Understanding and Treating Menstrual Mood Disorders

Naturopathic Approaches to PMDD

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Most women are very familiar with premenstrual syndrome (PMS), though how each individual woman experiences PMS can vary completely. Rapid fluctuations in sex hormones can lead to changes in energy, mood, and/or physical symptoms throughout her cycle, most predominantly during the last week of the luteal phase. For a woman with a consistent and normal menstrual cycle, this would be between days 21 and 28 of her cycle.

We can characterize PMS as including symptoms such as breast tenderness, bloating, fatigue, headaches, mood swings, and changes in appetite or cravings. Up to 80% of women report one or more of these symptoms without it disrupting their normal daily functioning.[1] However, for about 3–8% of these women, mental and emotional symptoms are so severe that multiple aspects of their lives are negatively impacted.[1]

Premenstrual dysphoric disorder (PMDD), now a distinct disorder in the DSM-5, is recognized as a collection of severe cognitive-affective symptoms at the end of a woman's luteal phase.[2] The etiology is still unknown, though many hypotheses have implicated changes in hormone levels and altered neurotransmitter modulation as having a drastic effect on a woman's affect, mood, and therefore behaviour as well. The inability for the body to adapt to these hormonal changes seems to be a culprit in the progression of PMS to PMDD, and may involve cortisol dysregulation.

Diagnosing PMDD

The criteria for the diagnosis of PMDD includes a list of 11 symptoms, where patients must present with at least five of those 11, and at least one of the following:[2]

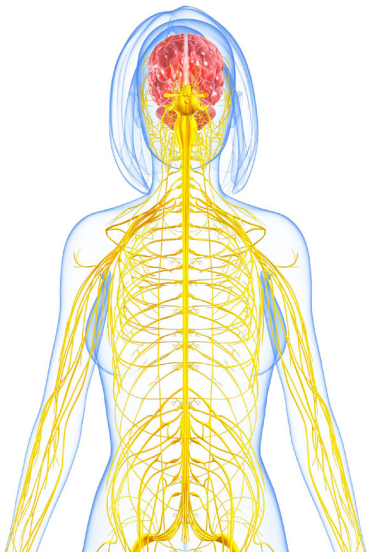
- Marked depressed mood,
- Marked anxiety,
- Marked affective lability (tearful and/or increased sensitivity),
- Persistent and marked anger or irritability.[2]

Other symptoms included in a diagnosis include difficulty concentrating, lethargy or fatigue, changes in eating patterns, changes in sleep (either insomnia or hypersomnia), breast tenderness, headaches, joint or muscle pain, and bloating. Specific to PMDD, the occurrence of these symptoms must considerably affect a woman's ability to function at work, school, and/or home. Relationships are often strained, and just getting through a normal day can seem like a daunting task.

Women commonly report depression and hopelessness, and some may even have suicidal thoughts. Due to the overlap in symptoms and high comorbidity between depressive syndromes and PMS/PMDD, it is thought that they share common neurological or neuroendocrinological substrates, and cortisol dysregulation has been implicated.[3] Some studies have tried using cortisol levels as a biomarker; however, the results are mixed due to a lack of consistency in methodology. Timing of cortisol assessment varied significantly across studies, as well as across subjects within the same study, while others combined PMS with PMDD symptoms.[3][4]

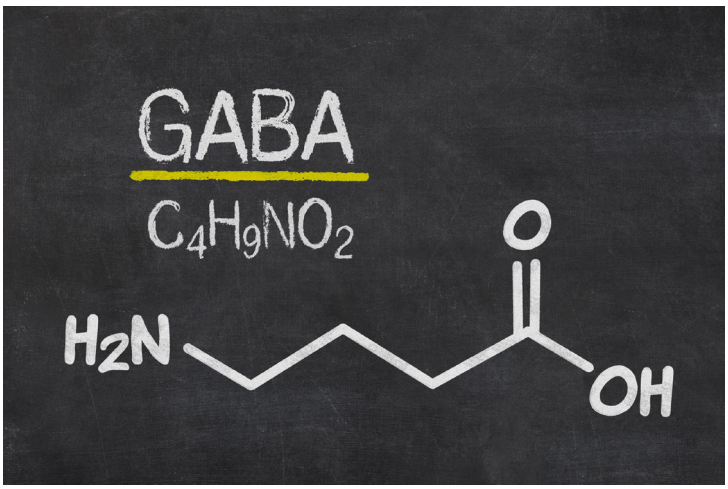
Understanding the Physiological Changes that Can Lead to PMDD

