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Original Article

Predictors of clinical response in a double-blind placebo controlled crossover trial of gabapentin enacarbil for restless legs syndrome

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ABSTRACT

Objectives: Restless Legs Syndrome (RLS) is a sensory-motor disorder which produces sleep disturbance. Using data from a large clinical trial of gabapentin enacarbil (GEn) we sought to assess the ability of baseline, and changes from baseline, in clinical trial endpoints to predict treatment response.
Methods: Data were derived from a randomized, double-blind, placebo-controlled, crossover polysomnography study of gabapentin enacarbil 1200 mg (n = 121) or placebo (n = 123). Efficacy evaluations included: sleep measures from polysomnography, subjective sleep measures, Suggested Immobilization Test (SIT) measures, and International Restless Legs Severity Scale (IRLS) and Clinical Global Impression-Improvement (CGI-I). Correlations were evaluated using Spearman's rank correlation coefficients. Predictors of treatment response were separately assessed for GEn and placebo using categorical IRLS and CGI-I outcomes. Stepwise logistic regression models ascertained which combination of baseline and change from baseline variables predicted response.
Results: Moderate to large correlations were observed between changes in the IRLS and changes in subjective sleep for both GEn and placebo, substantially larger for GEn than placebo. Small to moderate correlations were present between the change in IRLS and the change in SIT-discomfort for both GEn and placebo. In the stepwise regression, for both GEn and placebo, baseline and change from baseline SIT discomfort, as well as change in sleep quality, were strong predictors of response.
Conclusions: Changes in sleep quality, and baseline and changes in SIT discomfort were prominent predictors of treatment response for GEn and placebo. Predictors of treatment response may allow for more targeted enrollment in future clinical trials and may provide insights into the efficacy of RLS treatments.

Restless legs syndrome (RLS) is a neurological disorder characterized by an urge to move the legs and/or arms and is often accompanied or caused by uncomfortable sensations (eg, dysesthesias or paresthesias) in those extremities. The symptoms occur primarily at rest in the evening or at night and are at least temporarily relieved during movement of the affected limb [1]. Up to 85% of RLS patients also have involuntary, semi-rhythmic limb movements during sleep that are referred to as periodic limb movements of sleep (PLMS) [2,3].

Sleep is negatively impacted by the sensory symptoms of RLS as well as the associated PLMS. Sleep disturbance is a primary morbidity of RLS and is often the cause for patients seeking treatment. Studies have shown that RLS patients have clinically significant reductions in sleep efficiency, increased sleep latency, and reduced total sleep times [4].

There are four FDA-approved treatments for RLS which effectively address the core sensory symptoms and to some extent improve subjective and objective sleep quality [5]. Three of these medications are dopamine agonists (pramipexole, ropinirole, and rotigotine) and one is an alpha-2-delta calcium channel ligand (gabapentin enacarbil). Response rates with these agents vary between 40 and 70% depending on the medication and the study protocol [6]. However, predictors of treatment response in RLS clinical trials are nearly absent.

Clinical trials of these medications for RLS have used the IRLS as a patient-reported outcome, which includes questions addressing different features of the disorder. Other commonly used outcome

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measures include the CGI-I [7], subjective and objective (eg, from polysomnography) sleep measures, and (less commonly) data from SIT which requires 1 h of immobilization, during which frequent ratings of leg discomfort and measures of involuntary leg movements are recorded [8].

Although multiple measures of RLS severity are used in clinical trials to assess efficacy, previous studies have only examined the interrelationships of these instruments at baseline [3,9–12] or the associations between changes in the IRLS and the CGI-I during treatment [13,14]. Only one previous study [3] has examined the relationship of change in IRLS to PLM indices, demonstrating small to medium correlations in a trial of the dopamine agonist pergolide.

Using data from a large clinical trial of gabapentin enacarbil we sought to assess the correlations of changes in self-reported and clinician-reported clinical outcomes, objective and subjective sleep-related outcomes, and measures from the suggested immobilization test. Furthermore, among these variables we attempted to identify those which predicted substantial response to treatment, both at baseline and as a function of change during the clinical trial.

1. Methods

1.1. Study design

This data were derived from a phase 3, multicenter, double-blind, randomized, double-blind, placebo-controlled, 2-period crossover polysomnography (PSG) study of gabapentin enacarbil (GEn) 1200 mg or placebo taken once daily [4]. Eligibility criteria included a diagnosis of primary RLS as confirmed by clinical interview, RLS symptoms on 4/7 and 15/30 of the previous days, had an IRLS total score >15 at baseline, had significant sleep disturbance on item 4 of the IRLS, and had a PLMS index (PLMS per hour) >15 on actigraphy (average over five nights using both legs). Subjects were randomized 1:1 to a sequence of GEn:placebo or placebo:GEn. During each four week treatment period, subjects received one placebo or one GEn 600-mg extended release tablet on days one to three and two placebo or two GEn 600-mg extended-release tablets for the remainder of the period. A seven day taper (one placebo or one GEn 600-mg extended-release tablet) followed each treatment period, with a one week washout between periods.

