# Does pregabalin improve sleep disorders in fibromyalgia?

*A pregabalina melhora os distúrbios do sono na fibromialgia?*

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## ABSTRACT

**BACKGROUND AND OBJECTIVES**: Fibromyalgia is a chronic generalized pain syndrome accompanied by somatic symptoms, mainly represented by sleep disorders. Pregabalin is the main agent among pharmacological treatments.
**CONTENTS**: An electronic search was performed in the databases Lilacs, Pubmed/Medline, Scielo and ScienceDirect. The keywords used in English and Portuguese were "fibromyalgia"; "sleep disorder", "treatment"; "pregabalin"; "medicine"; "fibromialgia"; "distúrbios do sono", "tratamento"; "pregabalina"; "fármacos". Only articles of literature review, systematic review, meta-analysis and randomized clinical studies published between October 1992 and May 2018 were included.
**CONCLUSION**: Pregabalin is efficient and safe in the management of sleep disorders in patients with fibromyalgia because it reduces the number of awakenings and increases sleep duration.
**Keywords**: Fibromyalgia, Pregabalin, Sleep wake disorders.

## RESUMO

**JUSTIFICATIVA E OBJETIVOS**: A fibromialgia é uma síndrome de dor generalizada crônica, acompanhada de sintomas somáticos, representados principalmente por distúrbios do sono. Dentre os tratamentos farmacológicos, a pregabalina é o principal representante.
**CONTEÚDO**: Foi realizada uma busca eletrônica nas bases de dados Lilacs, Pubmed/Medline, Scielo e ScienceDirect, cruzando-se os seguintes descritores em língua inglesa e portuguesa: "fibromyalgia"; "sleep disorder", "treatment"; "pregabalin"; "medicine"; "fibromialgia"; "distúrbios do sono", "tratamento"; "pregabalina"; "fármacos". Foram incluídos somente artigos de revisão de literatura, revisão sistemática, meta-análise e estudos clínicos randomizados publicados no período de outubro de 1992 a maio de 2018.
**CONCLUSÃO**: A pregabalina é eficiente e segura no manuseio dos distúrbios do sono em pacientes com fibromialgia, pois diminui o número de despertares e aumenta o tempo de duração do sono.
**Descritores:** Fibromialgia, Pregabalina, Transtornos do sono-vigília.


## INTRODUCTION

Fibromyalgia (FM) is a syndrome characterized by chronic and generalized pain, with some somatic symptoms such as physical exhaustion, mood disorders, cognition difficulties and sleep disorders[1]. The specialized literature points to levels of prevalence of FM in the general population at between 0.2 and 6.6%; in urban areas, between 0.7 and 11.4%; in rural areas between 0.1 and 5.2%, and in special populations between 0.6 and 15%[2]. In Brazil, FM is present in up to 2.5% of the general population and prevails among females, especially among women aged between 35 and 44[3].
FM can affect patients' quality of life and functional capacity more significantly than other inflammatory conditions like rheumatoid arthritis and spondyloarthritis[4]. One single patient with FM can cost tens of thousands of dollars a year, with indirect costs representing the lion's share of total cost, involving loss of productivity, reduction in working hours, absenteeism, invalidity, unemployment, early retirement, informal assistance, and other direct costs[5,6]. Also, patients with FM also have several comorbidities (for example depression, anxiety, and sleep disorders), resulting in an extreme surge in general health-related expenses[5].
The physiopathology of FM is multifactorial and shows itself in the complexity and variety of the symptoms that patients have experienced[7]. Among the factors involved, we could mention the abnormal function of the autonomic and neuroendocrine systems, genetic influence, and environmental factors that could trigger the condition, like exposure to stress-causing elements[8]. The main physiopathological phenomenon of FM is central sensitization, characterized by the attenuation of the descending pain-inhibiting pathways and the favoring of the ascending pain-creating pathways[9]. These changes help to bring greater sensitivity to pain and persistence of generalized pain[8]. There is also an important change to the structure of sleep, which has an adverse effect on the quality of sleep and also favors a non-reparatory type of sleep[10]. Sleep disorders may be related to fatigue and the reduction of energy. They also may play a part in the intensification of pain[8], as they can harm the process of healing of damage to muscle tissue, thereby extending the transmission of sensory stimuli from the damaged muscular tissue to the central nervous system (CNS), thereby increasing the perception of muscular pain[8,11]. In turn, the increased pain may also help to intensify sleep disorders, thus maintaining the patient's feeling of fatigue and continuing the process of inadequate reparation of the muscular tissue[8,12].

