How does PMDD's neurological basis explain why its treatments are effective?

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Abstract

Premenstrual Dysphoric Disorder (PMDD) is a severe mood disorder characterized by intense emotional and physical symptoms during the luteal phase of the menstrual cycle. It affects an estimated 3-8%, or an estimated 50-140 million, of women of reproductive age globally. Notably, PMDD is not caused by an abnormality in hormone levels; rather, it is caused because the brain is overly sensitive to a woman's regular hormonal fluctuations. This paper examines how existing PMDD treatments—including hormonal contraceptives, selective serotonin reuptake inhibitors (SSRIs), and GABA-A receptor- and neurosteroid-targeted drugs—address its underlying mechanisms, including GABA-A receptor plasticity dysfunction, amygdala hyperreactivity, and serotonin transporter irregularities. Using a synthesis of neurobiological and clinical research, this paper finds that treatments intervening directly in these mechanisms, particularly SSRIs, show more consistent evidence than hormonal suppression alone, while the newer GABA-A and neurosteroid-targeted drugs are promising but need more testing. PMDD is complex to diagnose, but its cyclical timing and severity set it apart from other mood disorders or premenstrual symptoms. Understanding that PMDD is a distinct neurobiological condition, rather than a normal physiological reaction to hormone changes, is crucial for women to be accurately diagnosed and treated.

Introduction

Each month, the menstrual cycle is driven by a series of coordinated hormonal shifts, working to prepare a woman's body for ovulation and potential pregnancy. Throughout the four phases–menstrual, follicular, ovulation, and luteal–levels of hormones like estrogen and progesterone fluctuate (1). When these hormones peak in the luteal phase, they can be accompanied by premenstrual symptoms. Many women experience physical and emotional symptoms leading up to menstruation, known as Premenstrual Syndrome (PMS). However, for a smaller subset of women, these symptoms are more severe, directly impacting daily function and well-being. On top of physical symptoms such as bloating, aches, and digestive changes, these more severe cases can involve emotional instability, irritability, depressed mood, anxiety, diminished interest in daily activities, difficulty concentrating, fatigue, changes in appetite and sleep, and feelings of being overwhelmed (2). These intense emotional lows and physical symptoms, which can interfere with work, school, relationships, and everyday social interactions, characterize Premenstrual Dysphoric Disorder (PMDD).

PMDD is a severe condition affecting 3-8%, or an estimated 50-140 million, of women of reproductive age globally (2). After originally just appearing in the appendix of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) for further study, PMDD gained formal diagnostic recognition in the fifth edition (DSM-5) in 2013, where it was classified as a depressive mood disorder (3). This recognition established PMDD as distinct from other menstrual-related conditions, emphasizing the severity of its emotional symptoms during the luteal phase and impact on daily functioning. While some may have assumed that hormonal

issues may be to blame, research indicates that affected individuals generally have typical hormone levels, but exhibit heightened sensitivity to hormonal changes during the luteal phase, particularly fluctuations in progesterone (P4) and neurosteroids such as allopregnanolone (ALLO) (4).

Understanding that PMDD is a distinct neurobiological condition, rather than a normal physiological reaction to hormone changes, is crucial for women to be accurately diagnosed and treated. Despite its overwhelming symptoms, PMDD remains relatively understudied and severely underdiagnosed due to confusion surrounding where PMS ends and PMDD begins (4). Physically and emotionally, PMDD is described as a more extreme form of PMS (5), but because of various overlapping symptoms, many women dismiss their suffering as typical premenstrual symptoms. Since premenstrual symptoms are often brushed to the side as normal, many women do not know this diagnosis exists, or that they are able to get treatment.

Hormonal contraceptives, which suppress ovulation and stabilize hormonal shifts, are routinely prescribed for various menstrual issues. But, for symptoms this severe, with women falling into emotional crises, birth control may not be addressing PMDD in the most effective way, and other treatments may better target its roots. By understanding what is happening in the PMDD brain, the treatment options become clearer. Misunderstanding the neurological basis of PMDD can leave millions of women untreated. This paper explains the neurological mechanisms behind PMDD in order to understand how treatment can be addressed effectively, explaining how women can get the best treatment possible.

Differences in the PMDD Brain

While general premenstrual symptoms and PMDD are both triggered by hormonal fluctuations, the differences appear when looking at how the brain responds to them. Research points to several neurological differences in PMDD, including the brain's failure to adapt to changing neurosteroid levels (2), heightened activity in the amygdala (6), and an abnormal serotonin response during the luteal phase (7).