In the current analysis, efficacy evaluations were divided into four categories: objective sleep measures from PSG, subjective sleep measures, SIT measures, and clinical self-report measures. These measures were chosen as they constitute the primary and key secondary efficacy and exploratory variables for the clinical trial. PSG was assessed on an 8 h overnight study conducted at baseline and at the end of each treatment period. Wake time during sleep (WTDS) was calculated as was defined as the total amount of time spent awake after sleep onset until the last awakening; the number of awakenings during the sleep period (PSG-Awakenings) was calculated as the number of wake periods lasting at least 1 min after the onset of persistent sleep; sleep onset latency (SOL) was defined as the first three epochs of N1 or any epoch of N2, N3 or REM; total sleep time (TST), sleep efficiency (SE), wake after sleep onset (WASO), and the percentage of stage N3 sleep were all assessed. Multiple periodic limb movement of sleep (PLMS) measures were assessed from overnight PSG: PLMS associated with arousal per hour of sleep (PLMAI); PLMS associated with awakening per hour of sleep (PLMAWI); the number of PLM per hour of sleep (PLMSI); the number of PLM per hour during the combined wake and sleep period (PLMI); and the number of PLM per hour of wake (PLMWI).

Self-reported subjective sleep measures include the Subjective Post-Sleep Diary (SPSD) [15], which asks about sleep on the previous night and was completed for each of seven days prior to baseline and daily during each treatment period using an IVRS. The questions address the amount of time slept, the direct impact of RLS on sleep awakenings, how rested the subject felt in the morning, how restful the sleep was, and the quality of the sleep. The Medical Outcomes Sleep Scale (MOS) was completed at baseline and at the end of each treatment period. The MOS is a 12-item scale using a four week recall period; three domains of sleep were assessed: sleep disturbance, sleep quantity, and sleep adequacy [12].

SIT were performed for 1 h prior to each PSG visit and measured PLMs objectively (SIT PLMI) and included a subjective assessment of leg discomfort (SIT VAS) assessed every 5 min throughout the SIT.

Self-report clinical efficacy measures included the IRLS, which is a patient-rated disease severity scale based on RLS diagnostic criteria as developed by the International Restless Legs Syndrome Study Group [16]. The 10 questions evaluate the extent of sensorimotor symptoms of RLS and their impact on sleep, mood and daily activities on a scale of 0–4. The total IRLS was also calculated without question #4 which specifically addresses the effect of RLS on sleep so that non-sleep summary RLS symptoms could be compared to the separate sleep scales (MOS, SPSD). The Clinical Global Impression-Improvement (CGI-I) is a well-recognized and established psychometric instrument that are used to measure general clinical status in a variety of disease states. It was completed at each clinical visit and allowed the investigator to rate the subject's global improvement or worsening compared with the baseline.

1.2. Statistical methods

Post-hoc analyses were performed using data from the ITT analysis population. Missing data were imputed using the last-observation-carried-forward method. SAS v9.2 was used for all analyses.

Correlations between variables were evaluated using Spearman's rank correlation coefficients on change from baseline to Week four values. These coefficients range from −1 to 1, with higher values indicating stronger correlations. T-tests were used to test if the correlation coefficients were different from zero.

Predictors of treatment response were assessed for both GEn and placebo separately using IRLS responders (≥50% improvement from baseline) and CGI-I responders ('very much improved' or 'much improved') as the outcomes. Separate logistic regression models were utilized to assess if baseline and change from baseline variables predicted responses within treatment groups. Stepwise logistic regression models were also used to ascertain which combination of baseline and change from baseline variables predict response. The p-value to enter the logistic regression model in the stepwise procedure was 0.20 and the p-value to stay in the model was 0.25. Wald chi-square test p values are presented.

2. Results

2.1. Baseline characteristics

Patient demographics and baseline characteristics for each of the treatment groups have been reported previously and are summarized in Table 1. The ITT population included 131 subjects. Patients had moderate to severe RLS at baseline, mild difficulty with initial sleep onset but substantial problems with sleep maintenance and a high PLM index based on PSG and self-report measures. Correlations between efficacy variables at baseline are shown in Fig. 1.