Neurology Asia 2018; 23(1) : 27 – 33

Pregabalin for restless legs syndrome: A meta-analysis

[1]Rosemarylin L Or *MD FPNA*, [2]Aaron Mark Hernandez *MD FPCP*, [1]Anthony Piano *MD FPNA*

[1]Department of Neurology, [2]Section of Critical Care Medicine, Department of Medicine, The Medical City, Metro Manila, Philippines

Abstract

Background & Objective: Various pharmacologic agents are currently being used to alleviate the symptoms of restless legs syndrome (RLS). The most commonly used drugs are dopaminergic agents, but due to augmentation, alternative medications like pregabalin are being studied. This study aims to determine the efficacy and safety of pregabalin compared to placebo in the treatment of sensory and/or motor symptoms of patients with RLS by examining and integrating previous randomized controlled trials done on the subject. *Methods:* A thorough search in international and local databases of available randomized controlled studies of pregabalin for primary RLS were done from January 1940 until August 2015. *Results:* There were 3,708 studies identified, 4 studies meeting the inclusion criteria. Three independent reviewers assessed the studies for eligibility. Pooled results showed significant difference in the change in the International Restless Legs Syndrome scale score of -4.47 (CI -6.11 – -2.83), improvement in Clinical Global Impressions responders, total sleep time, sleep efficiency, sleep quality, change in wake time after sleep onset, and number of awakenings, all favoring pregabalin compared to placebo. There is no significant difference in the quality of life for pregabalin when compared to placebo. Adverse events of dizziness, somnolence, headache, and dry mouth were significantly increased (RR 13.18, 7.21, 3.47, and 5.27 respectively) in the 551 participants of the pregabalin group.
Conclusion: This meta-analysis indicates that pregabalin appears to be efficacious in the improvement of symptoms and sleep architecture of patients with RLS.

Keywords: Restless legs syndrome, pregabalin, Willis-Ekbom

INTRODUCTION

Restless legs syndrome (RLS), or Willis-Ekbom disease, has been described as a movement-responsive quiescegenic nocturnal focal akathisia usually with dysesthesias.[1] Previous studies reported the prevalence of RLS to be 5 to 10 percent in the general population, increasing with age until reaching the eight decade before declining, and more prevalent in women. Essential diagnostic criteria for RLS by the International Restless Legs Syndrome Study Group (IRLSSG) is an urge to move the legs accompanied by an uncomfortable sensation in the legs which is partially or totally relieved by movement and worsen during periods of inactivity. These sensations were noted to be worse in the evenings compared to during the day.[2] The REST general population study by Allen *et al*. in 2005 showed that more than 75 percent of those with RLS reported at least 1 sleep-related symptom such as disrupted sleep, inability to fall asleep and insufficient hours of sleep.[3] Many had reported daytime sleepiness, difficulty in concentration interfering with their daytime performance. The reduced quality of life in patients with restless leg syndrome was found to be comparable to that of other serious chronic medical illness such as clinical depression and type 2 diabetes mellitus.[3]

The goals in the management of RLS are to reduce or stop the troublesome symptoms during rest or sleep, reduce sleep disturbance, reduce daytime fatigue or somnolence and to improve the quality of life. Non-pharmacologic approaches include lifestyle modifications, mental alertness exercises, stretching exercises for posterior leg muscles, and application of heat with warm baths or heating pads are the initial therapy. Those who fail to respond to non-pharmacologic approaches are started on pharmacological therapy such as dopaminergic agents, benzodiazepines, opioids, anticonvulsants and iron supplementation. Dopaminergic agents are the most commonly used pharmacologic agent for RLS, but the complication of augmentation is common with these drugs.[4]

Address correspondence to: Rosemarylin L. Or, MD, FPNA, Department of Neurology, The Medical City, Ortigas Avenue, Pasig City, Philippines

Pregabalin and gabapentin are analogues to the inhibitory neurotransmiter, γ-aminobutyric acid (GABA) which has been found to be clinically useful in pain syndromes.[5] Their main mechanism of action is through the presynaptic binding to the alpha2-delta subunit of voltage-gated calcium channels, which lead to the reduction of neurotransmitter release, attenuating neuronal hyperexcitability and abnormal synchronization.[6] Oral gabapentin is absorbed slowly, its maximum plasma concentration attained within 3 to 4 hours, exhibiting zero-order kinetics, making its plasma concentration less predictable. Oral pregabalin, in contrast, exhibits first-order kinetics, is absorbed more rapidly, reaching its maximum plasma concentration within 1 hour.[7]

