ANTICONVULSANTS TO TREAT IDIOPATHIC
RESTLESS LEGS SYNDROME

Systematic review

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Abstract – Background: Restless legs syndrome (RLS) is a sensory motor disorder characterized by a distressing urge to move the legs and sometimes also other parts of the body usually accompanied by a marked sense of discomfort or pain in the leg or other affected body part. Many treatments have been used to minimize the discomfort of the disease, among them the anticonvulsant therapy. Aim: This review aims to evaluate the efficacy and safety of anticonvulsant treatment for idiopathic RLS. Method: Systematic review of randomized or quasi-randomized, double blind trials on anticonvulsant treatment for RLS. Outcomes: relief of RLS symptoms, subjective and objective sleep quality, quality of life, and adverse events associated with the treatments. Results: A total of 231 patients were randomized in three cross over studies and one parallel study. Three studies with carbamazepine, one with sodium valproate, and one with gabapentin, and they were very heterogeneous so we could not perform a metanalyses. Conclusions: There is no scientific evidence on RLS treatment with anticonvulsants for clinical practice.

KEY WORDS: restless legs, anticonvulsant.

Anticonvulsivantes para a síndrome das pernas inquietas idiopática: revisão sistemática

Resumo – Contexto: A síndrome das pernas inquietas (SPI) é uma desordem caracterizada por um impulso de mover as pernas e as vezes outras partes do corpo acompanhado geralmente por desconforto ou dor nas pernas ou em outra parte afetada. Muitos tratamentos tem sido utilizados para aliviar o desconforto causado pela doença entre eles os anticonvulsivantes. Objetivo: Este estudo objetivou avaliar a eficácia e segurança do tratamento da SPI com as drogas anticonvulsivantes. Método: Revisão sistemática de ensaios clínicos randomizados ou quasi-randomizados, duplo-cegos para o tratamento com anticonvulsivantes para SPI. Desfechos: alívio dos sintomas da SPI, qualidade subjetiva e objetiva do sono, qualidade de vida e efeitos adversos relacionados ao tratamento. Resultados: Um total de 231 pacientes foram randomizados em três estudos cross-over e um estudo paralelo. Três estudos avaliaram a carbamazepina, um estudo avaliou o ácido valproico e o outro a gabapentina, eles eram muito heterogêneos, o que impossibilitou a metanálise dos resultados. Conclusão: Não existe evidência científica, que o tratamento da SPI com anticonvulsivantes é eficaz e seguro, para a prática clínica.

PALAVRAS-CHAVE: pernas inquietas, anticonvulsivantes.

Restless legs syndrome (RLS) is a sensory motor disorder characterized by a distressing urge to move the legs and sometimes also other part of the body usually accompanied by a marked sense of discomfort or pain in the leg or other affected body part. The prevalence of RLS is estimated to be 5% to 15% in adults and it is more common in women, and was firstly reported in Brazil by Mattos Pimenta. RLS may be either idiopathic (primary RLS, which often has a familial component) or secondary, occurring with other medical conditions, particularly iron deficiency anaemia, pregnancy, or end-stage renal disease.

The most common pharmacological agents used in clinical practice for the treatment of RLS are levodopa,
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Dopamine agonists, opioids, benzodiazepines and anticonvulsants. Anticonvulsants are generally structural analogs of γ-aminobutyric acid (GABA) but in many cases the precise receptor(s) and biochemical function still remain unknown. It is suggested that novel receptor binding sites and an accumulation of GABA in different regions of the brain might be responsible for its effects in RLS. Its psychotropics and analgesics effects may be exerted, at least indirectly, through other neurotransmitters. In vivo the gabapentin antagonizes 3.4-diamopyridine-induced release of dopamine, nor-epinefrine and serotonin in the rat hippocampus, mesolimbic and striatal regions. These neurotransmitters, and in particular dopamine, are probably involved in the pathophysiology of RLS.7-9

Although anticonvulsants seems especially useful for treating mild to moderate RLS, particularly in patients reporting pain, the effectiveness of this class of drugs in the treatment of RLS is still controversial. In this clinical setting was relevant to conduct a systematic review to evaluate the clinical benefit of anticonvulsants for RLS.

