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Sexual dysfunction in patients with MDD treated with SSRIs - causes, measurement and prevention

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Abstract

Major Depressive Disorder(MDD) is serious psychiatric condition and they affect one in five people during their lifetime, the annual prevalence rates for the US population are 7.1% among adults, slightly more common among women (8.7%) than men (5.3%). Selective serotonin reuptake inhibitors are among the pharmacological agents most commonly used in the treatment of MDD.
The mechanism of action of antidepressants is not yet fully understood. Currently, it is believed that the mechanism of the so-called down-regulation, i.e. reducing the density of receptors in the postsynaptic membrane, in this case mainly 5HT2 receptors. All of the antidepressants in use today have some common side effects. The side effect that will be discussed in the broadest possible way in this paper are sexual dysfunctions appearing during the therapy. Measuring the degree to which a given substance affects the sexual function of a patient diagnosed with MDD encounters many difficulties on its way. There are currently several questionnaires enabling such an assessment, the most common are CSFQ, ASEX and SexFX. Also the major problem is Post SSRI Sexual Disfunction. A number of animal studies have proven that prolonged exposure to SSRIs leave permanent changes in the CNS, but unfortunately, similar studies have not yet been conducted in humans. The aim of this study is to present the problem of sexual dysfunction as a side effect of SSRI therapy, to present the causes and to propose a strategy to combat SSRI-induced sexual dysfunctions.

Key words: Sexual dysfunction; Depression; MDD; SSRI

Admission

Depression is defined as a group of mental disorders. This name refers to the depressive symptom complexes that occur in the course of affective disorders.

The symptoms of depressive syndromes include, first of all, depression manifested by depression, low self-esteem, low self-confidence, unjustified sense of guilt, inability to experience pleasure (anhedonia). Some patients also suffer from disturbances in the circadian rhythm - depression may result in both insomnia and excessive sleepiness. In extreme cases, recurrent suicidal thoughts are also reported.[1]

Major Depressive Disorder (MDD) affects one in five people during their lifetime, with annual prevalence rates in the US population of 7.1% among adults, slightly more common among women (8.7%) than men (5.3%). The group of adults in which the most frequent episode of MDD occurs are people aged 18-25 (13.1%).[4] It is worth noting that depression rarely occurs without the presence of comorbidities, and is often associated with chronic diseases, as well as with other mood disorders, such as comorbid anxiety.[6] It is estimated that only 50% of patients respond to available treatment.[5]

There are several models explaining the mechanisms of depression. neuroanatomical, biological, psychodynamic and cognitive-behavioral models. [1] [2]

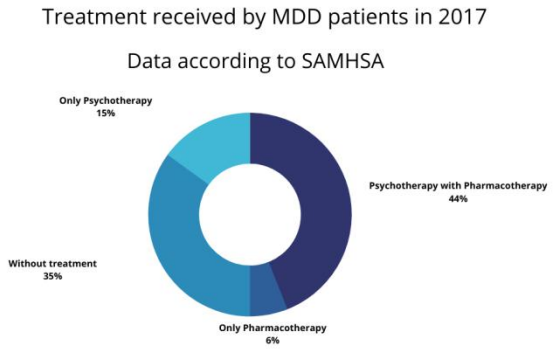
The psychodynamic model assumes that the underlying causes of depression are the mental conflicts between impulses, aspirations, desires, and deficits in mental functions. These deficits most often result from experiences during the development period.[34] The cognitive-behavioral theory, in turn, assumes that the depressed person has acquired cognitive maladaptive patterns and inadequate response patterns. He recognizes that they can be changed through the learning process, this theory finds its application in therapeutic practice, but it does not explain many somatic symptoms of depression and its accompanying biochemical phenomena.

