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USE OF FLUOXETINE IN DEPRESSION TREATMENT

¹Elisa Braga De Almeida, ²Ronivaldo Ferreira Mendes, ¹Mônica Cecilia Santana Pereira,
¹Viviane Amaral Toledo Coelho, ³Lilian Cristina Gomes Do Nascimento
and ¹Luiza Gobira Lacerda

¹Alfa Faculdade de Almenara, Almenara, Minas Gerais, Brazil

²Instituto Federal do Norte de Minas Gerais, Almenara, Minas Gerais, Brazil

⁵Department of Health Promotion, University of Franca, Franca, São Paulo, Brazil

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ABSTRACT

This study aimed to analyze the current literature approaches to the use of fluoxetine in the treatment of depression. It is an article based on bibliographical research published between the years of 2002 to 2018. A total of 70 studied contents were included, and after selective and meticulous reading, 19 papers and two dissertations were submitted to compose this review. It can be seen that depression is one of the most growing mental disorders in the population that can be identified by feelings of sadness, decrease or loss of interest in almost all daily activities. Its neurobiological causes are based on the monoaminergic hypothesis that follows the idea that depression is caused by a decrease in brain biogenic amines, serotonin, noradrenaline and / or dopamine. According to the selected articles, it can be evidenced that although there is a great variety of drugs available for the treatment of this pathology, the most used among them is fluoxetine, belonging to the class of antidepressants Selective Serotonin Reuptake Inhibitors, be considered to be more effective than the Monoaminoxidase Tricyclic antidepressants and Inhibitors because they have a once daily dosage, acceptable adverse effects, high tolerability, relative cardiovascular safety and a comparatively favorable cost.

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INTRODUCTION

Depression is a disease characterized as a "change in mood mood by a feeling of sadness, helplessness, significance or loss of interest in almost every activity of the everyday." In addition, depletion of energy caused by neurotransmitter deficiency, the example may trigger the symptom such as: "feeling of worthlessness or excessive guilt, appetite changes in relation to gain or loss of weight, insomnia or excessive drowsiness, noise complaints, fatigue, negative thoughts and increased concentration. In some cases the idealization of death may occur "(Neves, 2015). The World Health Organization estimates that today, in the world, "350 million people live with depression." The decision-making process on the disease and decision-making on stigmatization and discrimination (Abelha, 2014).

*Corresponding author: Elisa Braga De Almeida
Alfa Faculdade de Almenara, Almenara, Minas Gerais, Brazil

Fluoxetine is one of the most commonly used antidepressants today and has been marketed for several years under the name Prozac®. It was initially synthesized by the pharmaceutical company Eli Lilly and was the first selective serotonin reuptake inhibitor (SSRI) to be approved in 1987 by the Food and Drug Administration (FDA). It is estimated that approximately 40 million people are users of this drug, because it presents good tolerability, low cost and effectiveness (Negri and Rodrigues, 2018). It should be noted that fluoxetine has its marketing and dispensing regulated by means of Ordinance SVS/MS numer 344, dated May 12, 1998, and resolutions passed by the National Agency of Sanitary Surveillance (ANVISA). The prescription of fluoxetine is in special prescription in two ways (List C1 of Ordinance n° 344), and one of the routes is retained in drugstores or pharmacies for a minimum period of two years for future control of Sanitary Surveillance (Brasil, 1998). In fact, the diagnosis and maintenance of the pharmacotherapy of depressive patients is due to variations between doses, the

duration of treatment and the low occurrence of adverse effects. Given this contextuality, the use of SSRIs was consolidated as the first choice for the treatment of this pathology (Negri and Rodrigues, 2018). This research aimed to bring the discussion and the study in a scientific context whose main focus is focused on the approaches of the use of fluoxetine in the pharmacological treatment of depression.

MATERIALS AND METHODS

The present study was based on a bibliographical research, which consists of the survey and analyzes of theoretical references already published by printed and electronic means, where in the course of the research are observed and discussed methods, results and general conclusions about the chosen theme (Fonseca, 2002). Soon after defining the theme and the type of research to be developed, it was formulated to the following guiding question: Why is fluoxetine considered in the current day the medicine of first choice for the treatment of depression?