METHOD

Inclusion criteria

Study design: Parallel and cross-over randomized and quasi-randomized controlled trials; Participants: Patients who meet any clinical criteria for idiopathic RLS; Exclusion criteria: Studies with secondary form of RLS such as metabolic, neuropathic or renal disease; Types of interventions: All anticonvulsants drugs used for treatment of RLS; Comparison groups include: Placebo; no intervention and other category of drugs; Outcomes measures: Relief of RLS symptoms as measured by the International RLS Study Group Rating Scale for RLS (IRLSSG Rating Scale) was the primary outcome.10 Secondary outcomes were adverse events associated with the treatments (including augmentation); subjective sleep quality [any description about sleep quality, i.e., feeling like well-being, tiredness reduction]; objective sleep quality measured by night polysomnography (sleep efficiency, total sleep time, arousal index, PLMS index). The ethics committee of Universidade Federal de São Paulo/Hospital São Paulo approved the study.

The electronic search

The search strategies were run on December 2007 using the following terms and their synonyms: restless legs syndrome, Ekbom syndrome, periodic leg movement, periodic limb movement, PLM, PLMS, PLMD, síndrome de las piernas inquietas, síndrome das pernas inquietas, sindrome delle gambe senza riposo, syndrome des jambes sans repos, idiopathischen restless-legssyndrom. The search for trials was carried out through the Cochrane Library, Medline, Pubmed, Lilacs, Embase and Scielo. Besides the most traditional electronic databases, other sources were also considered: thesis indexed at BIREME/PAHO-WHO (Biblioteca Regional Medicina/Panamerican Health Organization); reference list of all recovered trials; additional information asked for the authors of primary studies by electronic mail.

Methodological quality of included studies

The studies were judged according to Cochrane handbook based on allocation concealment (randomization), blinding (performance and detection bias); and attrition bias.

Data analysis

Data synthesis and analysis was performed using the Cochrane Review Manager software, RevMan version 4.2.8. Dichotomous data (adverse events) were expressed as relative risk (RR). Weighted mean difference (WMD) was used when continuous data were available from included studies. We included crossover study designs if the reported results had their within-patients variation, as given by paired tests. For both dichotomous and continuous data, we used 95% confidence intervals (CI). The statistical analysis using random effect model was used to estimate the treatment effects as compared to placebo. Statistical significance was considered when p<0.05. Heterogeneity between estimated effects across studies was analyzed using the inconsistency test (I²), which describes the percentage of the variability in effect estimates due to heterogeneity rather than sampling error.6 Statistical heterogeneity was assumed in case I²>50%. According to the type of information available in the articles or by contacting the authors of primary studies, the results were pooled based on either endpoint or change from baseline as well as on subcategories of medication and time length of treatment.

RESULTS

We identified 1028 studies related to pharmacological treatment for RLS, among them eleven trials published related to anticonvulsant therapy. Four randomized clinical trials in English were included in this review for they fulfilled the inclusion criteria (Table 1). Seven trials were excluded (Table 2), six trials were not randomized ones (open-label), and one trial was excluded because it was a duplicated published.

A total of 231 patients were randomized in crossover and parallel design studies. Fifty patients were randomized in crossover studies (6 patients received carbamazepine, 20 received valproic acid, and 24 received gabapentin), and out of 181 patients were randomized in the parallel-arm trial (84 received carbamazepine, and 90 received placebo).

We found several subjective measures (visual analogue scales, patients global impression, clinical global impression, Pittsburgh sleep quality index, IRLSSG rating scale) and objective measures (polysomnographic measures) used in these studies such as describe below.
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IRLSSG rating scale – The patients with gabapentin compared to placebo reported that had a greater decrease in IRLSSG rating scale (WMD: –8.40; 95% CI –12.00 to –4.80; p < 0.001);

Patients global impression – There was no improvement in the scores of patients global impression (WMD: 20.5; 95% CI 13.30 to 27.70; p < 0.0001);

Clinical global impression – There was a lower and not statistically significant improvement in the scores of clinical global impression (WMD: –1.10; 95% CI –1.93 to –0.27; p < 0.01);

Pittsburg sleep quality index – There was a lower improvement in sleep quality (WMD: –2.90; 95% IC –4.01 to –1.79; p < 0.001);

Visual analogue scale – The results were not statistically significant (p=NS);

Polisomnographic measures – The patients with gabapentin compared to placebo reported a reduced PLMI (WMD: –9.70; 95% CI –18.84 to –0.56; p<0.05), showed a not statistically significant improvement of PLMAI (WMD: –1.10; 95%CI –4.70 to 2.50; p=NS), increased the total sleep time (WMD: –0.50; 95% CI –0.77 to –0.23; p=0.01), sleep efficiency (WMD: –9.80; 95% CI –13.95 to –5.65; p<0.0001), stage 1 (WMD: –22.80; 95% CI –41.92 to –3.68; p<0.05), and slow wave sleep (WMD: –22.30; 95% CI –42.25 to –2.35; p<0.05). The other measures, sleep latency (p=NS), stage 2 (p=NS), REM stage (p=NS), REM sleep latency (p=NS), and arousal index (p=NS) were not statistically significant (*NS= no significant).

