UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL
FACULDADE DE FARMÁCIA
TRABALHO DE CONCLUSÃO DE CURSO DE FARMÁCIA

ARE SELECTIVE SEROTONIN REUPTAKE INHIBITORS EFFECTIVE AGAINST FIBROMYALGIA SYMPTOMS?

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PORTO ALEGRE
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Trabalho de Conclusão de Curso apresentado ao Curso de Farmácia da Universidade Federal do Rio Grande do Sul como requisito à obtenção do título de grau de Farmacêutica.

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DEDICATÓRIA

A Deus, por Sua infinita bondade que me sustém. À minha família que foi minha base propulsora e, ao mesmo tempo, recanto seguro. À Bebê, minha gatinha, fonte de serotonina em momentos inóspitos.

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APRESENTAÇÃO

Esse Trabalho de Conclusão de Curso foi redigido sob a forma de artigo ao qual foi elaborado segundo as normas da revista PLOS ONE, apresentadas em anexo.

Title: “ARE SELECTIVE SEROTONIN REUPTAKE INHIBITORS EFFECTIVE AGAINST FIBROMYALGIA SYMPTOMS?”

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ABSTRACT

Introduction: Fibromyalgia (FM) syndrome is characterized by widespread chronic pain, depressive symptoms, poor sleep quality, and its correlates. Its pharmacological treatment is usually done with antidepressants and anticonvulsants, but this first line treatment is not fully available at Brazil’s public health care system.

Aim: to evaluate if the use of selective serotonin reuptake inhibitors (SSRI) is related to improved depressive symptoms and correlated symptoms.

Material and methods: 85 literate-women aged 30 to 65 years old with confirmed FM diagnosis were included. They were divided in 2 groups: SSRI users (n=25) and non-SSRI (n=60) users. To evaluate the severity of depressive symptoms, the Beck Depression Inventory - II was applied. The disability due to pain and the FM impact were evaluated by the Brazilian version of Profile of Chronic Pain Screen Questionnaire and Fibromyalgia Impact Questionnaire, respectively. For total sleep time (TST) and activity/rest rhythm measurements, the subjects were asked to wear a wrist actigraph.

Results: Both groups had shown moderate depressive symptoms (p=0.228). A hierarchical multiple regression analysis shows that the TST and SSRI use were negatively correlated to the severity of depressive symptoms (B=-1.513 p=0.03; B=-4.269 p=0.04) whether disability due to pain was positively correlated (B=0.595 p<0.001).

Conclusion: Our findings suggest that the use of SSRI can be a protective factor to FM patients with severe depressive symptoms and it can be a treatment option in FM that is available at Brazil's public health care system.

Introduction:

Fibromyalgia is a typical nociplastic pain disorder, with a world prevalence that ranges 2 to 5 percent[1], characterized by widespread chronic pain (persists more than three months), poor sleep quality, fatigue, cognitive dysfunction and depressive symptoms[2]. Besides that, a wide variety of psychological, behavioral and social issues can collaborate to its pathogenesis[3]. Furthermore, according to Schmidt-Wilcke & Clauw (2011), fibromyalgia patients have low levels or low activity of serotonin, norepinephrine and dopamine neurotransmitters that typically inhibit pain transmission[4].

In addition, as stated by Stahl (2009), the serotonin levels can impact both sleep function and pain intensity[5]. When there is some serotonergic deficiency, there is also an increase in production of substance P, that leads to allodynia and to sleep disturbances[6] thus, drugs with capacity to increase serotonin or decreasing substance P levels may help both sleep disturbances and pain perception[7]. Sleep disturbances are a common complaint on FM syndrome, it affects around 90% of

patients, and it comprehends lower total sleep time (TST), non-refreshing sleep, frequent awakeness and poor sleep quality[8].

Moreover, it is known that sleep disturbances play a role in depression[9]. It is important to state that the prevalence of major depressive disorder (MDD), over FM patients, is around 45% by self-administered screening symptom scales (SSS) and around 23% by clinician administered SSS[10]. Some of the depressive symptoms are, besides sleep disturbances, low mood, lack of energy, sadness, irritability, and an inability to enjoy life[11]. In addition, these symptoms affect the quality of life that comprehends life satisfaction, social relationships, functioning in daily activities and work, economic status and physical health[12-15].

Nonetheless, according to Galvez-Sanchéz et al. (2020), FM patients have lower quality of life, comprehending both physical, psychological and social levels of functioning, when compared with controls[13]. In addition, the chronic widespread pain experienced by these patients plays an influence over social relations, work status, house-hold light tasks performance, self-care routine and emotional distress[14].