In view of the question, a bibliographical survey of scientific articles published between the years of 2002 and 2018 was carried out, having among them only a reference equivalent to the year 1998 corresponding to Portaria SVS / MS n° 344, dated May 12, 1998 the requirement of prescription in two-way special prescription for the dispensation of fluoxetine. The research was guided by the electronic databases: Scientific Electronic Library Online (SciELO), Digital Library of Theses and Dissertations and Google Scholar. For inclusion criteria of the resulting articles, parameters such as; relevance to the topic, scientific articles and studies written in Portuguese, current information, or content from previous years if pertinent. The following Health Sciences Descriptors (DeCS) were used: "depression"; "Fluoxetine"; "therapeutic use" and "adverse effects". In this way, a total of 70 studied contents were covered, where through selective and meticulous reading the 20 papers, were submitted and three dissertations that presented in their contents specifications about the depression with inclusion to its neurobiological causes and external triggers, and theoretical studies and practical aspects that demonstrated the prevalence of the use of fluoxetine for the treatment of depression.

RESULTS AND DISCUSSION

Pathophysiology of depression: Depression is a "chronic and recurrent mood disorder" that over time fosters major disruptions and consequences for the well-being of the individual and those present in their environment (CRUZ *et al.*, 2010). The disease was discovered more than 25 centuries ago, and the term was used to characterize mental symptoms or conditions called melancholy, an emotional context of unhappiness, sadness and discouragement. Nonetheless, what now comes is the popularization of sadness in its most acute aspect (Gregoleti, Scortegagna and Portella, 2016). Gregoleti, Scortegagna and Portella (2016), emphasize that "depression is the main cause of" incapacitation "of the general population, ranking fourth among the top ten diseases", with an estimated second place in this ranking of pathologies until the year 2020. The most well-known manifestations of depression are related to social, psychic, hereditary, organic, religious, and economic factors; more specifically individuals living in their day-to-day situations of conflict, lack of affection, physical limitations, losses, family problems, among others, are more likely to develop a depressive symptomatology. However, it should be

noted that in fact not all individuals who share the same lifestyle may trigger the disease, depression has its particularity, individuality and factors such as predisposition, age, gender, heredity and influence of the environment (Araujo *et al.*, 2003). When speaking of depression, conception is only referred to as a synonym of sadness and seclusion. However, this pathology does not only include a single picture. Despite its categorically similar symptoms, depression presents a varied classification in several subtypes, for example; the depressive episode where the patient presents for a certain time a behavioral change; the major depressive disorder characterized by the recurrence of depressive symptoms and the symptomatology installed for more than six months; bipolar depression, recognized by episodes of euphoria; dysthymia, represented by a mild depressive picture where the individual suffers sudden or continuous mood swings for years; atypical depression, where there is a predominance of energy depletion, hypersomnia, increased appetite and weight; and finally, psychotic depression, which is related to the most severe type of depression with the presence of delusions and hallucinations (Canale and Furlan, 2006). Among the propositions on depression, the "monoaminergic hypothesis" is the most important study associated with the mechanism of action of antidepressants, confirmed by its efficiency in the treatment of depression. The "monoaminergic hypothesis" is one that emphasizes the idea that depression is due to a "lower concentration of brain biogenic amines, especially serotonin, noradrenaline and / or dopamine" (Almada, Borges and Machado, 2014).

Epidemiology: Depression is, admittedly, a worldwide public health problem that interferes in a decisive and intense way in the personal, professional, social and economic life of its patients (Jaegger, 2015). The WHO estimates that, in the world, "350 million people live with depression". Sadly, only half of these people get the care they need, becoming targets of "stigma and discrimination" (Abelha, 2014). Depression is one of the most common psychiatric illnesses today. It presents a prevalence of approximately 5% in the world population, however, and can reach 20% throughout the life. It is noteworthy that the risk for these depressive disorders has ranged from 10% to 25% in women, and from 5% to 12% in men. In addition, the disease affects 10% of individuals seeking health services for various reasons. At least 20% of patients with chronic diseases, such as cardiovascular disease and diabetes mellitus, suffer from depressive disorders, although the diagnosis is made in a small minority (Prietsch, 2015). The significant difference of predominant cases of depression in women can be explained by several factors, among them hormonal issues such as pregnancy, changes in the menstrual cycle, premenopausal, menopause, abortion, postpartum, in addition to the fact that a large majority of women spend at some point in their lives for some kind of overload, such as responsibilities at home, at work, single motherhood, which ends up generating a greater predisposition to develop depression. Unlike women that depression appears as a form of helplessness or hopelessness in men, the disease usually manifests itself in the form of anger, irritation and discouragement, which usually ends up being masked by the use of drugs, alcohol and even an acceptable routine and overworked (Canale and Furlan, 2006).

