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Resolution of Tremor Fluoxetine-induced in an Elderly Patient

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Authors' contributions

This work was carried out in collaboration between all authors. Author PCM designed the study, contributed for data collection and wrote the draft of the manuscript and supervised the work. Author FMO contributed for data collection and managed the literature searches. Author FRV managed literature searches and wrote the draft. All authors read and approved the final manuscript.

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Case Study

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ABSTRACT

Aim: To report a possible case of tremor fluoxetine-induced treated as Parkinson's disease in an elderly female patient noncompliant with the pharmacotherapy, with uncontrolled hypertension and using fluoxetine to treat depression.

Presentation of Case: Patient complained of sleepiness in the morning, agitation, anxiety, insomnia and mental confusion. Her greatest concern was about bilateral hand tremors which, in her view became, worse after biperiden was prescribed. Therefore, she stopped taking it. The initial medication was: omeprazole, losartan, biperiden, fluoxetine, atenolol + chlorthalidone, acetylsalicylic acid, atorvastatin and diazepam. Pharmacotherapeutic follow up was performed in order to check the necessity, safety and effectiveness of treatment.

Discussion: During the analysis of pharmacotherapy, the patient showed uncontrolled blood pressure and had difficulty complying with the treatment. Thus, in view of the complaints expressed by the patient, our first hypothesis was a possible serotonin syndrome related to fluoxetine use. We proposed a change in the fluoxetine regime and discontinuation of biperiden. As tremors persisted,

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we suggested the replacement of fluoxetine by sertraline, since a possible tremor fluoxetine-induced could explain the complaint. This approach solved the drug-related problem identified.

Conclusion: Tremors reported by the patient was identified as an iatrogenic event related to fluoxetine, which was solved by management of serotonin-reuptake inhibitors.

Keywords: Fluoxetine; sertraline; serotonergic syndrome; elderly; primary health care, pharmaceutical care.

1. INTRODUCTION

Serotonin-related adverse side-effects may be triggered by psychotropic drugs, simultaneous administration of two or more serotonergic agents or intentional poisoning [1]. Serotonergic syndrome is characterized by the presence of three or more signs or symptoms, such as: mental status changes (confusion, agitation, anxiety, disorientation) [2], neuromuscular hyperactivity (tremors, muscle rigidity, myoclonus, ataxy) or autonomic manifestations (hypertension, tachycardia, mydriasis, hyperthermia, vomiting, diarrhea) [3].

In addition, dopamine antagonists [4], neuroleptics, metoclopramide and tricyclic antidepressant drugs [5] may be associated with extrapyramidal adverse events, being characterized by movement disorders such as tardive dyskinesia, akathisia and dystonia.

In the general population, there are few reports of extrapyramidal symptoms. The incidence reaches 6% in the elderly population [4], since it depends on the affinity of these drugs for the receptor, their half-life and interactions with neuroleptics [5].

Preclinical studies have shown that fluoxetine may reduce the levels of dopamine in the nigrostriatal region of the brain, suggesting that selective serotonin reuptake inhibitors (SSRIs) can cause impairment in motor function in Parkinson's patients by reducing the levels of dopamine, by acting as fluoxetine as 5HT1A receptor indirect agonists [6].

According to American Geriatrics Society [7], fluoxetine is a potentially inappropriate medicine for the elderly, depending on the clinical condition of the patient. A review carried out by Preskorn [8] showed that sertraline has several characteristics that offer advantages over other members of SSRIs in treatment of elderly patients with major depression. Recently, Varallo et al. [9] described sertraline as a safer alternative treatment.

In this setting, we decided to report a case of tremor fluoxetine-induced in an elderly woman with uncontrolled hypertension, mental confusion and major depression treated with fluoxetine.