To treat these and other symptoms, the chronic pain's treatment target comprise central sensory processing modulation of either pain transmission (i.e., opioids, tricyclic antidepressants (TCAs) and serotonin-norepinephrine reuptake inhibitors (SNRI)) or neural excitability (i.e., opioids, anticonvulsants). The Food and Drug Administration (FDA) had approved some pharmacological interventions for FM: duloxetine, milnacipran, and pregabalin[16]. Besides that, amitriptyline, a TCA that is not approved by FDA for FM treatment, shows an improvement in quality of life and decreases sleep disturbances and fatigue among FM patients[17]. Nonetheless,

selective serotonin reuptake inhibitors (SSRI) are widely known for their effects on depressive symptomatology in patients with major depressive disorder (MDD).[18]

Despite the SSRI being the most prescribed antidepressant class[19], they do not affect chronic pain[20]. They are widely used in FM patients with MDD because dual antidepressants approved by FDA for FM (i.e., Duloxetine) are not available in the Public Health System. So, it is usually prescribed the combined use of TACs and SSRI, despite their benefits in this context are not known. Aligned with the perspective, we evaluated their possible impact on FM symptoms. We hypothesized that the SSRI intake might be useful as a mood regulator for fibromyalgia syndrome[20-21]. Thus, this study aims to evaluate if the use of selective serotonin reuptake inhibitors is related to improved depressive symptoms and correlated symptoms.

Material and Methods

Design overview, settings, and participants

This cross-sectional study was approved by the Ethics' Committee Board at Hospital de Clínicas de Porto Alegre, under project number 20170330, according to the Declaration of Helsinki. All participants provided written informed consent. Included eighty-five (85) literate women aged between 30 and 65 years with a confirmed diagnosis of fibromyalgia according to the American College of Rheumatology (ACR) criteria 2016[2].

Sample recruitment, inclusion, and exclusion criteria:

It was recruited sample convenience from the Hospital de Clínicas de Porto Alegre's Chronic Pain Service and Basic Health Unit, from other clinic units' referrals, and from public advertisements on the internet and in newspapers. Afterwards, the volunteers were contacted by phone and screened for eligibility. Our inclusion criteria

were to have a confirmed FM diagnosis according to 2016's American College of Rheumatology diagnostic criteria for fibromyalgia[2], certified by our experienced clinicians. The ACR diagnostic criteria comprehends presence of the symptoms for more than 3 months, generalized pain (presence of pain in at least 4 of 5 body regions) and widespread pain index (WPI) ≥ 7 and symptom severity scale score (SSS) ≥ 5 or WPI of 4-6 and SSS ≥ 9. Additionally, they must have a pain level over 6 on a Visual Analogue Scale (VAS) that ranges from 1 to 10, where 1 "no pain" and 10 "maximal pain" for the last 3 months and have FM as the principal pain cause. Our exclusion criteria were being pregnant, having a history of malignancy or uncompensated chronic diseases such as hypertension, diabetes and asthma, shift work, alcohol or drug abuse in the previous six months, neurological disorders, schizophrenia or bipolar disorder.

Instruments and Assessment Outcomes

All participants have completed a standardized sociodemographic questionnaire. All instruments were applied by a well-trained clinician.

Dependent and independent variables

The dependent variable was the depressive symptoms. The main interest independent variable was the sleep quality. Covariates included the intensity of chronic pain, disability due to pain, sociodemographic characteristics, clinical and psychiatric chronic disease, and use of psychotropic medications.

Outcome assessment

Depressive symptoms were accessed by the validated Brazilian version of Beck Depression Inventory-II, 21 items self-report questionnaire that measures depressive symptoms and severity[22-23]. The measurement is with a 4-point scale that

indicates degree of severity, items are rated from 0 (not at all) to 3 (extreme form of each symptom). The range is between 0 and 63, guidelines suggest that range 0-13 is minimal, 14-19 mild depression, 20-28 moderate depression, and 29-63 severe depression symptoms[24].

Assessment of pain and disability

a) Pain level assessment: To assess the pain level of our sample, we used the Visual Analog Scale (VAS), a widely used pain evaluation instrument on which the patient marks the intensity of his or her pain scaled from 0 (no pain) to 10 (maximal pain).

b) Functional disability due to pain: To evaluate the functional disability due to pain and the severity of it, we used the validated Brazilian version of Profile of Chronic Pain Screen Questionnaire[25]. It can measure both physical and psychological faces of this disease and its impact on daily life over the time range of one week. This questionnaire consists of 15 questions and is scored between 0 - 91. It comprises three dominions: Pain severity, disability due to pain and emotional burden.

c) Fibromyalgia impact: The Brazilian validated version of Fibromyalgia Impact Questionnaire[26] was used to assess the impact of FM in the quality of life of patients. It consists of 10 items, and the higher the score obtained, the greater the impact of fibromyalgia on quality of life (maximum total score is 114).