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The treatment of FM must be multimodal due to the heterogeneity of symptoms, and the strategies for treatment must include patient education, together with physiotherapy, psychotherapy, and pharmacotherapy[13]. Among all types of pharmacotherapy, anticonvulsants are the most commonly used, and pregabalin (PG) is the representative of this pharmaceutical class that has been approved for FM in the United States and another 25 countries[14], thereby being a safe and efficient option[15], with a satisfactory cost-benefit ratio[16]. With PG, many patients manage to obtain significant benefits regarding pain control, quality of life, and especially in sleep improvement. Moreover, the side effects, even though they are somewhat common, are normally mild and well tolerated in the long term, and may also be monitored in primary care[17].

Based on the above, a discussion on the relationship between PG and sleep in cases of FM becomes valid, so that the doctor may have the best possible grounding in establishing his or her conduct for the cases considered. Therefore, the purpose of this paper was, through a review of the specialized literature, to answer the question: *Does pregabalin improve sleep disorders in cases of fibromyalgia?*

## CONTENTS

An electronic search was carried out on the Lilacs, Pubmed/Medline, Scielo, and ScienceDirect databases, crossing the following descriptors in English and Portuguese: "fibromyalgia"; "sleep disorder"; "treatment"; "pregabalin"; "medicine"; *"fibromialgia"; "distúrbios do sono"; "tratamento"; "pregabalina"; "fármacos"*. We only included articles that reviewed the specialized literature or had systematic reviews, meta-analysis or randomized clinical studies, that were published between October 1992 and May 2018.

### Sleep in fibromyalgia

Among patients living with FM, 88% have reported sleep difficulties in one of the following domains: difficulty in falling asleep; difficulty in staying asleep; or waking up too early, while 63.05% of the cases have reported difficulties in two or more of these domains[18]. Patients with FM have daily impairment of the performance speed for complex cognitive tasks, together with a diffuse experience of pain and symptoms of non-restoration of sleep, including fatigue, bad mood, and drowsiness[19]. There is an important alteration in the structure of sleep, showing long latency periods at the start of sleep (meaning the time someone takes to fall asleep once the lights are turned off), an increase in stage 1 and reduction in stage 2, reduction in alpha-delta sleep, and an increase in the number of wakings-up during sleep[10,20,21]. The shorter duration of sleep stage 2 may predict the levels of pain as experienced in FM[20]. Sleep deprivation in healthy individuals can cause FM symptoms, including myalgia, sensitivity and fatigue. Moreover, mechanically, the lack of sleep also inhibits the pain-inhibiting descendant pathways, which are important for controlling and tackling pain[22]. The Pittsburgh Sleep Quality Index (PSQI) is a useful way to characterize and quantify sleep disorders in patients with FM[23]; as a rule, patients with FM show higher PSQI scores when compared to healthy individuals[24].