2. PRESENTATION OF CASE

A 63-year-old woman, diagnosed with major depression and uncontrolled arterial hypertension, was referred by her health care speech therapist to carry out pharmacotherapy assessment, since the patient reported noncompliance with the therapy after an episode of choking on 20 mg fluoxetine capsules. During the assessment, she complained of feeling drowsy in the morning, agitation, anxiety, insomnia, confusion and having difficulty adhering to the pharmacotherapy. Her greatest concern was about bilateral hand tremors.

In an attempt to alleviate the tremors, her physician had prescribed 40mg propranolol once daily, which was discontinued after two months. Owing to persistence of the symptom, this was replaced by 2 mg biperiden (twice daily). A psychiatrist made a hypothetical diagnosis of Parkinson's disease, since there was a family history this illness (her sister had been diagnosed with Parkinson's disease ten years earlier) and prescribed biperiden.

During pharmacological anamnesis, she reported taking omeprazole (20 mg once daily), losartan (50 mg twice daily), fluoxetine (20 mg twice daily), biperiden (2 mg twice daily), atenolol + chlorthalidone (50/12.5 mg once daily), acetylsalicylic acid (100 mg once daily), atorvastatin (40 mg once daily) and diazepam (5 mg once daily). Drugs were administered orally with water, omeprazole being ingested on an empty stomach and fluoxetine after meals, owing to esophageal discomfort, dissolved in water to prevent choking.

According to the patient, biperiden increased the tremors compared to the previous period when she used propranolol. For this reason, she chose

to discontinue it. Diazepam was usually taken only when she could not sleep, because she considered it a "strong" medicine. She also would prefer not to take fluoxetine, because of the choking episode and the difficulty in swallowing it. Her blood pressure was uncontrolled (average 197/97 mmHg).

Pharmaceutical assessment was conducted by the method of Pharmacist Work group of Drug Therapy (PWDT) [10] used to verify the criteria of necessity, effectiveness, safety and compliance with treatment, while the causes of safety problems were analyzed with reference to the Probability Scale of Adverse Drug Reactions [11]. To solve the problems, a priority list was drawn up, in agreement with the patient, and an action plan proposed.

The first action was to organize the patient's medication, to assist in her compliance with pharmacotherapy. Her pills were separated and arranged in a plastic box with labeled internal divisions and a schedule was attached to the box lid.

In addition, a change was suggested in the frequency of fluoxetine therapy to 40 mg once daily, in order to reduce adverse drug events, such as insomnia and daytime sleepiness. Through a report to her doctor, we also explained the reason for the withdrawing biperiden and suggested lower doses of fluoxetine, since, our first hypothesis was a possible serotonergic syndrome induced by fluoxetine.

One week later, blood pressure remained uncontrolled and tremors persisted. Hence, our second hypothesis was fluoxetine-induced tremors. According to the causality assessment [11], the event was classified as a possible adverse drug reaction (score=4), since propranolol, omeprazole, losartan, biperiden, diazepam and fluoxetine can all be related to tremors (score= 3). However, the frequency of this kind of occurrence is higher with fluoxetine (3-13%). Moreover, there was no other cause that could explain the tremors reported, since the patient did not use Over-the-Counter (OTC) drugs, or did she drink alcohol beverages or coffee habitually.

Therefore, a second report was produced, suggesting the replacement of fluoxetine (40 mg once daily) by sertraline (50 mg once daily). The replacement of fluoxetine by sertraline was carried out with a period of washout of four days,

after which an equivalent dose of the new SSRI was administered. Discontinuation symptoms are unlikely with fluoxetine. Guidelines for the switching of antidepressants recommend a four to seven-day wash-out period, to allow concentrations of fluoxetine and its active metabolite to decrease.

After two weeks of replacement, the patient reported no difficulty in ingesting sertraline, since the tablets were smaller than the fluoxetine capsules, and she did not complain anymore about morning sleepiness or insomnia. The doctor had discontinued diazepam and biperiden because she had no more tremors and her blood pressure was now under control (average 135/75 mmHg).