The emotional symptoms associated with PMDD are linked to the brain's hypersensitivity to stress, caused by a subsensitivity to neuroactive steroid hormones (2). Neurosteroids are hormones produced in the brain by neurons and glial cells that typically fluctuate across the menstrual cycle. The neurosteroid allopregnanolone (ALLO) is important to understand; the body breaks down progesterone into ALLO after ovulation, so the levels of ALLO mirror the rises and falls of progesterone (8), notably the sharp fall during the luteal phase. The role of ALLO is to boost the effect of GABA, a neurotransmitter that calms the body and brain by slowing down nerve cell activity. GABA works when it attaches to the GABA-A receptor, opening a channel to let chloride ions rush into the cell. This hyperpolarizes the cell, slowing the firing of the nerve's electrical signals, which calms the body. GABA-A receptors regulate this flow of ions by adapting in response to hormone changes throughout the cycle, which is known as plasticity (2). Effective plasticity matters because the receptor is able to adjust its calming response based on the shifts in ALLO. In PMDD, the receptor is not able to adapt normally. Research has found that when ALLO drops too quickly, the GABA-A receptor changes its subunit makeup, making it less sensitive, and in turn reducing the flow of chloride into the cell (2). An effective receptor would react to the lack of ALLO by shifting toward a subunit that increases its sensitivity (2). But in

PMDD, the receptor shifts to a subunit that is less responsive, reducing the calming effect from the chloride influx. As a result of this impaired receptor plasticity, the brain may struggle to regulate emotional changes, contributing to the emotional symptoms of PMDD.

Because the sharp decline of ALLO has such consequences, giving women more ALLO or progesterone could be a potentially effective treatment. But more research has found the emotional effects of ALLO are not limited to just low levels. Compared with the ALLO levels of a normal luteal phase, both higher and lower levels can trigger more severe emotional changes (2). These findings suggest that, rather than being an issue of low ALLO levels, PMDD may rather be an abnormal sensitivity at the receptor level. Since both unusually high and low levels of ALLO can worsen emotional symptoms, it points to a problem with the brain's ability to adapt to changing ALLO levels.

However, the brain is not just sensitive to that drop in progesterone. The amygdala, the brain region associated with emotional and social processing, is affected by the natural rise of progesterone after ovulation. Normally, the amygdala's activity is regulated through the prefrontal cortex, specifically the dorsolateral prefrontal cortex (dlPFC) and anterior cingulate cortex (ACC) (6). In women with PMDD, however, the amygdala becomes more reactive to emotional changes because communication with those areas is different. Using functional MRI (fMRI), one study compared 14 women with PMDD to 13 healthy controls during the follicular and late luteal phases. Only in women with PMDD did amygdala reactivity rise along with progesterone (6). This illustrates that the amygdala in women with PMDD is especially sensitive to the normal fluctuations of progesterone. This heightened reactivity may make it hard for emotions to be regulated and processed going into the luteal phase.

The same study also measured how activity in the amygdala and the prefrontal regulatory areas were connected, and found that this correlation was positive in women with PMDD but negative in healthy controls (6). In healthy controls, the negative coupling suggests the amygdala and regulatory regions counteract each other. In women with PMDD, the positive coupling suggests that the relationship between the two is not working as intended. Without the controlling areas counteracting the emotional activity, women with PMDD may have heightened reactivity. Additionally, an fMRI study showed that during the late luteal phase, women with PMDD have reduced activity in the right dlPFC (9), potentially making it more difficult to regulate that heightened emotional activity.

The amygdala may play a part in why social interactions can be hard for women with PMDD. The amygdala detects stimuli that are emotionally or socially significant (10)–cues in body language or faces that could be a threat–which can make its heightened reactivity in PMDD an issue. Gingnell et al. (6) also found that in women with PMDD, the amygdala became more reactive to social images than to non-social images in the luteal phase, also increasing along with progesterone levels. This means that women who already experience difficulty regulating emotions may also have stronger reactions to social cues, making social interactions more emotionally intense. Therefore, PMDD may interfere with a woman's relationships and social interactions.