### Pharmacological characteristics of pregabalin

PG is an $\alpha_2\delta$ ligand which belongs to the class of anticonvulsants, acting through bonding to the $\alpha_2$-$\delta$ subunit of the voltage-dependent pre-synaptic calcium channels, which results in a slower flow of calcium through the channels, possibly through interruption of transport and/or through the reduction of the flow of calcium towards the interior of the cell[25]. Later on, this reduced flow of calcium inhibits the pre-synaptic release of neurotransmitters, including glutamate and P substance, which are involved in the abnormal processing of pain, as seen in the patient living with FM[26]. PG can be administered on an empty stomach or together with food, without this having any significant clinical effects upon the degree of absorption thereof. The plasmatic concentrations reach a peak within 1 to 2.5 hours after the drug is applied, both for single and multiple doses[25]. Metabolization in humans is almost insignificant, given that approximately 98% of PG is excreted unchanged in the urine[27]. There is no need to monitor the routine concentrations of PG[27]. Due to the lack of bonding to the proteins and the negligible metabolism in the liver, PG may be safely combined with other pharmaceutical products and used in patients with kidney failure, when the dose is appropriate; in this case, withdrawal of the drug must be a gradual process[28]. Sedation, dizziness, peripheral edema, and xerostomia (dry mouth) are the most common adverse effects[29].

### Pregabalin in sleep disturbances in cases of fibromyalgia

The efficiency and security of PG as monotherapy in the treatment of patients with FM is well documented. A data analysis involving polysomnography was conducted on a cross-sectional, randomized and placebo-controlled study, investigating the effects of this pharmaceutical product and placebo, on sleep patterns in cases of FM. A total of 119 patients [103 (87%) women] were randomized (1:1) for PG (150 to 450mg/day) or placebo, during treatment period 1, and vice-versa for treatment period 2. There was a period of transition lasting two weeks, between the completion of period 1 and the start of period 2. The target dose of PG was between 300 and 450mg/day. PG, when compared to the placebo, reduced the number of awakenings during sleep, and increased the duration of sleep, with these effects being reflected and correlated with a reduction of "light sleep" (stage 1) and an increase in "deep sleep! (slow-wave sleep). More specifically, treatment with PG did not have an important effect in bringing about sleep, whether at the start of during the night, when sleep was resumed. On the contrary, treatment with PG resulted in a consolidation of sleep, by reducing the number of times someone woke up during sleep (that means leading to fewer alternations between sleep and awareness) and, in so doing, increased the duration of sleep, thereby reducing the fragmentation thereof[30]. Clinically, the beneficial effects of PG on sleep in patients living with FM are also shown by several different academic papers. A randomized and double-blind study, controlled with the use of a placebo, made use of PG (300mg, 450mg and 600mg/day) or a placebo, in adult patients with FM, for a total of 12 weeks. The sample had a total of 748 patients (with typical ages between 48 and 60, and who had FM for 9 to 10 years), and these were randomized into four groups. PG led to significant improvement in the quality of sleep, as also in the initiation and maintenance of sleep, as well as bringing down the rate of disturbances and occurrence of sleep-related problems. All doses showed significant improvements when compared with the placebo. However, the effects of the treatment were more significant for the groups of 450mg and 600mg, with regard to the daily scores of quality and sleep problems, respectively. Mediation

models showed that 43-80% of benefits regarding sleep (compared with the placebo) were direct effects of the PG, with the rest being the result of an indirect effect of the treatment, through pain relief[31]. Initial pain could be an important factor influencing the results of treatment with PG. Five clinical trials, randomized, double-blind, placebo-controlled made use of PG (at doses between 300 and 450 mg/day) in patients with FM and who experienced moderate to intense initial pain. Individuals aged ≥18 years had average scores of initial pain, on a zero to ten scale (≥4 and <7) or intense pain (≥7 and ≤10), without any difference being observed between the treatment groups. PG was efficient for 12 weeks, in reducing pain and improving quality of sleep among patients with FM and moderate to intense pain at the start of treatment, with a greater effect being observed among the subgroup with intense initial pain[32]. These results are confirmed by another randomized, double-blind, placebo-controlled study with the same posology [PG (300 mg/day, 450 mg/day and 600 mg/day) or placebo, given twice a day]. However, the treatment period was of 14 weeks, in a population of 750 patients with FM, selected at random, and placed in one of the four posology groups. The data shows that, when compared with the placebo, all three doses of PG showed a significant improvement in the scores for intensity of pain and quality of sleep[33].