The International Restless Legs Syndrome Study Group (IRSLSG) recommends considering the use of alpha2-delta ligand drugs as initial treatment for patients with severe sleep disturbance that is disproportionate to other RLS symptoms, comorbid insomnia or anxiety, RLE-related or comorbid pain, or a history of an impulse control disorder or anxiety.[8] Several small randomized controlled trials show that pregabalin and gabapentin to be efficacious for the treatment of RLS. A large multicenter study is not yet available which may provide a better estimate of the benefits and safety of the drugs.[5] An integrated analysis of three 12-week studies of gabapentin for moderate to severe primary restless legs syndrome by Van Meter *et al*. in 2012 showed that gabapentin significantly improved symptoms of restless legs compared to placebo.[9] To-date, the authors are not aware of large scale trial or meta-analysis for pregabalin in the treatment of RLS.

The primary objective of this meta-analysis is to determine the efficacy of pregabalin in the treatment of sensory and/or motor symptoms of RLS by examining and integrating previous randomized controlled trials done on the subject. We aim to determine the efficacy of pregabalin in improving sensory-motor RLS symptoms, sleep and quality of life based on measurable scales, and to identify any adverse effects of pregabalin when used in patients with RLS.

METHODS

Search strategy for identification of study

The researchers systematically searched the Cochrane Registry of Controlled Trials, MEDLINE, PubMED, EMBASE, LILACS, clinicaltrials.gov, and WHO international clinical trials register for trials from January 1940 to August 2015. Unpublished researches were identified by searching through electronically published abstracts from earliest indexing to 2015. Local databases such as Herdin, Online Public Access Catalog (OPAC), Philippine e-lib, Medical and Health Librarians Association of the Philippines (MAHLAP) and Philippine Education Research Journal (PERJ) were also reviewed. The researchers used various search engines using several search terms and combinations.

Criteria in considering studies for analysis

Inclusion criteria: The studies included were randomized controlled trials of pregabalin, with a Jadad scale score of ≥ 3, with subjects diagnosed with idiopathic RLS.

Exclusion criteria: The study excluded were those not randomized controlled trials, or randomized controlled trials with a Jadad score of < 3. Restless legs syndrome with secondary causes and other forms of restless leg mimics such as nocturnal leg cramps, peripheral neuropathy, radiculopathy, arthritic pains, positional discomfort, and pronounced or frequent unconscious foot or leg movements (e.g. hypnic jerks, habitual foot tapping, leg shaking, general nervous movements) were also excluded.

Study selection

The authors screened all abstracts identified by the search for potential eligibility. Three independent good clinical practice-certified reviewers were asked to screen the titles and content of the identified studies for eligibility. Those papers deemed potentially relevant to the study were obtained, and the full manuscripts reviewed for inclusion. The Cochrane Collaboration tool for assessing risk of bias was used for standardized quality assessment.[10] Internal validity of the studies was assessed using the Jadad scale, wherein randomization, double-blinding, and accounting of outcomes of the study population were scored. A score of less than three was regarded as poor quality for bias reduction.[11,12]

Types of outcome measures

The primary outcomes of this study included the total International Restless Legs Syndrome (IRLS) scale score change and the percentage of Clinical Global Impressions – Global Improvement

(CGI-I) responders, while secondary outcomes included Subjective Sleep Questionnaire (SSQ) categories such as quality of sleep, wake time after sleep onset (WASO) and number of awakening, polysomnographic measures such as total sleep time and sleep efficiency, and adverse effects.

Statistical analysis

All data were entered into Review Manager (version 5.3 software). The results of the studies were pooled using fixed or random effects models, after consideration of heterogeneity between the trials. Relative risk was computed for the adverse events noted in the pooled studies. The mean difference and confidence intervals were illustrated using Forrest plots. Results with a p value of less than 0.05 were considered to be statistically significant. Heterogeneity was assessed through the Mantel-Haenszel method and quantified using the I^2 test, with p values less than 0.15 considered as probable presence of heterogeneity.