There are several other hypotheses regarding the etiology of PMDD. In general, we find a sensitivity of the central nervous system to changes in reproductive hormones. This can be aggravated by genetic factors and stress.[2] Women with PMDD have an altered sensitivity to changes in progesterone, as well as to estrogen to some degree.[2]



In a normal menstrual cycle, ovulation causes the release of a developed follicle, or egg. Once released, this unfertilized egg, called the corpus luteum, releases its own progesterone. Progesterone levels continue to rise and peak at around 21 days. If it remains unfertilized, this corpus luteum begins to degrade, and progesterone and estrogen levels plummet. This is the body's signal that fertilization and implantation have not occurred, and thus it triggers menstruation.

Within this one week, from day 21 to day 28, progesterone goes from its highest level in the body to its lowest. Some researchers consider PMDD to be a reaction of progesterone withdrawal.[2] Both rat and human studies have shown that a rapid progesterone withdrawal is associated with increased anxiety, social withdrawal, and alterations in *gamma*-aminobutyric acid (GABA) receptor function.[2]



Decreased Progesterone, Allopregnenalone, and GABA

GABA is one of the main inhibitory neurotransmitters in the brain, and contributes anxiolytic effects.[5] Supplementing with GABA has been used to help treat patients with anxiety, mood disorders, as well as epileptic seizures.[6]

Allopregnanolone (ALLO) is a metabolite of progesterone which acts as a positive modulator of the GABA-A receptor. It is hypothesized that low ALLO can lead to increased anxiety, depressive symptoms, and increased stress reactivity.[2][3] Typically, ALLO increases in response to acute stress to enhance GABA transmission, therefore a blunted response may be due to a lack of ALLO in women with PMDD.[2]

Another observation of this affect is seen in the startle response to acoustic stimuli, as ALLO modulates the resulting stress response from loud sudden noises. Women with PMDD seem to have an increased startle response during the luteal phase of their menstrual cycles.[2]

One study measured GABA levels in premenopausal women and found a greater premenstrual decrease in plasma levels of GABA in women with PMDD in the luteal phase compared with healthy controls.[5] Another study investigated GABA and glutamine/glutamate levels in multiple areas of the brain via magnetic resonance spectroscopy (MRS). Reduced levels of GABA were found in women with PMDD in the

anterior cingulate cortex, the medial prefrontal cortex, and the left basal ganglia areas.[5] This may explain changes in mood and emotion regulation, premenstrually. Additionally, previous MRS studies have reported that patients with other mood disorders, including major depression and anxiety disorder, also have decreased brain GABA levels.[5]

This also helps to explain why selective serotonin reuptake inhibitors (SSRIs) are used as first-line therapy for PMDD, as they increase GABA levels in the brain.[5]