d) Sleep and activity/rest rhythm measurements: The subjects were asked to wear a wrist actigraph during 7 continuous days, and were oriented to always stay with the equipment on their non-dominant wrist, especially during their sleep time. The data were collected by ActTrust actigraph by Condor Instruments (São Paulo, Brazil). Each 60 seconds, the device recorded activity through an accelerometer, body temperature through an ibutton located inside the actigraph and light exposition

due to a light sensor caption The timezone was used to delimit the night period. All the data initiate at the same hour and day of the week to complete 7 day/night cycles. When data was missing, the period was adjusted to "awake". Through these parameters, we extracted the total sleep time (TST), temperature and activity amplitude and acrophase, Interdaily Stability (IS) and Intradaily Variability (IV), the onset time of the first 10 hours of more activity (M10) and the onset time of the first 5 hours of less activity (L5). These quantifications were measured by ActStudio Software Version 1.0.13 from Condor Instruments.

Efforts to Address Potential Sources of Bias

In order to reduce possible sources of bias, just one experienced and well-trained researcher was involved in all assessments. A highly skilled physician at diagnosing chronic pain conditions used the clinical scales.

Sample size

It was a convenience sample, N=85. It was performed a *post hoc* analysis to verify the power analysis. The effect size according to Cohen's was f^2= 0.42 between the groups, determined by R^2=0.30 and three predictors for an error type I <0.05 and error type II equal to 0.99. Analysis performed in GPower software 3 version[27].

Statistical analysis

To access the descriptive analysis of the sample, we performed an Independent-Samples T test, where the sample was divided into two groups according to the use of selective serotonin reuptake inhibitors. All values are presented as mean and standard deviation.

A hierarchical multiple regression analysis was conducted to examine the relative contribution of disability due to pain, total sleep time (TST), and SSRI use to

predict depression symptoms. Retained variables present statistically significant association (p-value < 0.05). The data were analyzed using SPSS 11.0© for Windows (SPSS Inc., Chicago, IL).

Results

Sample characteristics

Eighty-five patients were enrolled in this study. Twenty-five of them were SSRI users, and sixty were non-SSRI users. The social demographic data are presented in table 1.

Table 1 - Sociodemographic characteristics (n = 85)

	SSRI user (n = 25)	Non-SSRI user (n = 60)	p-Value
Characteristic	**Mean ± SD**	**Mean ± SD**	
Age (years)	49.36 (9.02)	47.95 (9.94)	0.542
Depressive Symptoms (BDI-II)	28.96 (9.902)	25.68 (11.85)	0.228
Pain level (VAS)	8.78 (1.23)	8.45 (1.29)	0.274
Dysfunction due to pain (B-PCS)	71.44 (13.51)	73.88 (12.71)	0.430
Fibromyalgia Impact (FIQ)	72.10 (14.61)	68.96 (16.52)	0.414
ACR Score	22.92 (4.192)	22.90 (3.438)	0.982

Total Sleep Time (TST) (hours)	7:32 (1:25)	7:51 (1:20)	0.353
Activity mesor	2264.63 (784.40)	1946.67 (570.48)	0.068
Temperature acrophase (hours)	06:56 (06:53)	05:47 (04:34)	0.365
Onset M10 (hours)	09:46 (02:08)	09:52 (2:09)	0.860
Onset L5 (hours)	07:55 (10:01)	09:25 (09:47)	0.523
Interdaily Stability	0.6440 (0.1691)	0.6718 (0.1262)	0.406
Intradaily Variability	0.4788 (0.0919)	0.4562 (0.0784)	0.253

$p<0.05$ was statistically significant.

There was no significant difference in depressive symptoms, evaluated through BDI-II, between the groups ($p=0.228$). Both groups had shown moderate depressive symptoms.

Assessment of factors associated with the severity of depressive symptom

A hierarchical multiple regression analysis shows the impact of the dysfunction due to pain, total sleep time, and usage of SSRIs on depressive symptoms in fibromyalgia. TST and SSRI use were negatively correlated to the severity of depressive symptoms. In other words, the subjects who use SSRI have more depressive symptoms than those who do not. In contrast, those who sleep less present more depressive symptoms. Data are presented in table 2.

Table 2 - The effect of dysfunction due to pain, total sleep time and usage of SSRI by fibromyalgia women on depressive symptoms.

