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A Review of Recent Reports on the Role of SSRI Use in Understanding the Pathomechanism and Treatment of Premenstrual Syndrome (PMS) as a Significant Clinical and Health Problem in Reproductive-Age Women

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ABSTRACT

Introduction. PMS affects 47% of women of reproductive age. It is a cyclical disorder responsible for somatic or mental symptoms during the luteal phase of the menstrual cycle. Etiology includes hormonal changes, GABA-A conduction disturbances, inflammation, genetic factors, and lifestyle. SSRIs are first-line medications used to treat severe PMS. Awareness of the pathomechanisms of the disease and the effects of treatment will allow us to better understand it, effectively treat it and minimize negative social and family consequences.

Aim of the study, Discussion of the mechanism of action of SSRIs, with particular emphasis on more recent reports on the etiology and treatment of PMS in women of reproductive age.

Materials and methods. A systematic review of the PubMed database from the last decade was conducted using the following keywords: PMS, PMDD, SSRI, allopregnanolone. Pediatric studies were excluded.

Conclusions. SSRIs have a favorable safety profile, few adverse events, are effective at low doses with continuous and intermittent administration, and have a short half-life. The best-studied SSRIs to date are sertraline and fluoxetine, which have a beneficial effect on

allopregnanolol levels and GABAergic conductance, as well as serotonin levels, which directly translates into a reduction in PMS symptoms in women of reproductive age. However, further research is needed to fully understand and utilize their mechanism of action in the symptomatic treatment of PMS.
Keywords: PMS, PMDD, SSRI, allopregnanolone

INTRODUCTION

More than half of women of reproductive age experience dysphoric or physical symptoms approximately 2 weeks before their expected menstruation.

Premenstrual syndrome (PMS) is a cyclical disorder in menstruating women, responsible for somatic or psychological symptoms, appearing in the luteal phase of the cycle, which may begin just after ovulation, i.e., up to 14 days before the expected period, and resolve by the 4th day of menstruation at the latest. Estimates suggest that it affects up to 47.8% of the population of women of reproductive age [1], while the most severe form of PMS in the form of PMDD – premenstrual dysphoric disorder – may affect up to 3–8% of women, making it a significant problem in society. [6]

PMS covers a wide range of symptoms, as many as 300, the most frequently mentioned of which are: mental symptoms include mood swings, lethargy, irritability, low mood, feeling of loss of control over the situation, anxiety, and physical symptoms: mastodynia (swelling and tenderness of the breasts), flatulence, digestive disorders, headaches with migraine-like features, and behavioral disorders include: a reduction in the ability to analyze visuospatial and cognitive abilities (2,3,4)

PMDD – premenstrual dysphoric disorder– is a more severe form of PMS. Its detection requires identifying at least 5 of the 11 listed symptoms in 2 consecutive cycles. The assessment may be extended to cycle 3 when symptoms from previous cycles are divergent. [6]

These symptoms include:

1) significant low mood, feeling hopeless, and lacking self-acceptance;
2) increased anxiety levels, increased tension, increased sensitivity
3) significantly affects instability;
4) persistent increased feelings of anger or increased irritability;
5) reduced interest in daily activities;
6) subjective feeling of difficulty concentrating;
7) lack of enthusiasm, easy fatigue;
8) overeating or bouts of uncontrollable hunger;

9) excessive sleepiness or insomnia;

10) feeling subjectively out of control or overwhelmed;

11) physical symptoms such as: breast tenderness, headaches, muscle or joint pain, feeling bloated, weight gain [24]

ETIOLOGY OF PMS AND PMDD

The etiopathogenesis of PMS and PMDD is not yet fully understood. There are several theories explaining the causes of symptoms in both disorders.

It is assumed that the classic symptoms of PMS are related to hormonal disorders appearing in the second phase of the cycle, related to the levels of estrogen and progesterone, which most often manifests itself as a deterioration of mood and an increase in anxiety [1] The levels of neurotransmitters such as serotonin, gamma-aminobutyric acid (GABA), glutamate, and even beta-endorphins may also be responsible for the symptoms of PMS. Nutritional deficiencies are also an important aspect, as they have shown an association between too high or too low weight and the occurrence of PMS in young women. Attention was also paid to dietary composition, as well as eating patterns and behaviors, in the etiology of PMS. [6]

Genetics

PMDD is assumed to have a heritability of 30–80% [5].