In addition to the changes in receptor sensitivity and amygdala reactivity, PMDD also demonstrates an abnormal serotonin response. The neurotransmitter serotonin regulates mood

through a process known as serotonin signaling (7). A serotonin transporter, 5-hydroxytryptamine transporter (5-HTT), found concentrated in the midbrain, reabsorbs serotonin back into the neuron after it is released into the synapse (7). This system keeps the serotonin signaling process balanced because leaving too much serotonin lingering outside the neuron would overstimulate receptors, but too little would leave mood unregulated as well. PMDD may be an issue of the latter. A study using positron emission tomography (PET) scan images found a significant difference in 5-HTT levels between PMDD patients and healthy controls. Approaching the luteal phase, women with PMDD showed an aggressive increase of 18% in 5-HTT availability in the midbrain, in contrast to healthy controls, who showed a decrease of 10% (7). With more transporters (5-HTT) bringing serotonin back into the neuron, there is little serotonin left outside of the neuron, which is needed to regulate mood. This may be another contributor to the intense emotional lows for women with PMDD.

Understanding the PMDD Diagnosis

Diagnosing PMDD is not as simple as recognizing its symptoms, since many of them overlap with regular premenstrual symptoms. Its symptoms are attributed to GABA-A receptor dysfunction, amygdala hyperreactivity, and serotonin irregularities, all triggered by the hormonal shift that follows ovulation, which is why the symptoms show up in a cycle. The anxiety, depression, and irritability that characterize PMDD, along with a worsening of insomnia, memory problems, difficulty staying focused, and fatigue in the premenstrual phase (11), can generally be apparent in typical premenstrual symptoms as well, though in a milder form. Because the symptoms look similar, PMDD is often missed or diagnosed late (4).

However, there are ways to distinguish PMDD from premenstrual symptoms or other mood disorders. First, severity can be an indicator. If the symptoms are severely impacting daily function, relationships, and work, unlike general premenstrual symptoms, PMDD should be considered. What ultimately distinguishes the PMDD diagnosis, though, is that cyclical timing. By DSM-5 standards, diagnosis requires tracking symptoms across two or more menstrual cycles, intended to catch this timing (3). These symptoms are also logged prospectively, or in real time, to address the unreliability of relying on memory, and to understand the severity. As one review puts it, "the on-off nature of symptoms in the luteal phase of the menstrual cycle is key to diagnosis" (12). The cyclical pattern of symptoms beginning in the luteal phase and resolving around menstruation separates PMDD from premenstrual symptoms or mood disorders. That cyclicality is also what makes it possible to time some treatments to the luteal phase specifically, as the following section explains.

Due to the DSM-5's strict criteria, many women are left on the border of diagnosis. One review reported that up to 18% of women were only one symptom short of meeting the criteria for PMDD, and that about 20% of reproductive-aged women have symptoms severe enough to cause significant impairment and warrant treatment (13). These findings suggest that many more women experience premenstrual symptoms to a debilitating degree but fall just short of PMDD diagnosis. This may be, in part, because PMDD is better understood as a spectrum rather than a single, uniform condition. Because women respond differently to SSRIs and to gonadotropin-releasing hormone (GnRH) agonists, Hantsoo and Payne (14) suggest that PMDD likely includes biological subtypes, and that future research should study it this way. More specifically, some women may experience symptoms driven more by GABA-A receptor

dysfunction, and others more by amygdala hyperreactivity or serotonin irregularities, which could help explain why the amount and severity of symptoms, along with treatment response, vary from person to person.

Treatments

Without treatment, PMDD may leave women in a functional state similar to major depression with a high suicide risk (15), on top of the already harsh physical symptoms. Understanding its basis changes the treatment goal from not only managing symptoms to also possibly intervening in one of those mechanisms. Hormonal contraceptives work to suppress the hormone fluctuations, but other treatments address the serotonin and GABA-A receptor irregularities directly. With this in mind, hormonal suppression may not be the best treatment, and other options such as SSRIs and GABA-A and neurosteroid-targeted drugs may be more targeted.

Hormonal Suppression

Oral contraceptives are often a first line approach, largely due to the fact that they are familiar, accessible, and well-established (16). Generally, they work by suppressing ovulation: the hormones in the pill send a message to the brain to reduce the hormones typically sent to release the egg. Because of this, the natural hormonal changes post ovulation, including the rise and fall of progesterone, do not occur (17). There are multiple types of oral contraceptive pills broadly prescribed, such as combined estrogen-progesterone, progesterone-only pills (16). Beyond functioning as ordinary birth control, some pills, like Yaz, are specifically formulated for PMDD. Yaz combines ethinyl estradiol (EE) and drospirenone, a synthetic progestin, in a combined oral contraceptive pill (COCP) (18). Together, these hormones suppress ovulation. Drospirenone has a relatively long half-life of over 30 hours, which allows its activity to extend further into the hormone-free interval (HFI) (18). Research suggests that combined oral contraceptives containing drospirenone and ethinyl estradiol may improve premenstrual symptoms that interfere with daily functioning in women with PMDD (19). But, some studies with second generation COCPs (containing norethisterone, levonorgestrel, and ethinylestradiol) showed less promising results, potentially because some synthetic progestins can produce PMS-like side effects (15). This suggests that the effectiveness of hormonal contraceptives for PMDD may depend on the specific formulation, since different progestins can have different effects. Yaz, which contains drospirenone, has demonstrated benefits for some women with PMDD.