RESULTS

The initial search terms "restless legs" , "Willis-Ekbom" yielded 3,708 results, after which the terms "randomized controlled trial, RCT, clinical trials" were used to further narrow down the search 171 papers. The addition of the term "pregabalin" yielded 5 studies: Garcia-Borreguero *et al*. 2014[13], Markun S. 2014[14], Allen *et al*. 2014[15], Allen *et al*. 2010[16], and Garcia-Borreguero *et al*. 2010.[17]

Upon review of the search materials and correspondence with the author, the article by Markun *et al*.[14] was excluded as it was a review article summarizing Allen *et al*.'s 2014 study of comparison of pregabalin with pramipexole for RLS.[15]

The included four studies have a total of 551 participants. These studies examined the efficacy of 300mg pregabalin in the treatment of restless legs syndrome compared to placebo. The study design, quality, and baseline characteristics of these randomized controlled trials are shown in Table 1. Based on both Jadad scores and Cochrane Collaboration tool for assessing risk of bias, the overall quality of the studies are of good quality. The pharmaceutical funding involved in all four studies had been noted, but all disclaimers were clearly stated in all studies. The lack of explicit detail of the sequence generation done in the 2014 study of Allen *et al*.[15] has also been recorded hence was given a Jadad score of 4/5.

Comparison of outcomes

Three studies were included to measure the efficacy of pregabalin compared to placebo using the change of total IRLS scores from the baseline (Figure 1). The results of the 2014 study by Garcia-Borreguero *et al*.[13] was not included due to the unavailability of baseline values of IRLS score. A definite improvement in the total IRLS score is noted in the pregabalin group compared to placebo [pooled mean difference of -4.47 (-6.11 - -2.83)].

Four studies were included to measure the efficacy of pregabalin compared to placebo using the percentage of CGI-I responders (Figure 2). The odds of subjective clinical improvement significantly appears to increase by 2.93 times with pregabalin compared to placebo [PMD 2.93 (2.06-4.15)]

Three studies (Allen *et al*. 2014[15], Garcia-Borreguero *et al*, 2010[17], Garcia-Borreguero *et al*, 2014[13]) measured total sleep time via polysomnography, the result of which yielded a pooled mean difference of 28.00 minutes (12.52 – 43.48) favoring Pregabalin over placebo Two studies measuring sleep efficiency (Allen *et al*. 2010[14], Garcia-Borreguero *et al*, 2010[17]) showed an improvement of the sleep efficiency of patients in the Pregabalin group compared to placebo. (Figure 3)

Two studies by Allen in 2010[16] and 2014[15] included measurement of quality of sleep based on the subjective sleep questionnaire in patients treated with pregabalin compared to placebo. A pooled mean difference of 11.10 (5.87 – 16.34) showed that there appears to be difference in quality of sleep favoring patients treated with pregabalin. These studies also included measurement of wake time after sleep onset based on subjective sleep questionnaire for both groups. A pooled mean difference of 11.10 (5.87 – 16.34) showed that there seems to be difference in change in wake time after sleep onset in patients treated with pregabalin compared to the placebo group.

Two studies (Allen *et al*, 2014[15], Garcia-Borreguero *et al*, 2014[13]) were included to measure the change in number of awakenings based on the subjective sleep questionnaire in patients treated with pregabalin compared to placebo. A pooled mean difference of -0.73 (-1.03 – -0.43) indicates possible difference in the number of awakenings in patients treated with pregabalin compared to the placebo group.

Two studies (Allen *et al*. 2010[16], Allen *et al*. 2014[15]) were included to measure the RLS-Quality of Life in patients treated with pregabalin

Table 1: Baseline Characteristics of the four included randomized controlled trials