Dysregulation in the serotonergic system

It is among the probable causes of PMDD. A PET study showed that the availability of the serotonin 1A (5-HT1A) receptor in the brainstem increases in control subjects, whereas it does not increase in women with PMDD. This significantly explains the effectiveness of SSRIs in the treatment of PMDD [7]

Allopregnanolone

In recent times, there have been many mentions of its impact on PMS and PMDD. Allopregnanolone is a neuroactive metabolite of progestogen, acting as a neuromodulator in GABA-A (receptors found primarily in the amygdala, where they help regulate emotional responses). In women with PMS/PMDD symptoms, an increase in allopregnanolone levels during the luteal phase causes a change in the conformation of the GABA-A receptor, leading to a paradoxical decrease in GABA conductance under the influence of allopregnanolone, which is not observed in women not experiencing PMS symptoms. [1,7,8]

Reduced levels of allopregnanolone, which is an agonist of GABA-a receptors, together with a decrease in the concentrations of hormones – progesterone and estrogen in the luteal phase of the cycle, induce secondary aldosteronism, through an increase in the volume of extracellular

fluid and changes in the renin-angiotensin system. This results in symptoms such as swelling, bloating, breast swelling, and mood, cognitive and behavioral disorders. [31]

Stress

Chronic stress in the body has been a topic of discussion for years regarding its role in the development of PMS/PMDD. One study of almost 4000 women found an association between traumatic experiences and PTSD and the occurrence of PMDD [10]. Numerous studies have shown a strong correlation between PMS/PMDD and stress. Their results indicated a significantly higher stress index in women experiencing PMS symptoms than in those in whom these symptoms were not observed. [11]

Inflammation

Recently, there has been a significant increase in interest in an overly exaggerated immunoinflammatory response to the presence of PMS/PMDD. Progesterone and estradiol levels in the late luteal phase show a decreasing trend. This decrease leads to the development of increased oxidative stress in the endometrium, which increases the synthesis of proinflammatory prostaglandins, chemokines, cytokines, and matrix metalloproteinases.[12]

TREATMENT OF PMS/PMDD

Due to its multifactorial etiology, treatment should be holistic and include both pharmacotherapy and non-pharmacological interventions. The following are distinguished:

Pharmacological treatments

- SSRI/SNRI antidepressants
- hormonal treatment
- contraceptive treatment
- treatment with GnRH agonists
- vitamin supplementation (Zinc, vitamin D, calcium, vit. From group B, Magnesium)

Non-pharmacological treatments

- cognitive behavioral therapy (CBT),
- regular physical activity,
- anti-inflammatory diet,
- herbal preparations (curcumin, saffron)
- acupuncture
- surgical methods

SSRIs are the first-line therapy for severe PMS [17], while non-pharmacological methods such as proper diet, exercise, CBT therapy, and the use of vitamins and herbal supplements may be

effective in relieving PMS symptoms in some women or provide an excellent alternative to supplementing pharmacological therapy. [25,26] There are also studies that demonstrate the effectiveness of acupuncture in relieving the symptoms of PMS by affecting the amygdala, but the mechanisms behind it are still unclear and require further research on this topic. [27] Surgical methods such as hysterectomy combined with bilateral removal of the ovaries and fallopian tubes appear to be very effective, but they have long-term consequences, including infertility and premature menopause. Less invasive methods include thermal endometrial ablation. This demonstrates the wide range of possibilities that can be used to treat the symptoms of PMS and how much remains to be done in fully understanding the mechanisms responsible for the development of symptoms and treatment options in premenstrual syndrome.

PHARMACOTHERAPY – SSRIs AS A FIRST-LINE TREATMENT

The latest guidelines of The Royal College of Obstetricians and Gynaecologists state SSRIs as first-line pharmacotherapy for severe PMS [17] They are highly effective in treating symptoms such as irritability and anxiety characteristic of PMS [19] Furthermore, numerous studies on the use of SSRIs in the treatment of PMDD have shown a reduction in symptom severity in 60 to 90% of patients with PMDD, with a range of 30-40% compared to placebo. [16]

SSRIs currently belong to the first-line pharmacological treatment. Many studies have been written about them, but the latest research indicates a broader model of their action, especially considering the role of allopregnanolone in premenstrual syndrome. In the classic use of SSRIs in the treatment of affective disorders, the therapeutic effect is achieved approximately 3-4 weeks after the start of treatment, while in the treatment of PMS/PMDD symptoms, the therapeutic effect is noticeable 3-4 days after the start of therapy. This indicates a different mechanism of action of these drugs when treating PMS symptoms than previously thought. [1] There are several hypotheses for their faster effectiveness in relieving the symptoms of PMS/PMDD than in classical use in psychiatric treatment. One of them is reduced serotonin concentration in peripheral blood in women with PMS during the luteal phase of the menstrual cycle [13]. SSRIs increase serotonergic neurotransmission by increasing serotonin concentration in the synaptic cleft [14,22]. Furthermore, recent studies have shown a correlation between increased serotonin uptake in the premenstrual period and the occurrence of PMDD symptoms in women. It has also been shown that the occurrence of depressive symptoms is closely correlated with an increase in the number of serotonin transporters in the body. These reports indicate that changing serotonin levels in extracellular sources may be key in alleviating PMS/PMDD symptoms [15]

