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Role of Stress and Inflammation in the Etiology, Treatment, and Management of Premenstrual Dysphoric Disorder (PMDD)

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Abstract

According to the DSM-5, Premenstrual Dysphoric Disorder (PMDD) is defined as a mood disorder characterized by physical, emotional, and behavioral symptoms that occur during the luteal phase and cause significant distress or impairment. While epidemiological studies highlight that PMDD occurs in 1.8-5.8% of menstruating individuals, this is a vast underestimation prevalence due in part to cultural and systematic factors that impact diagnosis. That said, it is imperative to conduct research on this debilitating condition and its impact on overall wellbeing. The objective of this review is to explore the role stress and inflammation plays on etiology, treatment, and management of PMDD. To ensure a thorough review, the inclusion criteria focused on studies published in peer reviewed journals on etiology (stress and inflammation in relation to PMDD) and the treatment and management of PMDD. Studies conducted on topics pertaining to genetics and serotonin dysregulation were not included. Additionally, research conducted prior to 2005 were also excluded from the review process. Overall, existing literature demonstrates that stress and inflammation has been found in individuals with PMDD. However, more research must be done on the potential therapeutic value of Yaz, other COCs, and anti-inflammatory agents in treatment of PMDD.

Keywords: Inflammation, Women's Health, Depression, Stress, Suicide

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1. Introduction

Premenstrual Dysphoric Disorder (PMDD), as defined in DSM-5, is a mood disorder marked by physical, emotional, and behavioral symptoms during the week before menses, the luteal phase. Diagnosis requires at least five symptoms related to mood, and additional physical and behavioral symptoms, which must cause significant distress or impairment limited to the luteal phase. For a full diagnosis, symptoms must be documented prospectively over two menstrual cycles, as retrospective reports only warrant a provisional diagnosis. PMDD affects an estimated 1.8–5.8% of menstruating individuals, although the actual prevalence may be higher due to patient difficulties with documentation (1). Considering PMDD's strong association with suicidality and significant impact on quality of life, further investigation is needed (2). This manuscript will review the role of stress and inflammation in the etiology, treatment, and management of PMDD. By viewing PMDD as a maladaptive stress response to luteal cycle hormonal fluctuations, it offers a framework for treatments targeting both the hormonal fluctuations and the physiological response.

Stress, Inflammation, and PMDD

Proposed etiologies for PMDD include genetics, serotonin dysregulation, and stress and inflammation. Studies show individuals with and without PMDD experience similar levels of peripheral ovarian hormones during the luteal phase; however, those with PMDD respond differently to luteal fluctuations, possibly due to the impact of stress and inflammation. A study of almost 4000 women found trauma and PTSD to be independently associated with PMDD. Repeated life stressors and social stressors have been shown to increase inflammatory markers such as C-reactive protein (CRP), interleukin-6, and interleukin-1β (3). Mood disorders have consistently been associated with inflammation, with increased pro-inflammatory cytokines seen in patients with mood disorders (4). In PMDD, there is a relative increase in inflammatory markers in the luteal phase. Additionally, elevated hs-CRP levels have been linked to emotional, behavioral, and physical symptoms of PMDD (5).

Treatment of PMDD

PMDD treatment targets both hormonal fluctuations and the resultant systemic response. Combination oral contraceptives (COCs) are a first-line treatment that stabilize luteal cycle fluctuations by preventing ovulation. Despite wide usage, COCs vary in composition, and research on their efficacy in treating PMDD remains limited. Drospirenone/Ethinylestradiol is the only FDA approved medication for treatment of PMDD, as it has been shown to improve emotional and physical symptoms in comparison to placebo (6). Its unique formulation and dosing schedule, 24 active pills followed by 4 placebo pills, differs from the standard 21-active, 7-placebo schedule that other COC's possess. Its longer dosing schedule for hormones is thought to contribute to its effect on mood in PMDD (7). Additionally, its progesterone derivative, drospirenone, possesses anti-androgenic and diuretic effects. Lastly, the systemic response to luteal cycle fluctuations has historically been addressed through selective serotonin reuptake inhibitors (SSRIs), luteal specific or continuous, alongside cognitive behavioral therapy (CBT), which has been effective at reducing mood symptoms of PMDD. (7).

2. Discussion

Fleshner (2017) proposed a mechanism linking stress, inflammation, and mood pathology, theorizing that exposure to stressors triggers the release of danger-associated molecular patterns (DAMPs) from injured neurons, which prompts creation of inflammatory markers increasing tryptophan breakdown, thus impairing serotonin synthesis and the body's stress response (8). In addition to existing literature, this supports the hypothesis that stress and inflammation play key roles in the pathophysiology of PMDD.
The unique formulation and dosing schedule of Drospirenone/Ethinylestradiol likely plays a key role in alleviating PMDD symptoms. Compared to levonorgestrel-based contraceptives, drospirenone has been shown to reduce water retention and weight gain (9). Prescribers should especially consider Drospirenone/Ethinylestradiol for patients experiencing these issues. For severe cases of PMDD, clinicians should explore extended dosing regimens, which can mitigate mood disturbances tied to hormone withdrawal during placebo intervals. Aside from potential breakthrough bleeding, extended dosing regimens have not been linked to significant adverse effects.

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Furthermore, the elevated inflammatory markers seen in PMDD suggest potential benefit from anti-inflammatory agents for PMDD, including dietary curcumin, omega-3 fatty acids, acetyl-salicylic acid, etc. These therapies have shown some success in mood disorders; however, they require more investigation as potential treatments for PMDD. Lastly, although CBT is established as the core psychotherapy intervention for PMDD, emerging therapies warrant exploration. Specifically, given the association between PMDD and PTSD, therapies such as eye movement desensitization and reprocessing, which reduces psychophysiological stress responses and enhances parasympathetic tone in PTSD populations, may be helpful as adjunct therapies (10).

3. Conclusion

Existing literature has shown a connection between stress, inflammation, and the pathophysiology of PMDD. However, additional research on the therapeutic value of Drospirenone/Ethinylestradiol and other COCs, as well as anti-inflammatory agents is necessary. In summary, a multidisciplinary approach addressing hormonal fluctuations, stress, and inflammation should inform clinical practice and guide development of therapies for PMDD.

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