Traditionally, oral contraceptives come in a 21/7 pack, or a 24/4 pack, meaning 21 days of active hormone pills followed by 7 hormone-free days, or 24 active days followed by 4 hormone-free days (13, 20). Even though it is not medically necessary, having the hormone-free interval (HFI) was designed to mimic natural monthly bleeding (16). For women with PMDD though, going without the pills lets the hormones drop and symptoms come back. This is why for women with PMDD, the 24/4 schedule, like Yaz's, is more commonly used because it has a shorter window without hormones. Some have hypothesized that continuous dosing, or skipping the HFI, would be more effective (21). But research has found otherwise, explaining, shortening or eliminating the HFI did not produce greater benefits than a placebo or a standard 21/7

regimen (20). In fact, this study adds to a body of randomized control trials (RCTs) where oral contraceptive effects for PMD treatment are nonsignificant, small, or short-lived (20). Even with continuous dosing and eliminating the HFI, women still reported symptoms similar to typical dosing (20). The authors note that this isn't an isolated finding, as multiple other studies have found oral contraceptive effects on premenstrual symptoms inconsistent, weak, or short-lived. Another potential downside is that, with hormonal contraceptives only working for as long as a woman keeps taking them, symptoms return unmanaged the moment she stops, whether to try to get pregnant or for any other reason. For this reason, birth control, which can be stopped at any point without consequence for most women, is not designed to be the sole treatment for women with PMDD planning to get pregnant. Although research on hormonal contraceptives has produced mixed results, they can be an effective treatment option for some women with PMDD. Because their effectiveness may depend on the formulation and dosing schedule, other treatments, such as SSRIs and emerging GABA-A and neurosteroid-targeted drugs, are also important to consider.

SSRIs

If PMDD's symptoms are partly attributed to too much serotonin being reabsorbed into the neuron, a solution could be at the synaptic level. Selective serotonin reuptake inhibitors (SSRIs) work by selectively binding to the 5-HTT protein. This blocks its ability to reabsorb serotonin back into the presynaptic neuron, and it stays in the synaptic cleft longer. In turn, this allows the receptor to be stimulated longer (22), helping serotonin signaling work more normally to regulate emotions. In addition to addressing the serotonin issue, SSRIs also have been found to raise ALLO levels. Research explains that fluoxetine, one type of SSRI, may prevent ALLO from being converted into 5α-dihydroprogesterone (5α-DHP) without interfering with serotonin reuptake (2). This means that fluoxetine may prevent ALLO from breaking down, potentially helping regulate GABA-A receptor function. Additionally, animal studies have found significantly increased ALLO concentrations in brain tissue following fluoxetine administration (2). Although this increase was measured in an animal study rather than in humans, it provides evidence that fluoxetine can affect ALLO levels, though further research is needed to establish whether the same effect occurs in humans. Most impressively, Gao et al. (2) report that SSRI treatment response rates for PMS/PMDD range from 60–90%, compared with 30–40% for placebo.

Compared to their use for depression, SSRIs appear to have a much faster onset of action when used for PMDD, with improvements in emotional symptoms occurring within the first 24 hours and reaching their peak around 48 hours (15). Since SSRI relief is quick and effective, this raises the hypothesis that SSRIs could work just as well even if only taken during the luteal phase, rather than continuously. Supporting this, research indicates that SSRIs are an effective first-line treatment for PMDD when administered either continuously or exclusively during the luteal phase (21). Given PMDD's cyclical nature, women may not need to take SSRIs continuously, since research supports taking them only during the luteal phase as an effective treatment option. Two things are interesting to note: SSRIs have relatively frequent side effects (15), and, possibly due to the different subtypes of PMDD, about 40% of women with PMDD do not respond to SSRIs (23). SSRIs remain a strong treatment option for many women with

PMDD given their high response rate, rapid onset, and flexible dosing; but, the variability in treatment response highlights the need for further research into PMDD subtypes.

GABA-A and neurosteroid-targeted drugs

Within the past few years, promising but still preliminary research has emerged on GABA-A and neurosteroid-targeted treatments for PMDD. Mainly, two different approaches targeting GABA-A receptors are being explored: steroid antagonists, such as sepranolone, and positive allosteric modulators, such as brexanolone and zuranolone (2).