Another hypothesis influencing the good effects of treatment with SSRIs is their probable influence on the simultaneous effect on serotonin receptors and an increase in the level of allopregnanolol in the brain, which indirectly influences the modulation of the function of GABAA receptors by strengthening their function, which actually translates into the relief of anxiety [9, 16, 17]

The rapid action of SSRIs in individuals with PMDD may also be related to the influence of 5-HT receptors on allopregnanolol levels in the brain, which indirectly contributes to modulating the function of GABAA receptors [15]

The advantage of SSRIs is the ability to select a treatment method for a patient without comorbidities, her lifestyle and her individual experiences of side effects or doctor preferences [20] because thanks to their rapid action they allow their use continuously or sporadically – only in the luteal phase. [17] It is certain that taking SSRIs periodically only during the luteal phase helps avoid the withdrawal syndrome associated with long-term antidepressant use. [18]

An important aspect to remember when treating continuous SSRIs is the need to gradually discontinue them to avoid the risk of side effects such as nausea or weakness. [18]

In the treatment of PMS/PMDD, the choice of drug should be selected according to the individual needs of the patient, her clinical situation, lifestyle and expectations, so as to minimize the risk of adverse drug reactions as much as possible. According to Marjorbanks et al., the entire SSRI group can be used to treat the symptoms of premenstrual syndrome [19], while the most common drugs in the literature for the treatment of PMS are fluoxetine, sertraline, paroxetine, citalopram, and escitalopram, of which the FDA has approved the first three, i.e., fluoxetine, sertraline, and paroxetine. [13]

Low doses of SSRIs are typically used to treat PMS/PMDD. There are several available schemes for their adoption:

1. Continuous regimen – taking the drug throughout the menstrual cycle at a constant dose.

2. Intermittent (luteal) regimen – use only during the luteal phase, from ovulation (or approximately 14 days before expected menstruation) to the onset of bleeding.

3. Semi-intermittent regimen – administration of a lower dose in the follicular phase, with its increase in the luteal phase.

4. Regimen „symptomatic" (on-demand) – initiation of therapy with the appearance of the first symptoms of PMS and continuation until the first day of menstruation [20].

In available studies, drug selection criteria were most often similar. They were concerned patients with known symptoms of PMS/PMDD, without known psychiatric diseases, aged 18

to 45 years, with regular menstrual cycles (lengths from 22 to 35 days), with a high probability of ovulation.

The most common side effects of SSRIs in the treatment of PMS/PMDD include fatigue, nausea, insomnia, decreased libido, dizziness, increased sweating, decreased energy or dry mouth, as well as diarrhea and constipation. Of these, fatigue, nausea, insomnia, and decreased energy were the most frequently reported adverse symptoms compared with the placebo group. [20]

SERTRALINE

Sertraline is one of the better-studied drugs belonging to the SSRI group, which, according to the latest guidelines of The Royal College of Obstetricians and Gynaecologists, is the first-line pharmacotherapy for severe PMS [17]. Additionally, it is one of 3 drugs approved for the treatment of PMS by the FDA. [13]

A 2024 study investigated whether sertraline administered during the luteal phase in women with PMDD had an effect on the hypothalamic–pituitary–adrenal axis and the concentration of its hormones or immunological markers. It was shown that sertraline used in the luteal phase caused an increase in allopregnanolol levels, which in turn predicted a lower cortisol peak. Furthermore, higher levels of the chemokine CXCL-8 were found to be associated with greater presentation of PMS symptoms. [21]

This can be understood to mean that sertraline treatment corrects interactions in the HPG-HPA axis (hypothalamus – pituitary – gonads and the hypothalamic – pituitary – adrenal axis), making the HPA axis more susceptible to allopregnanolone. This is subsequently associated with reduced peak cortisol and better control of HPA axis function [21]

The latest study conducted by the team on 35 control subjects and 27 women with PMDD (Miller et al., 2024) showed that the use of sertraline in people with PMDD significantly increased the level of the neuroactive steroid GABAergic – pregnanolone in the luteal phase, and a significant increase in the ratio of allopregnanoolol to progesterone levels and a decrease in 3α,5α-androsterone levels were observed. Researchers found no significant differences in neuroactive steroid levels between controls and participants with PMDD when not taking sertraline during the luteal phase [22]

A 2021 study examined the effect of sertraline on reducing anxiety-potentiated surprise in premenstrual dysphoric disorder. They concluded that women suffering from PMDD and responding to sertraline treatment have increased psychophysiological arousal during the luteal phase. This suggests that modulation of arousal reactivity is more difficult. On this basis, it can

be concluded that there is a disturbance in the functioning of GABA-AR receptors in the population of women with PMDD who responded to sertraline [23]