	Allen *et al*. 2010[16]	Allen *et al*. 2014[15]	Garcia-Borreguero *et al*. 2010[17]	Garcia-Borreguero *et al*. 2014[13]
Population	Idiopathic RLS (IRLS total score ≥15 at screening)	Idiopathic RLS (IRLS total score ≥15 at screening)	Idiopathic RLS (IRLS total score ≥15 at screening)	Idiopathic RLS (IRLS total score ≥15 at screening)
Median age in years	49.6 to 50.3 years	53.5 to 54.3 years	48.23 to 53 years	50.3 to 57.4 years
N	47 (for 300 mg per day Pregabalin)	361	58	85
Interventions in Pregabalin	300 mg per day	300mg per day	Mean dosage: 337.50 ± 105.6 mg per day	300mg per day maintenance dose
Interventions in other treatment	(i) Placebo (ii) Pregabalin 50 mg per day (iii) Pregabalin 100 mg per day (iv) Pregabalin 150 mg per day (v) Pregabalin 300 mg per day (vi) Pregabalin 450 mg per day	(i) Placebo (ii) Pramipexole 0.25mg per day (iii) Pramipexole 0.5mg per day	Placebo	(i) Placebo (ii) Pramipexole 0.5 mg per day - Randomization was done across 6 treatment sequences
Primary Outcome	Change in IRLS score	(i) Change in IRLS score (ii) Improvement in CGI-I evaluation	Change in IRLS score between baseline and week 12	WASO (number of minutes the participant was awake after onset of persistent sleep defined as 10-minute non-wake on electroen-cephalogram)
Secondary outcomes	(i) Improvement in CGI (ii) Improvements in the MOS-SS Sleep disturbance, Sleep adequacy, sleep quantity subscales and the 6- and 9-item sleep problems indices (iii) SSQ items (sleep latency, hours of sleep, number of awakenings, WASO, sleep quality) (iv) TST, sleep efficiency (v) Adverse events monitoring	(i) Limb pain, visual-analogue scale (ii) Quality of life (iii) Sleep assessments (WASO, sleep quality, number of awakening, TST, time to sleep onset) (iv) Adverse events monitoring	(i) Change in CGI severity scale (ii) RLS-6 scale (iii) MOS scale (iv) Sleep indices (PLMI, PLMAI, PLM during wakefulness index) (v) Adverse events monitoring	(i) PLMAI (periodic limb movement arousal index) (ii) Subjective TST (sTST) (iii) RLS-NDI (for pregabalin versus placebo) (iv) NAASO and SWS (for pregabalin versus pramipexole) (v) Adverse events monitoring
Jadad Score	5	4	5	5

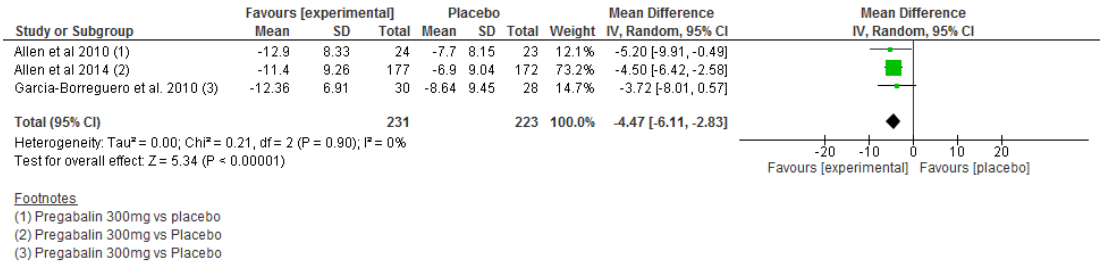

Figure 1. Forrest plot of the change in total IRLS score from baseline in patients with restless legs syndrome treated with pregabalin versus placebo

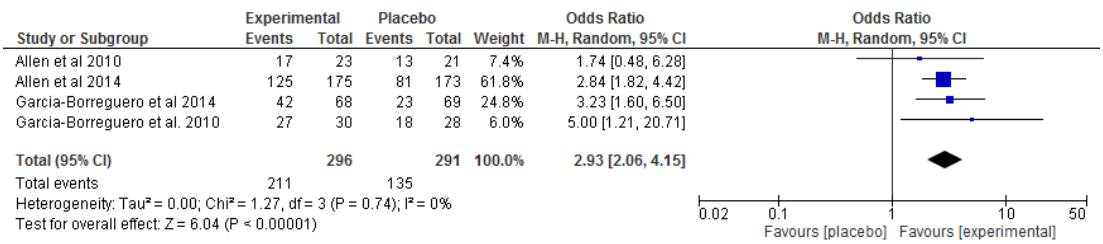

Figure 2. Forrest plot of the percentage of CGI-I responders in patients with restless legs syndrome treated with pregabalin versus placebo