Since PMDD is linked to an abnormal sensitivity response in GABA-A receptors when ALLO fluctuates, one strategy is to block ALLO from reaching the receptor in the first place. Sepranolone works that way, by blocking ALLO at the receptor level so GABA-A receptors do not have to respond, rather than having a faulty response that contributes to PMDD symptoms. In an initial placebo-controlled trial, sepranolone reduced PMDD total symptom scores by 75% (24), showing promising early results. A larger follow-up trial gave mixed results: a strong placebo response contributed to the treatment effect not reaching statistical significance, but further analysis at a lower dose still found significant effects (25).

Brexanolone and zuranolone work in the opposite way, supplying calming receptor activity directly rather than blocking ALLO, making up for what the faulty ALLO mechanism fails to do by stimulating the receptor themselves. Post Partum Depression (PPD) is similar to PMDD in the way that neurosteroid, such as ALLO, changes are believed to contribute to its onset (8), which is why these drugs approved for postpartum depression should be looked into for PMDD as well. Brexanolone was FDA-approved for PPD in 2019, and zuranolone gained FDA approval in 2023 (26); however, their effectiveness for PMDD has not been established, and brexanolone's approval has been withdrawn. Although their effects on neurosteroid-sensitive GABA-A receptors make them potential candidates for future PMDD treatment, clinical trials in women with PMDD are needed to determine whether they are effective. More research is also needed to establish the effectiveness of steroid antagonists, such as sepranolone, given the mixed results of clinical trials.

Discussion

The effectiveness of hormonal contraceptives, SSRIs, and neurosteroid-targeted drugs reflects both how they address PMDD's underlying mechanisms and the strength of the clinical evidence supporting them. Hormonal contraceptives aim to reduce the hormonal fluctuations that trigger symptoms, but research on their effectiveness, particularly for mood symptoms, has produced mixed results, even when the HFI is shortened or eliminated, and effectiveness may depend on the specific formulation. SSRIs have the most consistent clinical evidence among the treatments above. They directly affect serotonin reuptake and may also influence ALLO levels through a separate pathway, although evidence for this additional mechanism comes partly from animal studies. Neurosteroid-targeted drugs address GABA-A receptor dysfunction more

directly with sepranolone blocking ALLO at the receptor level, and brexanolone and zuranolone enhancing receptor activity. However, sepranolone has produced mixed results in clinical trials, and brexanolone and zuranolone have not been tested in women with PMDD. Overall, SSRIs currently have the strongest clinical support among these treatments, while inconsistent findings for hormonal contraceptives and limited evidence for newer treatments show that further clinical research is needed to determine how effectively these neurological mechanisms can be targeted to treat PMDD.

Conclusion

The symptoms of PMDD appear to be linked to three distinct neurobiological mechanisms: GABA-A receptor plasticity dysfunction, amygdala hyperreactivity, and serotonin transporter irregularities. Understanding how each of these mechanisms works helps explain why certain treatments may be effective and points toward more targeted options, though no single treatment yet works for every woman. Of the treatments examined–hormonal contraceptives, SSRIs, and neurosteroid-targeted drugs–SSRIs demonstrate the most consistent body of evidence by directly targeting the GABA-A and serotonin mechanisms. In contrast, hormonal contraceptives only suppress the trigger and depend heavily on the type of formula for PMDD, leading to inconsistent evidence. They also are not the most realistic long-term choice, especially for women planning to get pregnant. The emerging GABA-A and neurosteroid-targeted drugs show promise by acting at the receptor level, but they currently lack a consistent body of clinical evidence.

Despite the effectiveness of SSRIs, a percentage of women still do not respond to them. This may point to PMDD's biological subtypes, meaning the same three mechanisms likely present differently from woman to woman. Recognizing that PMDD is not a uniform condition explains why treatment response varies and highlights the need for continued research into these subtypes. Additionally, conducting more clinical trials for neurosteroid-targeted drugs will be crucial for developing effective options beyond SSRIs, possibly giving women who don’t respond to SSRIs another option.

Universally, understanding the basis of PMDD and addressing these research gaps may drastically improve patient care for women. Being able to spot the difference between PMS and PMDD has been a significant barrier, but increased clinical awareness and more formalized ways to track symptoms prospectively across cycles can make accurate diagnosis more accessible. Understanding PMDD as a distinct neurobiological condition rather than a normal reaction to hormone shifts and targeting treatment approaches accordingly can give women the best treatment possible.

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