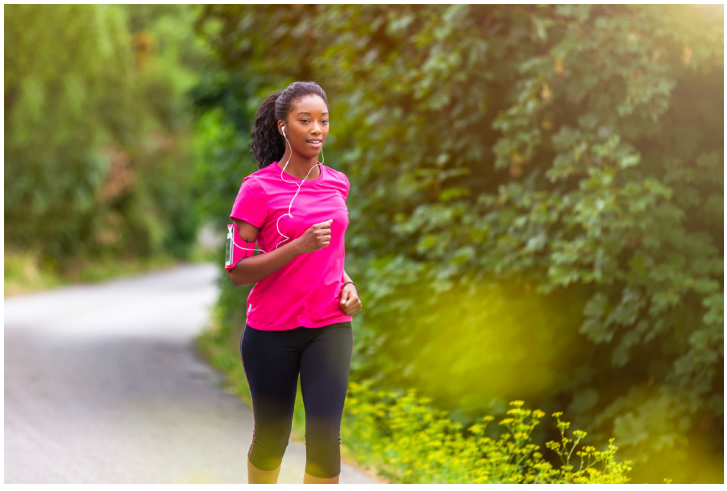
Treatment and GABA Synthesis

GABA is synthesized endogenously by the rate-limiting enzyme glutamic acid decarboxylase (GAD).[5] Lower GABA levels in women with PMDD could be due to dysfunctional GABA synthesis, or a dysfunctional enzyme in the GABA-glutamine-glutamate cycle.[5] Vitamin B_6, also known as pyridoxine hydrochloride or pyridoxal 5´-phosphate, is an essential cofactor for the functioning of the GAD enzyme,[7][8] and therefore may present part of a viable treatment option. This coincides with findings from one study that 50–100 mg of vitamin B_6 was able to reduce PMS symptoms by more than twofold compared to placebo.[1] That said, there was no greater response for doses larger than 100 mg, and caution must be exercised as neurological side effects can occur with doses greater than 300 mg.[1]

Multiple probiotic strains have also been shown to synthesize GABA themselves, and investigations showed they even contained the genes for GAD enzymes.[9] These effects were especially apparent in *Bifidobacteria* species, but also specific *Lactobacilli* species. These included *L. rhamnosus*, *L. brevis*, *L. plantarum*, *B. dentium*, *B. adolescentis*, and *B. angulatum*.[9]

Cortisol Function and Exercise

It's important to note the complexity of PMDD. Some symptoms may be more correlated to changes in cortisol levels than others. For example, anxiety, mood changes, and headaches are more related with cortisol dysregulation than those of breast swelling and acne, even though all of these are used to contribute to a diagnosis.[3]



Circadian rhythm disturbances due to cortisol have also been implicated in affective disorders. To assist investigations, it may be helpful to run a salivary cortisol panel, measuring cortisol levels upon waking, throughout the day, and before

bed. The goal is to observe whether there is a characteristic diurnal slope, as opposed to using single serum measurements or pooled measurements.[3] Additionally, identifying sleep patterns may also be an important consideration.[3]

Lastly, we notice a drop in *beta*-endorphin late in the luteal phase, due to changes in sex hormones.[10] This may perpetuate an opioid withdrawal reaction, resulting in PMS symptoms.[3] As opioids help to regulate the hypothalamic-pituitary-adrenal axis, it may be beneficial to improve endorphin levels via exercise.

Although not tested in women with PMDD, one study of nonathletic females with PMS reported a significant reduction in symptoms after eight weeks of moderate aerobic exercise.[10] The regimen consisted of aerobic exercise three days per week for 60 minutes each, starting by targeting 60% of the participants maximum heart rate, and work up progressively to 80% maximum heart rate by eight weeks.[10]

A separate study from 2003 illustrated that six months of regular physical activity was able to reduce symptoms of anxiety, which the authors attributed to an increase in endorphin levels.[10]

Multiple forms of movement and exercise can be beneficial for women specifically. In addition to reducing stress and premenstrual symptoms, exercise helps improve vascular activity and increases bone density.[10]

In general, treatment plans for PMDD should be geared toward the individual, and attempts should be made to identify areas of dysfunction including cortisol, sleep cycles, GABA synthesis and response, and changes in progesterone levels.

Treatments that may be considered as part of a patient plan include vitamin B_6, *Bifidobacterium* probiotics, exogenous progesterone or progesterone-modulating herbs such as chastetree berry,[1] exercise, exogenous GABA, and other agents which help increase GABA levels such as L-theanine.[11]

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