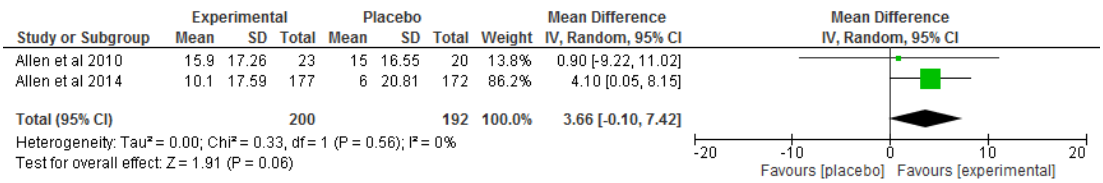

Figure 3. Forrest plot of RLS-Quality of Life in patients with restless legs syndrome treated with pregabalin versus placebo

compared to placebo (Figure 3). A pooled mean score difference of 3.66 (-0.10 – 7.42) points towards possible benefit in the quality of life in patients treated with pregabalin compared to the placebo group.

Adverse effects

The adverse events of patients treated with pregabalin compared to those in the placebo group showed significant difference in the risk ratio for dizziness, somnolence, dry mouth, and headache found in patients treated with pregabalin compared to placebo (Figure 4). The results however is heterogenous for dizziness, somnolence and headache and only the adverse effect of dry mouth showed a homogenous result.

DISCUSSION

RLS was often described as an urge to move the legs, caused by uncomfortable sensations in the legs. Studies done by Hening et al, and Trenkwalder et al. showed a peak of this symptoms during the time immediately after midnight.[2,18,19] The onset of sleep required a period of rest. RLS symptoms hinders sleep initiation and maintenance of sleep as the method to relive the symptoms will likely interfere with sleep.[2] A higher clinical RLS severity is correlated with reduced sleep efficiency, making sleep disturbance one of the primary morbidities of the disorder.[2,20]

Several trials had reported the effects of pregabalin in alleviating the symptoms of RLS. The smaller sample sizes of these trial, however, made achieving a significant conclusion difficult. Some of these trials used subjective scales to measure treatment efficacy, and others had employed objective polysomnographic measurements. This study pooled the data derived from the four randomized-controlled trials and had found that pregabalin significantly improved RLS symptoms on both the subjective and objective

