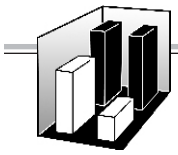

Mario F. P. Peres, MD, PhD

Fibromyalgia and Headache Disorders

Häuser W, Bernardy K, Uçeyler N, Sommer C: **Treatment of fibromyalgia syndrome with gabapentin and pregabalin: a meta-analysis of randomized controlled trials.** *Pain* 2009 Jun 17 (Epub ahead of print).

Rating: •Of importance.

Introduction: The key symptoms of fibromyalgia (FM) are chronic widespread pain, fatigue, and sleep disturbances/nonrestorative sleep. Most patients suffer from additional somatic and psychological symptoms. There is a high prevalence of comorbidities with other functional somatic syndromes and primary headache disorders. Treatment of FM is symptom-based, aiming at alleviating pain, fatigue, sleep disturbances, and psychological symptoms, as well as improving physical and social functioning. Until now, neither pharmacological nor nonpharmacological treatment options could cure the entire range of FM symptoms. Recently, evidence-based guidelines on the management of FM were published to give patients and physicians an orientation within the continuously growing number of studies on the therapy of FM [1].

This clinical trials report focuses on a very important article for the field by Häuser et al., a systematic review and meta-analysis evaluating the effects of treatment with pregabalin and gabapentin on FM-related symptoms.

Aims: In evidence-based medicine, systematic reviews and meta-analyses are considered to ensure the highest quality for specific recommendations. Systematic reviews and meta-analyses are available for some treatment options of FM, which were highly recommended by two guidelines: aerobic exercise [2], antidepressants [3], and multicomponent therapy [4]. No systematic review or meta-analysis is available on pregabalin, the first drug licensed for FM by the US Food and Drug Administration. Therefore, the authors are commended for having conducted this study.

Methods: The methodology was appropriate, and the meta-analysis was performed according to the QUORUM (quality of reporting meta-analyses) guidelines and the recommendations of the Cochrane Collaboration. Studies included followed diagnostic criteria of the American College of Rheumatology for FM, a randomized clinical trial design with a control group receiving pharmacological placebo and a treatment group receiving gabapentin or pregabalin, with data published as a full article or available at www.clinicaltrials.org.

Results: The literature search gave 127 citations involving FM, gabapentin, pregabalin, and clinical trials. Of the 117 excluded articles, 97 did not evaluate gabapentin and pregabalin in FM, 7 were double hits of controlled studies (ie, found in at least two data sources), and 13 were reviews. In the end, five studies with usable information by outcome design were included.

Strong evidence for the efficacy of gabapentin and pregabalin in reducing pain and sleep disturbances was found, but with small effect sizes. The pooled NNT (number needed to treat) to achieve a moderately important clinical change in pain (at least 30% reduction) was eight. Evidence against a favorable effect on depressed mood, anxiety, and fatigue appeared. There was conflicting evidence on the improvement of health-related quality of life (HRQOL) by both drugs. Pregabalin at dosages of 300, 450, and 600 mg per day was better than placebo, but the dosages did not differ regarding pain reduction due to the small effect size. Side effects such as dizziness and somnolence increased as the pregabalin dose was increased. Pregabalin at 150 mg per day did not differ from placebo.

Discussion: This systematic review, which includes meta-analysis, shows that gabapentin and pregabalin reduce pain and sleep disturbances, but not other key symptoms such as fatigue, depressed mood, and anxiety in FM. Quality-of-life improvement was not evident. Excessive sleepiness and dizziness were the main side effects reported. Because only one study was available on gabapentin with a rather small number of patients, this article does not allow a conclusive comparison of gabapentin and pregabalin.

The authors agree with study limitations because demographics and comorbidities of study participants and the amount of co-medication were not reported; therefore, these possible sources of heterogeneity could not be examined. The outcomes for fatigue, depressed mood, and HRQOL of two published studies could not be included into the meta-analyses because the necessary data were not given in the publication and not provided by the authors upon request.

The findings presented here are partially consistent with current reviews on the pharmacological treatment of FM with pregabalin. Pregabalin has a multidimensional effect in the treatment of FM and is associated with a clinically significant improvement in several outcome measures related to core symptoms of the syndrome. However, other relevant issues, such as side effects, lack of significant effect on fatigue, depression and anxiety, and conflicting evidence on

quality of life, do not make pregabalin a source of euphoria as a single treatment option in FM.

Comments

Pregabalin and gabapentin are structural analogues of the neurotransmitter γ-aminobutyric acid (GABA). These medications are second-generation anticonvulsants, also called neuromodulators, and are α-2-δ ligands that bind to and modulate voltage-gated calcium channels. By diminishing the release of glutamate, norepinephrine, and substance P, gabapentin and pregabalin may act as analgesic, anticonvulsant, and anxiolytic.

Quality of life should be an issue of debate in FM treatment with pregabalin; further studies are necessary to clarify the conflicting evidence on the effectiveness of pregabalin in HRQOL. This may occur because of the relevant effect on pain and sleep but high levels of reported side effects with drug treatment. In addition, improvement in sleep disturbance (lack of sleep) may cause excessive daytime sleepiness in some patients; therefore, pregabalin dose should be monitored according to the effect on the patient's sleep quality. Restless leg syndrome is prevalent in FM, disrupting the patient's sleep pattern. Pregabalin may be effective in sleep quality by treating a possible underlying restless leg syndrome in the patient.

GABAergic drugs are available treatment options for various conditions. Although pregabalin is approved for FM and significantly reduces pain and sleep disturbances, it lacks a relevant effect on fatigue, depression, and anxiety symptoms. Therefore, clinicians should consider nonpharmacological approaches for the patient, such as physical exercise, psychotherapy, and other therapeutic options (eg, other drugs such as antidepressants), to manage anxiety, depression, and fatigue and to improve the quality of life of patients with FM.

Acknowledgment

Dr. Mario F. P. Peres is affiliated with the Instituto Israelita deEnsino e Pesquisa Hospital Albert Einstein. Correspondence should be sent to Al Joaquim Eugenio de Lima, 881 cj 708, 01403-001, Sao Paulo, Brazil. E-mail: marioperes@yahoo.com.

Disclosure

No potential conflict of interest relevant to this article was reported.

References

1. Carville SF, Arendt-Nielsen S, Bliddal H, et al.: **EULAR evidence-based recommendations for the management of fibromyalgia syndrome.** *Ann Rheum Dis* 2008, **67:**536–541.
2. Busch AJ, Barber KA, Overend TJ, et al.: **Exercise for treating fibromyalgia syndrome.** *Cochrane Database Syst Rev* 2007: CD003786.
3. Häuser W, Bernardy K, Üçeyler N, Sommer C: **Treatment of fibromyalgia syndrome with antidepressants: a meta-analysis of randomized controlled trials.** *JAMA* 2009, **301:**198–209.
4. Häuser W, Bernardy K, Offenbächer M, et al.: **Efficacy of multicomponent treatment in fibromyalgia syndrome: a meta-analysis of randomized controlled clinical trials.** *Arthritis Rheum* 2009, **61:**216–224.