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Original Article

The effects of pregabalin on sleep disturbance symptoms among individuals with fibromyalgia syndrome

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ABSTRACT

Objectives: Sleep disturbances are common in patients with fibromyalgia (FM). The objective of this analysis was to evaluate the effects of pregabalin on sleep in patients with FM.
Methods: Analyses were based on two randomized, double-blind, placebo-controlled trials of pregabalin (300 mg, 450 mg, and 600 mg daily) in adult FM patients. Sleep outcomes included the Medical Outcomes Study (MOS) Sleep Scale and a daily diary assessment of sleep quality. Treatment effects were evaluated using analysis of covariance. Clinically important differences (CID) in the Sleep Quality Diary and MOS Sleep Disturbance scores were estimated using mixed-effects models of changes in scores as a function of patients' global impressions of change. Mediation modeling was used to quantify the direct treatment effects on sleep in contrast to indirect influence of the treatment on sleep via pain.
Results: A total of 748 and 745 patients were randomized in the respective studies. Patients were predominantly Caucasian females, average age 48–50 years, on average had FM for 9–10 years, and experienced moderate to severe baseline pain. Pregabalin significantly improved the Sleep Quality Diary ($P < 0.001$), MOS Sleep Disturbance ($P < 0.01$), MOS Quantity of Sleep ($P < 0.003$), and MOS Sleep Problems Index scores ($P < 0.02$) relative to placebo. Treatment effects for the 450 mg and 600 mg groups exceeded the estimated CID thresholds of 0.83 and 7.9 for the Sleep Quality Diary and MOS Sleep Disturbance scores, respectively. Mediation models indicated that 43–80% of the benefits on sleep (versus placebo) were direct effects of pregabalin, with the remainder resulting from an indirect effect of treatment via pain relief.
Conclusions: These data demonstrate improvement in FM-related sleep dysfunction with pregabalin therapy. The majority of this benefit was a direct effect of pregabalin on the patients' insomnia, while the remainder occurred through the drug's analgesic activity.

1. Introduction

The American College of Rheumatology (ACR) defines fibromyalgia syndrome (FM) using two criteria: (1) chronic widespread pain, and (2) pain upon digital palpation over at least 11 of 18 anatomically defined tender point sites [1,2]. In addition to pain, common co-morbid symptoms associated with FM include sleep disturbances, fatigue, morning stiffness, affective disorders, chronic daily headache, dyscognition, irritable bowel syndrome, and irritable bladder [3]. In a series of focus groups and symptom ranking exercises, clinical experts and patients agreed that while pain is the cardinal symptom of FM, it is important to also assess fatigue, impact on sleep, health-related quality of life, depression, and cognitive difficulties [4]. Therefore, assessing the effectiveness of new therapies requires accurate documentation of a multidimensional array of clinical manifestations.

Sleep disturbances, including the occurrence of non-restorative sleep, are very common in patients with FM [5,6], and it is important to better understand their origin and responsiveness to treatment. Many patients believe their pain is disruptive to their sleep. However, studies suggest that in the general population, pain frequency may be related to sleep duration [7], and selective disruption of sleep in healthy individuals may result in hyperalgesia and musculoskeletal tenderness that mimics FM symptoms [8,9]. Not only does there appear to be a reciprocal relationship between sleep and pain in patients with chronic pain conditions including FM [10–12], but a recent study of patients with FM showed that

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sleep dysfunction was predictive of subsequent pain levels over a one-year period [13]. Because of these contrasting observations, the causal relationship between sleep dysfunction and pain in FM merits further investigation.

Two randomized, double-blind, placebo-controlled trials of pregabalin (Lyrica®) for the management of FM provided an opportunity to explore co-morbid sleep disturbances. While change in pain from baseline was the primary efficacy outcome in these trials, validated measures of sleep dysfunction were also included as secondary endpoints. This paper summarizes treatment-related effects on sleep dysfunction and co-variation among pain and sleep outcomes. This research was funded by Pfizer, Inc., the manufacturer of pregabalin, and several of the co-authors are employees and shareholders of the company.

2. Methods

2.1. Studies and subjects

Data were collected from two clinical trials evaluating pregabalin for the management of FM in the United States (US): Mease et al. (1056) [14] and Arnold et al. (1077) [15]. The study designs for these trials have been described elsewhere [14,15]. In brief, both studies were randomized, double-blind, placebo-controlled trials of 3 doses of pregabalin (300 mg/day, 450 mg/day, and 600 mg/day). Study patients for both trials were ⩾18 years of age with FM defined by ACR criteria [1]. During the baseline phase, patients were required to have an average daily diary pain score of at least 4 on a numeric rating scale (NRS) ranging from 0 (“no pain”) to 10 (“worst possible pain”). Additionally, a score of at least 40 mm on the 100 mm visual analogue scale (VAS) of the Short-Form McGill Pain Questionnaire [16] was required at screening and randomization study visits.