Pharmacological treatment of depression and mechanism of action of fluoxetine: According to Serra (2014), the drugs used in the treatment of depressions are called antidepressants, drugs that restore the physical and emotional health of the

person without changing their personality. These drugs are increasingly effective in controlling and treating depression, with a duration of at least four to six months, as the effect of these medications tends to take up to a few weeks. In fact, the diagnosis and maintenance of pharmacotherapy in depressive patients has been increasingly prevalent. The methods of treatment of this pathology are based on the biological, psychological and social aspects of the patient, which leads in most cases to pharmacological treatment. In terms of efficacy, the different antidepressants do not differ significantly, however, it is worth mentioning those in which the cost, the side effects and the risk of suicide are variable, which results in different choices in the specific therapy for each patient. In this sense, it is possible to observe that there is no standard antidepressant for the treatment of depression, however, there is a great availability of drugs that act through different mechanisms of action which allows an optimal choice of therapy even for depressions resistant to certain treatments (Neves, 2015). In view of this variety of drugs available for the treatment of this condition, the first SSRI to be discovered was fluoxetine in 1972, which proved to be a highly selective antidepressant for inhibition of serotonin (5-HT) reuptake, low toxicity (Neves, 2015). When this new class of medication was made available on the market, it had a great impact in relation to the treatment of cases of depression. SSRIs are currently considered to be more reliable than the classes of Tricyclic antidepressants and Monoamine Oxidase Inhibitors (MAOIs) (Prietsch, 2015).

The treatment of depression can be observed in phases until the patient obtains a complete remission of their symptoms (Fleck et al., 2009). Negri and Rodrigues (2018) point out that currently about 40 million people are using this drug. In addition to its commercialization under the name Prozac®, fluoxetine can be found with consecutive trade names: Eufor®, Daforin®, Prozen®, Fluox®, Fluxene®, Nortec®, Psiquial® and Verotina®. As can be observed, the studies listed show the prevalence of the use of fluoxetine for the treatment of depression. As part of the list of drugs standardized by the Unified Health System (SUS), Brazilian public health system, following the norms recommended by the WHO. To meet most of the population's health problems, fluoxetine is distributed free of charge by the Brazilian government, increasing the access of the large access to treatment (Mariz and Menezes, 2012). Regarding the mechanism of action, it is possible to make sure that the SSRIs were developed with the aim of reducing the affinity for the adrenergic, cholinergic and histaminergic receptors and to increase the affinity with the serotonin reuptake pumps, being part of the third generation antidepressants. Regarding treatment options for depression, fluoxetine is the drug of first choice due not only to its efficacy but also to its high tolerance. Fluoxetine is a drug capable of potently and selectively inhibiting serotonin (5-HT) reuptake, potentiating serotonergic neurotransmission. The mechanism of action of fluoxetine is linked to the inhibition of 5-HT neuronal reuptake and the resulting increase in "serotonergic neurotransmission" in the Central Nervous System (Jaegger, 2015). Fluoxetine acts by stimulating and enhancing "serotonergic neurotransmission" in the synaptic cleft and in what concerns 5-HT, since it participates in the regulation of mood, sleep, sexual activity, appetite, heart rhythm, sensitivity to pain, activity motor and neuroendocrine functions. In addition, it is well tolerated at therapeutic doses with low risks. Regarding pharmacokinetics, its bioavailability is high and its plasma

concentration is obtained from six to eight hours (Machado, 2018). Fluoxetine has a daily dosage of 20mg to 80mg, its metabolism occurs through the hepatic route and is usually eliminated by the urinary route (Negri and Rodrigues, 2018). The use of fluoxetine should be initiated at low doses (eg. 5mg to 10mg) with a gradual and gradual increase. When the optimal dose is reached, it is necessary to wait four to six weeks to evaluate the therapeutic response. The withdrawal of the drug should be gradual, to avoid possible abstinence (Mariz and Menezes, 2012).

