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Effect of Gabapentin Enacarbil on Individual Items of the International Restless Legs Study Group Rating Scale and Post-Sleep Questionnaire in Adults with Moderate-to-Severe Primary Restless Legs Syndrome: Pooled Analysis of 3 Randomized Trials

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ABSTRACT

Purpose: Few studies have investigated restless legs syndrome (RLS) treatment effects on individual International RLS Study Group Rating Scale (IRLS) items. We assessed the effects of gabapentin enacarbil (GEn) on individual IRLS items and their correlation with sleep disturbances in adults with moderate-to-severe primary RLS.

Methods: Data were pooled from the randomized, double-blind, placebo-controlled, 12-week studies of XP052, XP053, and XP081 for adults who received GEn (600 or 1200 mg) or placebo once daily. Adults had primary RLS, IRLS total score ≥ 15, and RLS symptoms >15 days during the month before screening and for ≥ 4 of the 7 consecutive evenings at baseline. End points included mean change from baseline to week 12 in individual IRLS and post-sleep questionnaire (PSQ) items. For IRLS items, least squares mean treatment differences were calculated from a mixed model for repeated measures. For PSQ items, Cochran–Mantel–Haenszel row mean scores tests with integer scoring were used. Correlations between IRLS and PSQ items were assessed by Spearman's rank coefficients. Safety profile outcomes included treatment-emergent adverse events (TEAEs) and serious TEAEs.

Findings: The modified intent-to-treat population included 671 patients (GEn 600 mg = 161; GEn 1200 mg = 266; placebo = 244). GEn significantly improved mean [SE] differences versus placebo for all IRLS items at week 12, including severity of sleep disturbance (GEn 600 mg, −0.4 [0.10]; GEn 1200 mg, −0.4 [0.09]), daytime tiredness (−0.4 [0.09]; −0.4 [0.08]), RLS severity (−0.4 [0.10]; −0.3 [0.08]), impact on daily affairs (−0.3 [0.07]; −0.3 [0.07]), and mood disturbance (−0.2 [0.07]; −0.3 [0.06]); all $P<0.001$). For PSQ items, significant ($P<0.01$) improvements occurred with both GEn doses versus placebo at week 12. The correlations between IRLS and PSQ items for change from baseline to week 12 were moderate to strong, and all correlations were significant ($P<0.001$). The most frequent TEAEs were somnolence (GEn 600 mg, 20%; GEn 1200 mg, 23%; placebo, 5%) and dizziness (GEn 600 mg, 14%; GEn 1200 mg, 22%; placebo, 5%).

Implications: GEn significantly improved individual IRLS items and sleep disturbance versus placebo. Correlations between IRLS and PSQ items were moderate to strong. This was not a formal meta-analysis and was not powered to compare the GEn doses. Nevertheless, our study finds that the benefits of GEn extend to individual IRLS items and supports the importance of sleep quality in RLS treatment. ClinicalTrials.gov identifiers: NCT00298623, NCT00365352, and NCT01332305. (*Clin Ther.* 2016;▮:▮▮▮–▮▮▮) © 2016 Elsevier HS Journals, Inc. All rights reserved.

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INTRODUCTION

Restless legs syndrome (RLS), also known as Willis–Ekbom disease, is a sensorimotor disorder characterized by an urge to move the legs; this is caused or accompanied by unpleasant sensations in the legs.[1] Symptoms generally begin or worsen during inactivity and in the evening and are temporarily relieved by movement.[2] RLS symptoms can range in severity, from mildly annoying and infrequent to severely disruptive of sleep and daytime activities.[1] Approximately 80% of patients with RLS experience periodic limb movements of sleep, which disrupt sleep and consist of repetitive motions of the feet and occasionally of the hip and knee during sleep.[3,4] RLS affects ~2% to 3% of the adult population,[4–7] occurs roughly twice as often in women than in men, and has a lower prevalence in Asian populations than in Western populations.[5,8]

Sleep disturbance is the primary clinical symptom of RLS.[4] A recent survey of patients with RLS found that 85% of respondents reported sleep as the area most affected by RLS.[9,10] Disturbed sleep has notable daytime consequences, which include exacerbation of depression, daytime drowsiness, and lack of concentration—all of which can negatively affect quality of life.[11] However, patients with RLS must also cope with symptoms beyond those related to sleep. Patients with RLS frequently report that sensations are painful, and conditions such as painful neuropathy and somatoform pain disorder are often comorbid with RLS.[12,13] Therefore, evaluation and treatment of the varied RLS symptoms are important components of the overall management of RLS.

The International RLS Study Group Rating Scale (IRLS) is the gold standard for evaluating RLS symptoms and the consequences of RLS, such as disturbances in mood and sleep.[14] The IRLS consists of 10 individual items, each rated by patients from a scale of 0 to 4 points. The IRLS total score serves as the primary end point for nearly all therapeutic studies of RLS and has been validated in cross-sectional studies[15]; however, few studies have examined the effects of various RLS treatments on individual IRLS items.

Gabapentin enacarbil (GEn) is an actively transported prodrug of gabapentin that is absorbed by high-capacity nutrient transporters located throughout the large and small intestines. A member of the α-2-δ ligand class of drugs, GEn provides sustained, dose-proportional exposure to gabapentin and has low interpatient variability.[16] The US Food and Drug Administration has approved GEn at a dose of 600 mg for the treatment of moderate-to-severe primary RLS in adults, making GEn the only non-dopaminergic medication approved for this patient population.[17] Data from 3 randomized, double-blind, placebo-controlled studies (XP052, XP053, and XP081) found that adults with moderate-to-severe primary RLS experienced marked improvements in primary RLS symptoms after treatment with GEn compared with placebo.[18–20] In a previous pooled analysis of XP052, XP053, and XP081, GEn 600 and 1200 mg significantly improved the primary end points of IRLS total score and investigator-rated Clinical Global Impression-Improvement compared with placebo.[21] The most frequently reported treatment-emergent adverse events (TEAEs) in these studies were somnolence and dizziness.

The present analysis was conducted to examine responses to individual items of the IRLS and the effect of treatment with GEn on these responses in a pooled modified intent-to-treat (MITT) population of adults with moderate-to-severe primary RLS from the XP052, XP053, and XP081 studies. Furthermore, given the negative effect of RLS on sleep and the importance of improving sleep when treating patients with RLS, this analysis also examined the correlations between individual IRLS items and sleep outcomes after treatment with GEn assessed by post-sleep questionnaire (PSQ).

PATIENTS AND METHODS

Study Design and Patients

The XP052, XP053, and XP081 study designs and patient populations were published previously (ClinicalTrials.gov identifiers: NCT00298623, NCT00365352, and NCT01332305).[18–20] To summarize, each study was a 12-week, placebo-controlled, double-blind, randomized trial that enrolled adults with moderate-to-severe primary RLS, as defined by