In his work from 2024, Jespersen et al. report that SSRIs, including sertraline, are highly likely to be effective in reducing overall self-assessment of premenstrual symptoms in women with PMS and PMDD. [20]

FLUOXETINE

According to Maranho et al., in their preclinical studies, low doses of fluoxetine may cause increased allopreganolone concentrations in the brain. Furthermore, low doses of fluoxetine likely have little or no effect on the serotonergic system, while also having the ability to interfere with progesterone metabolism, making them appear to have the potential to alleviate PMS symptoms. According to Maranho, 10mg/day of fluoxetine best alleviated the emotional symptoms of PMS, while a dose of 5mg/day also seemed to have some effect. The researchers in this study concluded that administering fluoxetine during the luteal phase of the cycle, approximately 7 days before the scheduled menstrual date, had the most beneficial effect, reducing symptom severity by 40% in approximately 70% of the women studied, compared with the placebo group. [28]

A 2025 study examining intermittent fluoxetine in premenstrual dysphoric disorder proposed that fluoxetine slows estrogen degradation in the late luteal phase, increasing estrogen levels and thereby reducing PMDD symptoms. This study hypothesized the use of potent CYP3424 inhibitors that do not have an anxiolytic depressant effect to better understand the mechanism of fluoxetine's rapid action and, in the future, perhaps find a variant for treatment with non-SSRI drugs for women who cannot tolerate SSRI treatment. [29]

ESCITALOPRAM

In their work, Gröndal M. et al. confirmed, in line with previous reports, a significant reduction in self-assessed irritability and anger during the luteal phase in women using escitalopram, as well as a higher level of urgency and a lower level of sensation-seeking during the luteal phase compared to the follicular phase of the menstrual cycle. [30]

SUMMARY AND CONCLUSIONS

Premenstrual syndrome (PMS) is a significant problem in society, affecting up to 47% of the population of women of reproductive age. It is a cyclically recurring disorder in menstruating women, responsible for somatic or mental symptoms that appear during the luteal phase of the

cycle. The etiology of PMS is not fully understood, but its development is characterized by multiple components, including dysregulation of the serotonergic system, the effect of allopregnanolone on GABA-A neuromodulation, and the presence of chronic inflammation, genetic factors, and lifestyle factors. There are many treatment paths for premenstrual syndrome. Pharmacological treatment can be distinguished, which includes SSRI/SNRI antidepressants, hormonal treatment, contraception, GnRH agonists, vitamin supplementation, as well as non-pharmacological treatment, which includes cognitive behavioral therapy (CBT), regular physical activity, an anti-inflammatory diet and herbal preparations. The use of SSRIs as first-line therapy for PMS is undoubtedly effective in relieving symptoms, but it should be remembered that this is a complex syndrome that pharmacotherapy alone will not solve the problem. To achieve the highest possible treatment effectiveness, a holistic approach to the problem should be used, including pharmacotherapy and non-pharmacological methods such as psychotherapy, acupuncture, lifestyle changes by increasing physical activity and incorporating an appropriate diet. The choice of drug delivery mechanism is certainly a major advantage of SSRIs, allowing us to tailor the drug to the patient's lifestyle, how she feels while taking the drug, reported side effects, and comfort. SSRIs are among the most studied drugs in the symptomatic treatment of PMS/PMDD. They have a relatively favorable safety profile, relatively few reported side effects, and are effective even at low doses. Many of the most recent reports on the use of SSRIs in the treatment of PMS are based on the hypothesis of the involvement of allopregnanolone and its concentrations in the development of PMS symptoms. Of the latest reports on sertraline, the most relevant is its positive effect on allopregnanolone levels during the luteal phase of the cycle, which in turn translates into lower cortisol levels and is consistent with lower stress levels in women experiencing PMS symptoms. It is also worth noting reports regarding the involvement of GABAergic receptors in response to sertraline and, thus, allopregnanolone levels in women experiencing symptoms of premenstrual syndrome. Recent work on fluoxetine also shows a positive effect of its use on allopregnanolone levels, even at low doses. Additionally, the researchers concluded that the intermittent fluoxetine regimen is most beneficial in alleviating PMS symptoms in women. In the case of escitalopram, a new study was conducted that confirmed its effect in reducing feelings of anger and showed a higher level of urgency in the studied women suffering from PMS. The above reports show that we still do not know the exact mechanism of action of SSRIs and the etiology of PMS symptoms in women during the reproductive period. However, recent reports on allopregnanolone and its effects on women's menstrual cycles offer great hope for an even better understanding of this problem than before. The topic of premenstrual syndrome, although long

known and researched, still requires further research as it is a significant health and social problem, still affecting approximately 50% of women of reproductive age worldwide.

Supplementary materials:

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