According to the biological model, neurotransmission disorders in the central nervous system lie at the root of the occurrence of depressive disorders. The major role is played by disturbances in serotonin, norepinephrine and, to a lesser extent, dopamine-dependent transmission. This hypothesis is supported by numerous studies using antidepressants such as serotonin reuptake inhibitors (SSRI), norepinephrine (SNRI) and / or dopamine. [3]

Treatment of MDD

According to the data for 2017, of the total number of patients diagnosed with MDD, 35% did not receive any of the forms of treatment, 15% received psychotherapy, 6% received pharmacological treatment, while the largest

proportion - 65% of patients used both combined forms of treatment therapy.[10] [Dig.1]



Selective serotonin reuptake inhibitors are among the most commonly used pharmacological agents in the treatment of MDD. This group of drugs, introduced in the 1980s, shows the highest efficacy in combating MDD episodes, remaining in the group of first-choice drugs, demonstrating higher efficacy than amine monoxygenase inhibitors used with less frequency.[7] The mechanism of action of antidepressants is not yet fully understood. The therapeutic effect is not strictly induced by the increase in neurotransmitter concentration as it might initially appear. The argument for the fact that other factors are also important is the fact that despite the relatively short time from taking drugs to the increase in amine levels in the synaptic clefts, the clinical effects do not appear immediately, but over a longer period of time, i.e. 2-3 weeks. Currently, it is believed that the mechanism of the so-called down-regulation, i.e. reducing the density of receptors in the postsynaptic membrane, in this case mainly 5HT2 receptors.[9]
The SSRI group includes, among others citalopram, paroxetine, fluvoxamine, setraline, and fluoxetine (the most widely used antidepressant in the world). [9]

Side effects of antidepressants

All of the antidepressants currently in use have some common side effects, which vary in severity depending on the group. These are i.a. dry mouth due to anticholinergic effects, confusion, dizziness, insomnia, tachycardia, gastrointestinal disturbances, and sometimes hepatotoxic effects.[9] Another side effect, which will be discussed in the broadest possible way in this paper, is sexual dysfunctions appearing during therapy. In the light of recent meta-analyzes, among the drugs that can induce this type of disorder, agents affecting serotonin are of particular importance. For example, with an overall rate of sexual dysfunction attributed to antidepressant drugs of 40%, it was 2% of patients taking bupronion, compared with 98% of those taking citalopram. [12] This fact directs further considerations towards drugs with a serotoninergic profile of action. The problem of sexual dysfunction resulting from antidepressant therapy is even greater as it does not only affect the patient's quality of life, but causes the patient to abandon the therapy. According to one study conducted by Rosenberg at the Cornell Medical Center in New York, sexual dysfunction was at the root of decisions to discontinue treatment in 15% of patients, making it the most common cause of treatment discontinuation. Equally striking is the fact that half of the respondents did not discuss the quality of sexual life with the doctor conducting the therapy. [11] This fact is also confirmed by previous studies by S. Bula and X. A. Hu. [35, 36]
The mechanism responsible for the disorder is the increase in serotonin concentration in the cortico-limbic synaptic spaces. Moreover, the overall decrease in dopaminergic conductivity and the reduction of nitric oxide synthesis in the course of treatment also undoubtedly affect sexual function. Summing up the above mechanisms, one should take into account disruptions in several areas, including the occurrence of sexual arousal, the course of an erection and reaching orgasm.

Assessment of the severity of sexual disorders

The measurement of the degree to which a given substance affects the sexual function of a patient diagnosed with MDD encounters many difficulties on its way. The first of them is the fact that certain disorders, as well as a reduced frequency in the field of sexual life, may be

