

DRUG INTERACTIONS AND POSSIBLE SEROTONIN SYNDROME IN A PATIENT WITH FIBROMYALGIA

INTERACCIONES MEDICAMENTOSAS Y POSIBLE SÍNDROME SEROTONINÉRGICO EN UN PACIENTE CON FIBROMIALGIA

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DEAR EDITOR

Depression associated with fibromyalgia can be treated with selective serotonin reuptake inhibitors (SSRI) as fluoxetine, paroxetine or citalopram; or with serotonin–norepinephrine reuptake inhibitors (duloxetine or milnacipran) (1, 2). In patients with fibromyalgia, several meta-analyses have demonstrated the effectiveness of antidepressants, particularly the tricyclic antidepressant (TCA) amitriptyline, which reduce the pain, fatigue, depression, and sleep disturbances. Additionally, tramadol, pregabalin, and gabapentin are other treatment options.

Bruxism is a rare secondary effect related to drugs with potent serotonergic activity. However, the use of TCAs, SSRIs, and opioid analgesics have been associated to serotonergic syndrome (3, 4). The incidence of serotonergic syndrome is about 17% in patients with migraine, depression, anxiety and panic disorder (5); nevertheless, the incidence is still unknown in patients with fibromyalgia. The serotonergic syndrome is characterized by signs and symptoms of agitation, tachycardia, increased tension, tremor, fever, dyspnea, diarrhea, mental confusion, and insomnia (3-5). In this context, we report a possible drug-induced bruxism in a patient with fibromyalgia associated with depression.

A complete and integral pharmacotherapy assessment of a 46 years old Caucasian woman diagnosed with fibromyalgia associated with depression was performed according with the Strand et al (2004) proposals (6). The medications used by the patient were: amitriptyline 25mg, (0-0-1); tramadol *retard* 150mg (1-0-1); acetaminophen 650mg (1-1-1); simvastatin 20mg, (1-0-0), and esomeprazole 20 mg, (1-0-0). After six months of the treatment initiation, she reported gnashing of her teeth. The patient's drug related needs were comprehensively assessed and, once the problems were detected, a report was sent to her physician to propose changes in the pharmacotherapy, in order to minimize the negative clinical outcome (bruxism) experienced by the patient (table 1).

An unsatisfied pharmacotherapeutic problem of necessity was noted, since the patient had complained of pain that she tried to solve with the increase of acetaminophen dose. In order to understand and quantify her pain perception, an analgesic ladder of zero to ten was developed (zero intolerable pain and ten without pain). Patient reported pain perception between two-three. So, a potential drug-drug pharmacodynamic and pharmacokinetic interaction was identified among tramadol, acetaminophen and amitriptyline, which may be associated with the development of serotonergic syndrome. Thus, we proposed to the physician the discontinuation of acetaminophen and the replacement of tramadol by pregabalin (150mg/day) (table 1).

Table 1. Management of drug therapy of the patient, in order to minimize or prevent the symptoms associated with serotonergic syndrome.

Initial pharmacotherapy	Drug related problems identified	Pharmaceutical intervention	pharmacotherapy proposed
Amitriptyline 25 mg (0-0-1)	Ineffectiveness and safety (adverse drug reaction by drug-drug interaction)	It was recommended the dose increment of amitriptyline (75mg is the defined daily dose for fibromyalgia treatment). The main safety problem identified may be associated with tramadol and acetaminophen metabolizing. The discontinuation of acetaminophen and replacement of tramadol solved the safety problem detected. The absence of effect of amitriptyline was resolved by the increase of dose (of 25mg to 50 mg).	Amitriptyline 50mg (0-0-1)
Tramadol <i>retard</i> 150mg (1-0-1)	Ineffectiveness and safety (adverse drug reaction by drug-drug interaction)	Substitution by pregabalin (150mg/day), since there is a decrease of serotonergic effects by the introduction of a drug with comparable effectiveness to tramadol.	Pregabalin 75mg (1-0-1)
Acetaminophen 650mg (1-1-1)	Necessity (unnecessary) and safety (drug-drug interaction)	Discontinuation of the drug, since it has not clinical benefits plus drug interaction with amitriptyline.	None
Simvastatin 20mg (1-0-0)	Ineffectiveness	Change in the treatment regimen. It was recommended the administration at evening (0-0-1).	Simvastatin 20mg (0-0-1)

Patient's physician accepted the management of pharmacotherapy proposal. In the following days after suspension of acetaminophen, and the replacement of tramadol by pregabalin, the negative outcome was resolved. Regarding the pain treatment, the patient classified the symptom between seven-eight, according to analgesic ladder.

Data suggest that the patient experienced a serotonergic syndrome, since after the proposed pharmaceutical intervention the signs and symptoms reported by patient disappeared. The identification of serotonergic syndrome is primarily based on exclusion, and strong suspicion based on a patient's current drug therapy.

Amitriptyline and tramadol are drugs with serotonergic action, which inhibit the reuptake of serotonin and noradrenalin. In addition, the main metabolic pathway of tramadol is through the CYP2D6 enzymes, which may be partially inhibited by amitriptyline. Consequently, the tricyclic antidepressant may inhibit the metabolism of tramadol, interaction that can be a significant factor contributing to serotonin syndrome (7). Moreover, amitriptyline and acetaminophen compete for hepatic conjugation with glucuronic acid and sulfuric acid, delaying its elimination. Furthermore, the interruption of acetaminophen promotes the cessation of pharmacokinetic interaction.

A possible pharmacodynamic and pharmacokinetic interaction between amitriptyline, tramadol and acetaminophen may explain the bruxism as a clinical manifestation of serotonergic syndrome. The negative outcome was treated by the replace-

ment of tramadol by pregabalin and by the discontinuation of acetaminophen.

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