In both studies, patients were randomized to treatment after a 1-week baseline phase, although there were some minor differences in design between the two trials. In the 1056 study, patients were dose-adjusted to the randomized dose over a 1-week period prior to receiving an assigned study dose for 12 weeks, while dose-adjustment in the 1077 study occurred over a 2-week period prior to receiving assigned study doses for 12 weeks. Additionally, in the 1077 study, patients with a 30% or greater reduction in pain VAS from screening to randomization were discontinued prior to randomization to exclude potential placebo responders from the study: 19 of the 1195 (1.6%) screened eligible patients were discontinued from the study and excluded from the analysis. The primary efficacy endpoint in both studies was change in patient-reported average daily diary pain score from baseline to end-of-treatment. This report focuses on the secondary efficacy endpoints related to sleep dysfunction using a standard assessment instrument administered at baseline and end-of-treatment study visits and self-reported sleep quality collected in a daily diary.

2.2. Sleep outcomes

2.2.1. Sleep Quality Scale

In the daily diary assessment, patients reported the quality of their sleep over the past 24 h on an 11-point NRS ranging from 0 (“best possible sleep”) to 10 (“worst possible sleep”) [17–19]. Patients were instructed to complete the scale in the morning upon awakening. The baseline scores were computed as the average rating over the 7 days prior to taking study medication. The end-of-treatment score was computed as the average rating over the last 7 days during which the patient was receiving study medication. Higher scores indicate poorer sleep, thus negative change scores indicate improvement.

2.2.2. MOS Sleep Scale

The sleep assessment instrument included in both studies was the Medical Outcomes Study (MOS) Sleep Scale. This extensively validated, self-report instrument consists of 12 items that evaluate initiation and maintenance of sleep, respiratory problems during sleep, sleep duration, perceived adequacy of sleep, and daytime somnolence [20,21]. For 10 of the items, patients respond to questions on how often each symptom or problem applies to them on a 6-point categorical scale ranging from “all of the time” to “none of the time.” An item on sleep latency, i.e., the time required to fall asleep, is answered on a 5-point categorical response scale ranging from “0 to 15 min” to “more than 60 min,” and an item on Quantity of Sleep is reported as the average number of hours slept each night. Initial psychometric evaluation of the MOS Sleep Scale in patients with FM suggested that it is an appropriate measure of FM-related sleep problems; the favorable measurement properties provided evidence of the validity and reliability for the assessment of sleep disturbance and treatment effects [22].

In the 1056 study, patients were asked to respond to the MOS Sleep Scale questions based on their experience during the past 4 weeks. In the 1077 study, a one-week recall was used in response to Food and Drug Administration guidelines recommending use of patient-reported outcomes with shorter recall periods [23].

Patients’ responses to the MOS Sleep Scale were aggregated into 6 subscale scores and the 9-item Sleep Problems Index score. The subscales were Sleep Disturbance (initiation and maintenance of sleep), Snoring, Awakening Short of Breath or with Headache, Quantity of Sleep, Sleep Adequacy, and Somnolence. The Quantity of Sleep subscale score documented the number of hours of sleep per night (possible range from 0 to 24 h). The remaining subscale scores ranged from 0 to 100. For the Sleep Adequacy subscale, higher scores reflected more adequate sleep. For all other subscales, higher scores indicated more severe sleep dysfunction.

2.3. Statistical analyses

Treatment effect analyses were based on end-of-treatment scores. When an end-of-treatment scale score was not available, the last observed score was carried forward (LOCF). Data from all randomized patients who received at least one dose of study medication were included in the analyses. Treatment effects were evaluated using analysis of covariance (ANCOVA) models with treatment and center as factors and corresponding baseline sleep scores as covariates. All statistical tests were 2-sided and analyses were performed using SAS version 8 [24].

To further evaluate treatment effects, the relationship between changes in sleep and changes in pain was evaluated using Pearson correlation coefficients. The absolute values of correlations were considered low if they were ⩽0.30, moderate if they were between 0.30 and 0.50, and high if they were ⩾0.50 [25].

Two additional analyses focused on the key sleep outcomes of the Sleep Quality Diary and the MOS Sleep Disturbance subscale. The Sleep Quality Diary provides an overall assessment of sleep quality and the MOS Sleep Disturbance subscale reflects those areas of sleep that are particularly relevant to patients with FM.

The first analysis evaluated the clinical relevance of the magnitude of observed treatment effects associated with these two sleep outcomes by using established methods to estimate the change that can be considered clinically important [26]. Changes in the Sleep Quality Diary and MOS Sleep Disturbance scores were analyzed as a function of patients’ self-reported global impression of change (PGIC) using mixed-effects models [27]. The PGIC is a categorical scale with reference to baseline using 7 levels: very much improved, much improved, minimally improved, no change, minimally worse, much worse, or very much worse. It allows patients to rate their overall change with treatment based on clinical