Adverse events – The side effects occur in 48% of patients taking gabapentin, malaise and abdominal pain were the most common. No cases of augmentation phenomenon were described.

Telstald

Subjective measures – In subjective analyses reported by patients both placebo and carbamazepine decreased the

Table 2. Characteristics of the trials excluded in this review.

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<th>Study</th>
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<td>Zucconi25 1989</td>
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<td>Sorensen26 1984</td>
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number of attacks, but carbamazepine was more effective than placebo (p=0.02).

Adverse events – The side effects were not described in these studies and seven drop outs were described (reason not related to the treatment).

Lundval \(^{18}\)

Subjective measures - The study reported in subjective measures improvement in 50% of patients, and other 50% reported insufficient improvement. No statistical analyses were performed in this study.

Adverse events – The side effects reported were mild gastritis, sweating, dizziness and vomiting and two drop outs were described (reason by the lack of the effect of carbamazepine).

Eisensehr \(^{19}\)

Subjective measures – Slow-release valproic acid significantly decreased the subjectively rated intensity of RLS complaints (WMD: -1.70; 95% CI -3.02 to -0.38, p=0.022) and duration of symptoms (WMD: -92.30; 95% CI -231.76 to 47.06; p=0.007) compared to placebo.

Polissoomnographic measures – Total sleep time (p=NS), wake after sleep onset (p=NS), PLMAI (p=NS), stage 1 (p=NS), stage 2 (p=NS), stage3/4 (p=NS), stage REM (p=NS), PLMI (p=NS), and arousal index (p=NS) were not statistically significant.

Adverse events – The side effects headache, drowsiness, and difficulties falling asleep were the most common adverse events and there were no drop outs.

DISCUSSION

Overall the methodological quality of the studies was considered as adequate (A) in two studies (Borregueiro \(^{16}\), Eisensehr \(^{19}\)), and unclear (B) in the others two studies (Telstald \(^{17}\); Lundval \(^{18}\)). On the other hand, almost all included studies were classified as “low risk” of systematic error, according to methodological quality of included studies.

The methodological quality of the carbamazepine included studies (Telstald \(^{17}\); Lundval \(^{18}\)) was considered poor, where data and methods reported in these articles were not described by the authors with sufficient details, even after contact by e-mail we also could not retrieve further information from the authors. However the studies about slow-release valproic acid (Eisensehr \(^{19}\)) and gabapentin (Borregueiro \(^{16}\)) showed good methodological quality and the results for continuous outcome measures were satisfactory. But their short-term follow up, which ranged from three to twelve weeks, was not possible to estimate the efficacy of treatment before doing long-term evaluations.

It may be a source of bias that different treatment sequences were not separated by washout periods. However, in Eisensehr \(^{19}\) study outcome variables were measured at the end of each treatment sequence, when (based on the half lives of the drugs) there was probably no effect of the drug taken before. A washout period was present in Borregueiro \(^{16}\) study, the one week washout period was probably based on the half life of the drug either, but there is no evidence that its clinical action is short-lasting, and its duration seems not sufficient to avoid a carry over effect of gabapentin.

Overall, the drugs were well-tolerated, except in Borregueiro \(^{16}\) study, when 48% of patients had side effects taking gabapentin but no patients dropped out because of them.

Augmentation syndrome, which consists of an abnormally severe pattern of RLS, is a common reason for changing medications \(^{22}\) and an important clinical problem noted on other therapies, such as levodopa and dopaminergic agonists. It is important to note that no cases of augmentation were reported with anticonvulsant therapy in a short-term follow up. The present reviewers advise physicians who are in charge of treatment for RLS patients to be aware of the augmentation syndrome in a long-term follow up.

There is no evidence that pharmacological treatment for RLS with anticonvulsant is effective and safe. Future trials should follow internationally published guidelines for reporting trials. Well designed randomized clinical trials are needed to assess the efficacy and safety of anticonvulsant therapy for Restless legs syndrome.

REFERENCES

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