3. DISCUSSION

Fluoxetine is a psychoactive drug indicated for the treatment of depression, obsessive compulsive disorder and bulimia, which acts by inhibiting the reuptake of serotonin in the central nervous system (CNS), by blocking 5HT_{2A/2C} receptors. Furthermore, it binds to alpha (1)-adrenergic and muscarinic receptors, which may affect both cardiovascular and central nervous systems, causing tremors. Daily dose should not exceed 80 mg/day, 20 mg/day being the initial and recommended dose for the elderly [12].

According to our pharmacotherapeutic assessment, the case appears to involve polypharmacy, complicated by fluoxetine, with its long half-life, accumulation of active metabolite, and P450-related drug-drug interactions. In addition, the patient may have an inadequately treated depressive disorder that could present with Parkinsonism features (psychomotor slowing, hunched posture, and agitation), uncontrolled blood pressure(which may also have contributed to cerebral vascular disease, another cause of tremor and Parkinsonism) and adverse cognitive effects secondary to biperiden (an anticholinergic) and diazepam.

The possibility of a serotonin syndrome could explain the symptoms and their resolution when fluoxetine was discontinued. Another potential contributor to tremor was intermittent and recurrent withdrawal from diazepam, which also has a long half-life and active metabolites, and which the patient took irregularly.

Fick et al. [13] consider that fluoxetine is potentially harmful to elderly people, regardless of their clinical condition or diagnosis, on account

of this long half-life, risk of causing excessive CNS stimulation, leading to sleep disorders and increased agitation. Hence, Varallo et al. [9] suggested sertraline as a therapeutic equivalent, that has less anticholinergic, sedative, hypotensive and cardiac effects [14], as which is common with other SSRIs, is also a first-line treatment of choice for major depressive disorder [15].

However, the American Geriatrics Society [7] classified SSRIs (fluoxetine, citalopram, paroxetine and sertraline) as inappropriate drugs, depending to the diagnosis and clinical condition of the elderly. The reason for avoiding them in certain clinical conditions is the likelihood of occurrence of adverse events such as ataxia, impaired psychomotor function, syncope and fall, increasing the risk of fractures.

Nevertheless, although the SSRI drugs have the same mechanism of action, there are important clinical differences among them. Firstly, the pharmacokinetics of sertraline is the same in adult and elderly patients, where as patients develop a raised plasma concentration of fluoxetine and its active metabolite (norfluoxetine). Secondly, SSRIs differ in their potential for pharmacokinetic interactions with other drugs. Fluoxetine and its active metabolite are potent inhibitors of the hepatic P450 IIDE isoenzyme, while sertraline has a much weaker inhibitory effect on this activity. Inhibition of cytochrome P450 isoenzymes may cause an increase in plasma levels of several drugs [8]. Furthermore, fluoxetine shows non-linear pharmacokinetics, long half-life (five days), active metabolite and steady-state of six to eight weeks (greater in the elderly). On the other hand, sertraline has greater potency on inhibition of reuptake of serotonin. Moreover, its half-life is 26h; it has no active metabolite and has steady-state of seven days [16].

Considering these points, we elaborated a second report to the doctor, suggesting the replacement of fluoxetine by sertraline, as we believed it would be more effective and tolerable. Sertraline is safer than fluoxetine, is safer for the elderly, as it causes a lower incidence of agitation, anxiety, sleepiness, mental confusion, tremors and uncoordinated movement; it also led to a lower rate of treatment discontinuation than fluoxetine [17].

After this pharmacotherapy management, the patient had no more complaints, since it

contributed to pharmacotherapy adherence, eliminated hand tremors and improve the effectiveness of antihypertensive therapy and, therefore, the control of blood pressure. Therefore, it was very likely that the patient had developed tremors fluoxetine-induced.