The time for the effects of PG on cases of FM to be felt was also studied. A total of 2,747 patients with FM (aged between 18 and 82) were included in an analysis involving four trials of 8 to 14 weeks' duration, placebo-controlled, with PG at a fixed dose (150 to 600 mg/day), to establish the time for immediate and sustained clinical improvement in intensity of pain and quality of sleep. In the treatments with PG, there were significant improvements to pain and sleep patterns, at the end of the study, when compared to the placebo, with the immediate responses occurring between 1 and 2 weeks after the start of treatment. The time elapsed up until the start of clinical improvement, based on the quality of sleep, was also calculated. At least 25% of the patients who received PG obtained a sustained clinical improvement on the 2$^{nd}$ day, compared with the 9$^{th}$ day in the case of those who received a placebo, and at least 50% of those who received PG showed a sustained improvement to sleep on the 11$^{th}$ day. The value of the 50$^{th}$ percentile cannot be calculated for the placebo group, as at no moment did 50% of the placebo-treated patients show a sustained clinical improvement to sleep patterns. The authors thus concluded that both the immediate and sustained clinical improvements in sleep quality and intensity of pain occurred more quickly among the patients using PG when compared to the placebo group[34].

Even though most studies on PM are mainly concentrated on the treatment with monotherapy, PG can also be safely combined with other pharmaceuticals and may make the sedation more serious when combined with depressants of the central nervous system[28]. A study compared a combination of PG-duloxetine to each monotherapy. Using a crossed delineation, randomized and double-blind, in 4 periods, patients with FM received the maximum tolerated placebo dose, PG (450mg), duloxetine (120mg) and a combination of pregabalin and duloxetine, for 6 weeks. At the end of the appraisal period, the pharmacological combination outperformed the placebo and the monotherapies, in a multitude of different results, mainly the improvement in pain and the quality of sleep[35]. One study compared the combination of PG with trazodone (an antidepressant) versus trazodone-based monotherapy. Trazodone was administered (50 to 300mg/day) to 66 patients with FM, for 12 weeks. Next, 41 of these patients also received an addition of PG (75 to 450mg/day) to the treatment, for 12 weeks. Even though the monotherapy was able to promote benefits related to the reduction of pain and improvement of sleep, the pharmacological combination gave even better results, both regarding the reduction of pain and improvement of sleep patterns[36].

Since patients with FM often show comorbidities, in some cases, the treatment of FM shall be together with the treatment of any other conditions[5]. In order to appraise the efficiency and security of PG in patients with FM and comorbid depression, taking antidepressant drugs at the same time, a crossed study, randomized and double-blind, with 2 periods and 2 subgroups, placebo-controlled, consisted of two periods of treatment for 6 weeks, separated by a two-week washout period. Patients with FM and aged ≥18 years old, taking a stable dose of a selective serotonin recapture inhibitor, or an inhibitor of serotonin/norepinephrine for depression, were randomized, at a proportion of 1:1, to receive PG/Placebo or placebo/PG, at 300 or 450mg/day. The antidepressant was continued throughout the study. When compared to the placebo, the average final scores for pain intensity had a statistically significant reduction in the use of PG. Also, there was an important improvement regarding anxiety, depression, and particularly of sleep quality. The authors thus reached the conclusion that PG can be given together with antidepressants, without in any way affecting the treatment of the depressive syndrome and also helping to improve both situations[37].

Even though the indicated dose of PG for effects on sleep in cases of FM is 300 or 450mg divided into two applications a day, we recommend a gradual increase based on weekly increments, based on the tolerability of adverse effects and the therapeutical response[28]. PG shows a good profile regarding the safety of adverse effects and tolerability of patients with FM, in long-term monitoring (14, 26 or 52 weeks)[38,39].

## CONCLUSION

PG is a safe and efficient drug when dealing with sleep disorders in patients with FM due to the reduction in the number of awakenings and increases in the duration of sleep.

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