caused by the presence of depressive disorders themselves. Moreover, depression rarely occurs without other comorbidities. [1] An important fact in this aspect is, for example, the increased risk of metabolic syndrome in the course of depression, which often significantly reduces the quality of sexual life. [14] Another factor is the increased risk of substance abuse and addiction in this group of patients, which undoubtedly also affects the quality of their sex life. [15] In the light of the above information, it is obvious that a thorough examination in this area should include the measurement of the degree of sexual dysfunction before starting pharmacotherapy and monitoring its changes in the course of treatment. In order to evaluate these variables, scales are needed to provide an assessment by patients of the quality of their sex life in a way that enables comparisons to be made with groups treated with other agents or with a placebo group. There are currently several questionnaires enabling such an assessment, the most common are CSFQ, ASEX and SexFX. [16], [17] Each of the questionnaires has its own specificity and focuses on a different aspect of the study of functions. Of these, the SexFX questionnaire stands out. While the remaining questionnaires mainly measure subjective quality of life, the scale first takes into account the frequency of sexual experiences in terms of the occurrence of desire, sexual arousal and orgasm over time, which makes it the most reliable in research on the side effects of pharmacotherapy. [17] The ASEX scale was designed for similar purposes, but it has some drawbacks, for example it does not report pain or sexual stress. [18]

Sexual dysfunction induced by SSRIs and genetic markers

For some time, genetic sequences that can modulate the body's response to SSRIs have been an additional factor in studies measuring the relationship between SSRI treatment and the occurrence of sexual dysfunction. The first such studies appeared as early as 2009, it was hypothesized that the development of sexual disorders during treatment with drugs from the SSRI group depends on changes in the serotonin transporter gene - SCLA4 [19]. In the following years, studies were also carried out on the 5-HTTLPR gene, which showed that the deletion or insertion of 44 pairs in the promoter region is important in the context of the course of therapy and exposure to side effects. It was shown that carriers of the longer allele show a better response to treatment with an increased risk of sexual dysfunction. [18] Another significant marker in the context of the impact of SSRIs on sexual dysfunction is the variability in the range of ACBC1 gene variants of unknown function, and more precisely its rs1128503 variant. In one study conducted at the University of Michigan by Michel Bly on a group of 82 people diagnosed for an episode of depression according to The Hamilton Scale, taking fluoxetine, who had no evidence of sexual dysfunction prior to treatment initiation, was re-measured by CSFQ after treatment initiation. A significant correlation was found proving that people with the rs1128503 variant of the ACBC1 gene (possible TT, TC, CC variants) were more susceptible to sexual dysfunction than people with the CC allele. [20] Another factor taken into account in the studies were single-nucleotide polymorphisms in genes encoding glutamate receptors, the effect of which on depressive disorders was confirmed in previous studies [21]. In one of the studies carried out on a group of 114 patients treated with fluoxetine (n = 11), citalopran (n = 14), paroxetine (n = 25), fluoxetine (n = 28) and escitalopram (n = 36), the impact of GR1K1, GR1A1 and GR1A3 gene variants on sexual dysfunction was analyzed. Despite the initial lack of correlation, secondary analyzes showed that the common polymorphism of the rs 1994268 variant in the GR1A1 gene is associated with sexual dysfunction in patients receiving SSRIs due to depression [22]. These results undoubtedly lead to an increase in the share of personalized medicine in the treatment of depression. However, they should be interpreted with a certain degree of caution until they are confirmed in larger, better differentiated groups of respondents.

The prevalence of sexual dysfunction and the type of SSRI taken

An excellent source of knowledge about the side effects of pharmacotherapy is RxISK, an independent internet portal, created in 2012 and since then collecting information about all available drugs and their side effects. In 2013, the portal published series of articles on sexual dysfunctions in the course of treatment with SSRIs, finasteride and retinoids, which resulted in an interest in the subject and an increase the number of submitted reports. The substantive value of the reports is ensured by a series of structured questions that must be answered by each respondent reporting a side effect. Metrics, medical history as well as confounding factors (pregnancy, smoking, long-term use of other psychoactive substances) are considered. The cause and effect relationship between the measure and the side effect is also analised []. 3033 reports of adverse events resulting from pharmacotherapy have been filed in the RxISK database, of which 300 relate to sexual dysfunction.