4. CONCLUSION

The replacement of fluoxetine by sertraline proved to be safer and more effective for the elderly patient by reducing symptoms of agitation and mental confusion, eliminating hand tremors and allowing the control of blood pressure, as well as aiding her adherence to therapy. Therefore, a possible hypothesis is that the symptom of tremors was an adverse event caused by fluoxetine.

CONSENT

All authors declare that 'written informed consent was obtained from the patient for publication of this case report.

RESEARCH ETHICS COMMITTEE

This study was approved (n. 244 688) by the Ethics Committee in Research of the Faculty of Pharmaceutical Sciences Campus Araraquara - UNESP – "State University Julio de MesquitaFilho".

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Boyer EW, Shannon M. The serotonin syndrome. *N Engl J Med.* 2005;352:1112.
2. Ganetsky M, Brush E. Serotonin syndrome – what have we learned? *Clin Ped Emerg Med.* 2005;6:103.

3. Bodner RA, Lynch T, Lewis L, Kahn D. Serotonin syndrome. Presentation of 2 cases and review of the literature. *Medicine (Baltimore)*. 2000;79:201.
4. Gormeley N, Watters L, Lawlor BA. Extrapyramidal side-effects in elderly patients exposed to selective serotonin reuptake inhibitors. *Human Psychopharmacol*. 1997;12:139–143.
5. Topiwala A, Chouliaras L, Ebmeier KP. Prescribing selective serotonin reuptake inhibitors in older age. *Maturitas*. 2014;77:118–123.
6. Yamato H, Kannari K, Shen H, Suda T, Matsunaga M. Fluoxetine reduces L-DOPA-derived extracellular DA in the 6-OHDA-lesioned rat striatum. *Neuroreport*. 2001;12:1123–1126.
7. American Geriatrics Society (AGS). American Geriatrics Society Updated Beers criteria for potentially inappropriate medication use in older adults: The American Geriatrics Society 2012 Beers Criteria Update Expert Panel. *J Am Geriatr Soc*. 2012;60:616–631.
8. Preskorn SH. Recent pharmacologic advances in antidepressant therapy for the elderly. *Am J Med*. 1993;94:2S–12S.
9. Varallo FR, Oliveira FM, Mastroianni PC. Safety assessment of essential medicines for elderly people: A bibliographic survey. *Braz. J. Pharm. Sci* [online]. 2014;50:269–284.
10. Strand LM, Cipolle RJ, Morley PC. Documenting the clinical pharmacists activities: back to basics. *Drug Intell Clin Pharm*. 1988;22:63-67.
11. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther*. 1981;30:239-245.
12. Sthal SM. Antidepressants Classics, Selective Serotonin Reuptake Inhibitors Serotonin and Norepinephrine Reuptake of Inbidores. In: Sthal SM, editor. *Psicofarmacologia: Base neurocientífica e aplicações práticas*. 2nd ed. Cambridge University Press: New York; 2002.
13. Fick DM, Cooper JW, Wade WE, Waller JL, Maclean JR, Beers MH. Updating the beers criteria for potentially inappropriate medication use in older adults: Results of a US consensus panel of experts. *Arch Intern Med*. 2003;163:2716–2724.
14. Hardman JG, Limbird IE. Goodman & Gilman. *As bases farmacológicas da terapêutica*. 10. ed. Rio de Janeiro: Mc Graw-Hill; 2003.
15. Gourion D, Perrin E, Quintin P. Fluoxetine: an update of its use in major depressive disorder in adults. *Encephale*. 2004;30:392-9.
16. Goodnick PJ, Goldstein BJ. Selective serotonin reuptake inhibitors in affective disorders – 1: Basic pharmacology. *J Psychopharmacol*. 1998;12(3 suppl B):3-S20
17. Ohno Y, Shimizu S, Tokudome K. Pathophysiological roles of serotonergic system in regulating extrapyramidal motor functions. *Biol Pharm Bull*. 2013;36:1396–1400.

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