Drug interactions and adverse effects of fluoxetine:

Pharmacological therapy of depressive disorders employs several classes of drugs, therefore those available and most used have similarities with regard to their efficacy. However, SSRIs are those that are denoted with fewer side effects, in addition to having a long half-life, and can therefore be administered in a single dose, consequently decreasing the number of patients in treatment abandonment (Colet et al., 2015). Although antidepressants are shown to be safe and effective, it is recommended and necessary that consideration be given to their use, since these drugs are capable of causing adverse effects in various organ systems. The use of SSRIs is related to gastrointestinal disorders, agitation, insomnia, headache, panic, sexual dysfunction, anxiety and tremors. It is important to emphasize that in addition to these side effects that may be caused, a large part of the patients who treat depressive disorders are holders of so-called polypharmacy, that is, they use several medications concomitantly, thus becoming more susceptible to drug interactions (Colet et al., 2015). Within the SSRIs, the antidepressant fluoxetine occupies a prominent place and is determined as the first choice for pharmacological treatment of depression. Among the possible drug interactions related to its use may be highlighted the combinations with benzodiazepines, clozapine, warfarin and neuroleptics and also the possible interactions with the tricyclic antidepressants (Mariz and Menezes, 2012).

Table 1. Possible drug interactions with the use of fluoxetine

Drugs	Drug interactions
Benzodiazepines	Increased plasma levels of benzodiazepines
Clozapine	Increased plasma levels of Clozapine
Warfarin	Increased plasma levels of warfarin
Tricyclic antidepressants	Potentiation of the effects of Tricyclic antidepressants
Neuroleptics	Increased plasma levels of neuroleptics

Mariz and Menezes (2012)

Importance of pharmaceutical care in the pharmacological treatment of depression:

Currently, depression is known as a mood disorder, which should be directly identified and treated, is clearly a disease that is not related to the character of the individual and not to the will of the individual. In this context, the term depression does not refer only to a depressed state, but rather to a complex of syndromes identified by changes in mood, psychomotricity, and an immense variety of somatic and neurovegetative disorders (Neves, 2015). It is worth mentioning that the existence of innumerable treatments, the amount of adverse effects caused by the use of the medication, the difficulty of adherence and the patient's permanence to the treatment, are a hindrance to the conclusion and satisfactory result of their pharmacotherapy. In this aspect, adherence to antidepressant treatment is relatively low, ranging from 40 to 90% in different studies, with an average of 65%. The clinical response does not occur immediately and usually varies,

showing its effects between the second and fourth weeks of use. Faced with the facts, the pharmacist can play a significant role in home guidance, since he / she is the one who has the adequate pharmacotherapeutic knowledge, thus having the responsibility of developing orientation actions and providing educational subsidies so that the patients cared for adherence to pharmacological treatment (Freitas and Oliveira, 2012).

In the eyes of public health, pharmacies are extremely important places to seek care, pharmacists are the health professionals who are more generally available to the population; in this sense, the services provided by them are as important for the care of the patient as the services performed by doctors and other professionals in the area, which endows the community pharmacists with the opportunity to assist their patients individually and can provide objective information such as dose, dosage form and duration of treatment. Also providing more specific knowledge, such as why the use of such a drug, including and making explicit its risks and benefits. Thus, pharmacists contribute with their actions in support of the health system, however, it still needs to expand its scope of action to a greater achievement of public trust (Navas, Silva and Vidal, 2008).

Concluding comments: As elucidated in the course of the work, depression is a disease of high incidence, causing extreme debilitation and incapacity in the present society, which can manifest itself in the various stages of life, in its various types and subtypes. It presents a multiplicity of social, psychic, hereditary, organic, religious and economic causes. Its most well-known neurobiological causes are related to the monoaminergic hypothesis, which derives from the idea that depression is caused by a decrease in brain biogenic amines, in large proportion to serotonin, noradrenaline and / or dopamine. The pharmaceutical industry, despite providing a wide therapeutic range related to the pharmacotherapy of depression, evidences and proves in the studies listed the prevalence of the use of fluoxetine for the treatment of these disorders, due to the fact that the drug is currently more effective and safe than antidepressants Tricyclics and Monoamine Oxidase Inhibitors in different classes of depression, denote a once-daily dosage, acceptable adverse effects, high tolerability, relative cardiovascular safety and a comparatively favorable cost. In addition, fluoxetine is part of the list of standardized drugs dispensed by the SUS, which facilitates the access of the large population to its acquisition. Depression presents as a complex of syndromes identified by changes in mood, psychomotricity and by an immense variety of somatic and neurovegetative disorders that requires adequate and specialized multidisciplinary and pharmacotherapeutic treatment and follow-up depending on the type or subtype of depression. In this aspect it was evidenced the importance and the necessity of a pharmaceutical professional to develop actions of orientations and provision of educational subsidies so that the patients attended can adopt to the pharmacological treatment effective and safe form with the prescription drugs.

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