Most of the cases (72%) are related to the use of SSRIs. Among them there are reports on the use of various funds belonging to this group, including Paroxetine, Setraline, Fluoxetine, Escitalopram, Citalopram, Vanflexin and Fluvoxamine. The largest number of reports of all SSRIs is related to Citalopram and its enantiomer Escitalopram (40% of reported cases). This is at least thought- provoking fact because these drugs do not belong to the most commonly used SSRIs.

Post SSRI Sexual Disfunction

A number of animal studies have shown that prolonged exposure to SSRIs leave permanent changes in the CNS, unfortunately, similar studies have not yet been conducted in relation to humans. [23][24]

In one of the studies, conducted by Dawid Healy, patients associated in an online community of people complaining about sexual dysfunctions remaining after the end of therapy were taken into account. 120 patients who used RxISK to submit the report were selected from the group

In each of the analyzed cases, the reported symptoms included: orgasm delay, lubrication disorders in women, and decreased skin sensation in the genital area. [25] The last-mentioned symptom seems to be the most significant factor as it may lead to other disorders in the sexual sphere. Despite the lack of hard evidence, the most probable hypothesis seems to be that increasing the concentration of peripheral serotonin impairs the nerve endings, which is most evident in the region of the labia and peroneal nerve endings, which are most involved in the genital area innervation. [26] However, the interest in the presence of PSSD (Post Traumatic Stress Disorder) in professional environments seems to be insufficient. In one of the psychological studies conducted by the Netherlands Pharmacovigilance Center, involving a small group of patients with previously completed SSRI therapy, patients admitted that they felt a lack of interest and a deficit of care from the medical community. This fact is more striking in view of the fact that there are well-documented cases of individuals suffering from persistent dysfunction after the end of therapy who have committed suicide [27] .This underlines the importance of caring for patients also after successful therapy, as the above-mentioned examples show that the side effects of treatment can lead to consequences identical to those that the therapy was intended to prevent.

Strategies for combating SSRI-induced sexual dysfunction

In recent years, a number of studies which focus on the possibilities of preventing or reducing the size of adverse events resulting from SSRI therapy have been published. Pharmacological strategies are worth presenting, as well as general observations of the course of treatment and doctor-patient communication, the improvement of which would give a chance to reduce the frequency of the phenomenon. Pharmacological strategy studies have tested the use of testosterone, bupropion, and $5HT_2$ and

$5HT_3$ agonists. [28] [29] [30] In the case of bupropion, the action is based on increasing the secretion of dopamine, which has beneficial effects in fighting sexual dysfunction. In one of the studies conducted by E. Fooladi, the use of 150 mg of the sustained-release agent was tested twice a day on a group of 42 patients. Improvement of sexual function in the field of desire and orgasm, compared to the placebo group, was observed after 4 weeks of treatment. [28] A similar effect may be caused by other agents affecting the level of dopamine, e.g. methylphenidate and dectroamphetamine. [30] Another strategy that does not come without side effects is to alter the agonism of 5HT receptors. One of the curative from this group with clinically proven action is Mitrazepine [33] but its use is associated with uncontrolled weight gain, [32] which significantly limits its potential. Another solution is the use of the $5HT_{2A}$ receptor antagonist - cyproheptadine, however, it is associated with sedation occurring in the course of treatment. [31] In women with PSSD (Post Traumatic Stress Disorder), 12 weeks of therapy with testosterone patches at doses of 300 micrograms clearly increase the number of sexually satisfactory experiences. The effectiveness of the therapy was confirmed in a study conducted on a group of 44 women, including 10 postmenopausal women. [28] Unfortunately, drugs containing testosterone are not approved for use by women in many countries, which limits the versatility of this solution. The strategy with the lowest risk of additional side effects is the replacement of SSRIs with viladazone, which is also a serotonin reuptake inhibitor, and an agonist of the $5HT_{1A.,}$ receptor, which in studies on rats did not show the potential to induce sexual dysfunction.[33]

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