Variables	B	SE	Beta	p-Value
Dependent variable: Depressive symptoms on BDI-II				
Dysfunction due to pain (B-PCP:S)	0.595	0.075	0.677	<0.001
Total Sleep Time (TST)	-1.513	0.705	-0.183	0.035
SSRI Non-Users	-4.269	2.057	-0.172	0.041
Constant - (BDI)	2.10	7.325	-	0.772

R^2= 0.450; $p<0.05$ was statistically significant

Discussion:

These findings highlight that the SSRI use and lower TST is associated with higher severity in depressive symptoms. Also, disability to pain is related to higher depressive symptoms in FM.

The converse relationship of SSRI with the depressive symptoms in the multivariate analysis indicates that it can be a protective factor of these medications, in the sense that the more severe the patient's condition, considering depressive symptoms, the greater the use of the medication. This result is relevant to supporting clinicians' practice in prescribing this class of medicine for FM. Its importance is to give some arguments for further randomized clinical trials to investigate the benefits of SSRIs combined with TCAs widely prescribed in the public health system for economic reasons since these two classes of medications are available in Brazil`s public health system. Based on this rationale, and in the high prevalence of Major Depressive Disorders and Anxiety Disorders as comorbidities of FM, this result is important for the clinical setting.

It is relevant to state that both SNRI and TCA can inhibit the norepinephrine (NE) reuptake besides the inhibition of serotonin reuptake unlike most of the SSRIs. The NE is a neurotransmitter mostly inhibitory, although, 5HT plays a role on either facilitation or inhibition[28]. It is also known that NE can enhance analgesic effects, through a2-adrenergic receptors localized over the dorsal horn of the spinal cord. The α2-adrenergic receptors are coupled to the inhibitory G protein (Gi/o), that inhibits the presynaptic calcium voltage-gated channel, inhibiting the release of excitatory neurotransmitters from primary afferent fibers[29-30]. Moreover, a curious fact is that, according to Verdu et al. (2008), among SSRI antidepressants, only fluoxetine (20–80 mg/day, mean dose 45 mg/day) was found to be superior to placebo in a study with 60 female patients in improving pain, fatigue and depression, but not

number of tender points[31]. It is important to state that fluoxetine is a SSRI which can inhibit the NE reuptake in higher dosis[32], so, it might explain its use and efficacy over FM symptoms.

In addition, sleep disorders are an overlap symptom between depression and fibromyalgia[8]. Poor sleep quality, reduced total sleep time and not refreshing sleep are some of the experiences reported[8]. In a Cochrane review[20] , there was no significant improvement on sleep disturbances with the use of SSRI when compared to placebo in a fibromyalgia sample. Some studies have revealed that SSRI induces sleep fragmentation, increased sleep and REM sleep latency and decreased REM sleep and sleep efficiency, when compared with health controls, in patients with depression[33]. Although, another study, with patients with depression, showed that the use of this antidepressant class improved subjective sleep, the analyzed sample had a longer TST, a better sleep quality and higher sleep efficiency, measured by the Pittsburgh Sleep Quality Index[34]. Nonetheless, our sample does not show any difference between the group that used SSRI and the group that did not, otherwise, the patients who had a longer TST, had less depressive symptoms. The short sleep duration has been linked to higher scores in depression[35] decreased quality of life, chronic health problems such as hypertension, metabolic syndromes, obesity and mental disorders[36] which corroborates with our results. Furthermore, the poor sleep quality and its correlates, can reduce the ability to cope with pain[8].

In addition, our results showed that the disability due to pain corroborates to increase the depressive symptoms. It might be explained by the pain influence over the impossibility to enjoy leisure activities, over relationships, over self-care routine and over work status[37]. The disability due to pain is highly prevalent over chronic pain disorders and age. Psychiatric factors, such as anxiety, depression and pain

catastrophizing, are associated with disability[38]. Besides, this functional impairment seems to be more severe among FM patients when compared with other chronic medical conditions[39].

Furthermore, it is known that FM patients have sleep issues such as reduced sleep duration, poor sleep quality and sleep disturbances, and it can exert some influence on pain perception, disability due to pain, depressive symptoms and quality of life. In our sample, we observed that reduced sleep duration plus disability due to pain can significantly influence the severity of depressive symptoms, and, interestingly, the use of SSRI also helps to explain this augmented result. This conclusion might be elucidated by the severity of physiological dysfunction over this population and the need of NE reuptake inhibitors to control FM symptoms.

This study presents some limitations, further randomized double-blind controlled trials should compare the non-inferiority of fluoxetine combined with TCA with the duloxetine. The relevance to testing this combination is to produce evidence for their widespread prescription based on the specialist indication by the restriction of drugs in the public health system.

Conclusion

Thus, both reduced total sleep time and augmented functional disability due to pain can influence the presence of depressive symptoms in this population as well as the use of SSRI and our findings suggest that the use of SSRI can be a protective factor to FM patients with severe depressive symptoms and it can be a treatment option in FM.

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