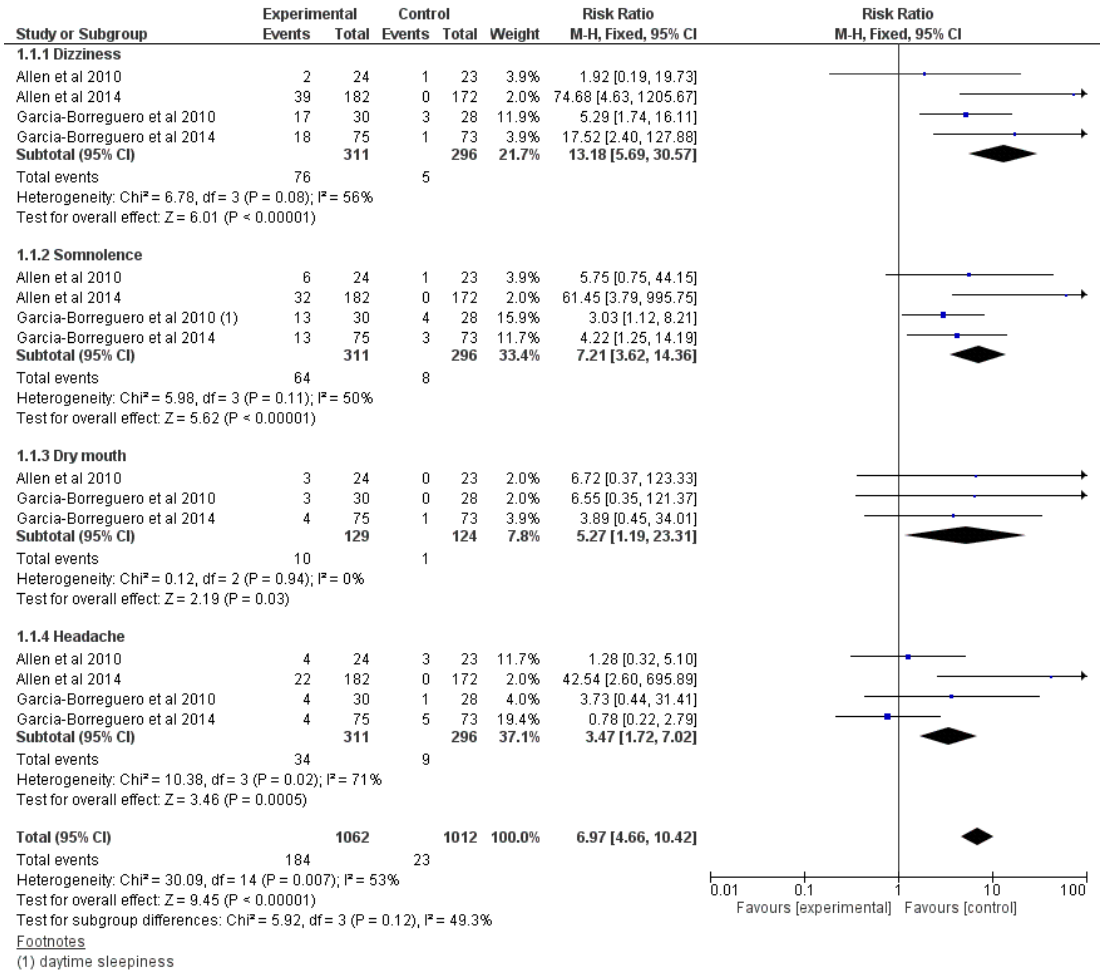

Figure 4. Adverse events in patients treated with pregabalin versus placebo

fronts. There is a significant improvement in IRLS scores and percentage of CGI-responders post-treatment. A similar result was reported by Allen et al. in 2014 where a greater reduction in IRLS scores and higher proportion of CGI- improvement responses were noted with pregabalin compared to pramipexole and placebo.[15]

The pregabalin group reported significantly better quality of sleep and lesser wake time after onset of persistent sleep as well as decreased number of awakenings per night compared to placebo. The total sleep time by polysomnography was significantly improved in the pregabalin group. Sleep reduction is one of the main causes in reduced quality of life in RLS patients.[21] In improving sleep quality and decreasing the amount of awake time during the night, pregabalin was able to address the sleep disturbance of RLS.

Adverse events were more common with Pregabalin compared to placebo. Dizziness, somnolence, dry mouth and headaches were significantly more common in the pregabalin group. These were the common causes of treatment discontinuation in previous trials.[13,17,20,22] Although common, the adverse events mentioned were mild and resolved upon treatment discontinuation. Upon reviewing the adverse event profile of pregabalin, these adverse events were found to appear in a selective dose-response pattern. Dizziness, somnolence and dry mouth were reported to present at the pregabalin dose of 150 mg per day.[23] Administration of pregabalin at night partially improves their tolerability and with the effect of somnolence, may partly contribute in improving sleep architecture.[17] Although the study results showed a trend towards an improved quality of life, it is recommended that more randomized-controlled trials be done to adequately assess the improvement on the quality of life after pregabalin treatment. Larger sample size papers or additional randomized controlled trials added to this meta-analysis may provide more robust and

direct conclusions. It is also recommended that a future meta-analysis may be done combining both pregabalin and gabapentin once studies with dosage equivalence were available for both drugs. The available randomized controlled trials mostly used 300mg of pregabalin and 600mg of Gabapentin, both of which are not of equivalent dosage after conversion.[24] A possible source of bias of the four included studies is their pharmaceutical funding, although all authors had stated this in their disclaimers.

In conclusion, although it has no significant effect in the quality of life in terms of formal predictive models, Pregabalin appears to be efficacious in the improvement of symptoms and the sleep architecture of patients with restless legs syndrome, indirectly improving quality of life. Adverse events were common, but mild, eventually resolving upon discontinuation of treatment.

DISCLOSURE

Conflict of Interest: RL Or and AM Hernandez have none to declare. A Piano is presently a member of the advisory board for Torrent Pharmaceuticals, Philippines.

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