictors of end-of-treatment 50% pain response. The 11 predictive models were linear, nonlinear, and tree based, and all predictors in the training dataset were ranked according to their variable importance and normalized to 100%.

Findings: The training dataset comprised 9187 patients, and the testing dataset had 6114 patients. To adjust for the high imbalance in the responder distribution (75% of patients were 50% responders), which can skew the parameter tuning process, the training set was balanced into sets of 1000 responders and 1000 nonresponders. The predictive modeling approaches that were used produced consistent results. Baseline characteristics alone had fair predictive value (accuracy range, 0.61–0.72; κ range, 0.17–0.30). Baseline predictors combined with pain change at week 1 had moderate predictive value (accuracy, 0.73–0.81; κ range, 0.37–0.49). Baseline predictors with pain change at weeks 1 and 3 had substantial predictive value (accuracy, 0.83–0.89; κ range, 0.54–0.71). When variable importance across the models was estimated, the best predictor of 50% responder status was pain change at week 3 (average importance 100.0%), followed by pain change at week 1 (48.1%), baseline pain score (14.1%), baseline depression (13.9%), and using pregabalin as a monotherapy (11.7%).

Implications: The finding that pain changes by week 1 or weeks 1 and 3 are the best predictors of pregabalin response at 6 weeks suggests that adhering to a pregabalin medication regimen is important for an optimal end-of-treatment outcome. Regarding baseline predictors alone, considerable published evidence supports the importance of high baseline pain score and presence of depression as factors that can affect treatment response. Future research would be required to elucidate why using pregabalin as a monotherapy also had more than a 10% variable importance as a potential predictor. (*Clin Ther.* 2017;39:98–106) © 2017 The Authors. Published by Elsevier HS Journals, Inc.

Key words: neuropathic pain, observational study, predictive modeling, predictor, pregabalin, treatment response.

INTRODUCTION

The International Association for the Study of Pain defines neuropathic pain (NeP) as "pain caused by a lesion or disease of the somatosensory system" that can

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be classified as central or peripheral, depending on the location of the damage.[1] In a National Health and Wellness Survey conducted across 5 European countries (United Kingdom, France, Germany, Italy, and Spain), patients with NeP (compared with patients who had pain associated with another condition) were significantly more likely to experience severe daily pain, sleep problems such as insomnia, anxiety, and depression.[2] In addition, ~4 of 5 of these patients reported having ≥1 comorbid non-NeP pain condition. This survey also reported that patients with NeP had higher rates of absenteeism and presenteeism, lower rates of labor force participation, and direct medical costs that were approximately double those of patients with pain that was not considered NeP. In a retrospective chart review conducted in the United States, treatment of NeP was associated with adjusted total mean annualized costs of US $27,259 (95% CI, 25,199–29,319), including direct medical costs to payers, direct costs to subjects, and indirect costs per subject.[3] Moreover, pain severity levels were also associated with differences in the number of comorbidities, prescription medications, visits to physicians' offices, and lost productivity (all $P < 0.0001$).

Another study evaluated a large database of patient information from general practitioners in Germany, including 275,685 patients with NeP and an equivalent number of age- and sex-matched patients without NeP.[4] Compared with this control cohort, patients with NeP were significantly more likely to have comorbid conditions such as circulatory system disorders, depression, and anxiety, as well as to be prescribed pain-related medications, have referrals to clinical specialists, or have been given physician recommendations for excused labor force absences. These studies underscore the significant health and economic impact of NeP in Germany.

Pregabalin (an alpha2-delta agonist, antiepileptic drug) in Germany is indicated for the treatment of NeP and as an adjunctive therapy for adult patients with partial-onset seizures. Data from several randomized, double-blind clinical trials have shown that pregabalin is efficacious and well tolerated for the treatment of NeP related to various conditions (ie, diabetic peripheral neuropathy, postherpetic neuralgia [PHN], spinal cord injury [SCI]).[5–16] An observational study in Germany also found that the majority of patients treated with pregabalin experienced a significant reduction in NeP, with 4 of 5 of these patients achieving ≥30% pain reduction and 2 of 3 reporting >50% pain reduction.[17] These patients also reported a significant reduction in sleep interference.

To improve treatment of chronic pain, it would be useful to identify clinical and demographic characteristics that might be predictive of a better treatment response to pregabalin. To our knowledge, however, few studies have been published that have evaluated potential predictors of pregabalin response in NeP, and none has been published focusing on a German population. Studies in another chronic pain condition, fibromyalgia, have used logistic regression[18] and random forest[19] models with data from electronic medical record databases, which have identified patient characteristics that may facilitate better and earlier diagnosis.

In the present analysis, we applied similar modeling approaches, as used in the aforementioned electronic medical record studies, to evaluate clinical and demographic characteristics of patients with a different chronic pain condition, peripheral NeP, to identify potential predictors of treatment response to pregabalin. Early results of this analysis were presented as a poster at the 35th Annual Meeting of the American Pain Society.[20] The dataset used was from a large observational NeP study conducted in Germany.[17]

PATIENTS AND METHODS

Study Design, Patient Selection, and Treatment

Study A0081061 was a 6-week, prospective, noninterventional, drug-monitoring study of patients who were treated with pregabalin for NeP from 2004 through 2005 (the first year after its approval to market in Germany).[21] To be included in this observational study, pregabalin (150–600 mg/d) could be used either as monotherapy or in combination with some other active therapy for NeP. The patients were adults (≥18 years of age) with a diagnosis of peripheral NeP of any etiology, based on the expert judgment of their treating physician. The clinical specialties of the physicians (N = 5808) who collected data for this study included general practitioners (68%); internists (16%); anesthetists, neurologists, orthopedists, and psychiatrists (4% each); and surgeons (2%).

Study Assessments

Patients were evaluated during clinic visits at baseline as well as at weeks 1, 3, and 6, or if they discontinued the study before completion. At these