Premenstrual dysphoric disorder

INTRODUCTION
UP to 80% of all women of reproductive age experience some physical, emotional or cognitive change associated with their menstrual cycle. Commonly described as premenstrual syndrome (PMS), physical symptoms are common, and include breast tenderness, weight gain, bloating and headaches. Women with PMS also experience irritability and dysphoria, and often seek several complementary treatments. While PMS causes considerable regulatory morbidity, it is on the less severe end of a spectrum of menstrual cycle related disorders.

At the other end of the spectrum is PMDD — premenstrual dysphoric disorder. This affects about 2-8% of females of reproductive age and is a severe, debilitating depression with the premenstrual cycle phase. The whole spectrum of menstrual cycle related mood disorders remains poorly understood. This How to Treat will focus on the severe entity of PMDD.

HISTORY
REPORTS of mood and behaviour relating to the menstrual cycle can be traced back to the ancient Greeks. Hippocrates attributed several negative psychological and behavioural symptoms to “retained menstrual blood”. In many ancient cultures, women’s menstrual cycles were the subject of taboos, superstitions, and associated with a range of physical and mental symptoms. Isolating the menstruating woman and controlling her behaviour through cultural and religious laws still occurs today. Given the widespread, long-standing historical interest in women’s menstrual cycles it is curious that the earliest documentation of psychological changes associated with the premenstrual cycle phase appeared quite late — in 1931, by psychoanalyst Karen Horney. She described increased tension, irritability, depression and anxiety in the week preceding menstruation.

Over the ensuing decades, the existence of PMS has been debated, with concerns about the medicalisation of biological rhythms by using the illness descriptor “syndrome”. Others have argued that epidemiological studies have shown only small incidences of premenstrual mood changes in population studies and thus have called for reconsideration of the entity of PMS. A major confounding factor in such studies is the lack of true measurement of cyclical psychological symptoms in relation to a specific menstrual phase. In contrast, clinical trials aiming to provide treatments for women with PMS characterise the symptoms and measure their onset and offset. Such work, as well as clinical experience, underlines the very real existence of hormone-related changes in mood and behaviour for some women.

Formal PMDD research can be found in Robert Frank’s 1931 study of 45 women with ‘premenstrual tension’. Frank noted the cyclical occurrence of depressive symptoms associated with the menstrual cycle that would disappear shortly after the onset of menstruation. The term ‘premenstrual tension’ was used until the 1970s when it was replaced by the term ‘premenstrual syndrome’ or PMS, which remains widely used today. The first reference to a premenstrual disorder appeared in the DSM-III-R at the end of the manual in ‘Additional Codes’ under the name ‘late luteal phase dysphoric disorder’ (LLPDD). The condition’s name was changed to premenstrual dysphoric disorder (PMDD) and included in the DSM-IV in 1994. PMDD is recognised as a clear depressive disorder in DSM-5 with strict criteria for diagnosis. Controversies surround the diagnosis of PMDD, Feminist theorists have offered the most vociferous critique of the PMDD diagnosis. The main contention is that the inclusion of the disorder in the DSM reflects a destructive view that a woman’s biology can make her...
psychiatrically disordered, and that a woman's naturally occurring cyclical changes will not be unnecessarily pathologized. It is further contended that psychological linking of PMDD to the menstrual cycle will lead to the 'medicalisation' and subsequently, marginalisation of women's premenstrual experiences. 15-17 Clinical symptoms as a minimum variable definition for PMDD. A standardised rating scale – the California Premenstrual Assessment Scoring System (C-PASS) – has been proposed to validate PMDD as a diagnosis. 18 The C-PASS is a standardised scoring system for the diagnosis of PMDD using two or more menstrual cycles of daily symptom ratings using the Daily Record of Severity of Problems (DRSP). The C-PASS is successful in providing a construct validity of the PMDD diagnosis, and a measure of severity. 19-21 However, this can lead to variation and sociocultural considerations raised around the DSM-5 diagnosis. This rating scale is available on computerised and hard copy formats, and is an excellent objective measurement tool.

The diagnosis of PMDD is often overlooked in women who present with cyclical mood disturbances that are not in the exact premenstrual (luteal) phase of a regular cycle. Indeed, very much the name of this condition is a clinical diagnosis from diagnosing PMDD if women present with irregular cycles or with different onset times for intermittent severe or mild symptoms. Hence, it is vital for clinicians to work in an empowering manner with their patients to elicit clinical symptoms and listen to the women's observations.

Key points underlying a clinical diagnosis of PMDD (but not necessarily according to DSM-5 criteria) appear in box 1. Above all, the patient will often describe symptoms that will become evident every month, she has a "sudden depression for no reason." Many of the author's patients have clicked their fingers to demonstrate the sudden onset and offset of this condition – which is a significant diagnostic clue. It is important to act on the patient's information and make a presumptive diagnosis of mood disorder related to gonadal hormone fluctuation as a more broad-spectrum diagnosis. Ensure that details of any and all suicidal ideation, plans and attempts are carefully noted. Just because the depression is cyclical does not mean it is less serious, and PMDD has an associated mortality by suicide. 22

By recognising that the patient's cyclical depression may be due to a different set of biological variables than those causing a current major depressive disorder, or bipolar affective disorder, we can consider different treatment options and validate patient's observations – all leading to hopefully improved outcomes.

CAUSES OF PMDD

It is important to take a holistic approach to understand and manage any mental health issues. PMDD is a severe form of depression and is influenced by psychological and environmental factors. However, the most obvious factor in the onset and offset of PMDD is the hormonal fluctuations that control the menstrual cycle and the impact of these on neurochemistry. It is important to note that the reproductive (gonadal) hormones – oestrogen, progesterone and testosterone – have potent central effects. These reproductive hormones also have great influence over the neurochemistry responsible for thoughts, behaviours and emotions. The connection between reproductive hormones and mental health is clear. 23 It is not surprising that some women experience depression, anxiety and other mental health issues associated with their menstrual cycles. 24 Above all, it is critical to underline that PMDD is a brain disorder, not a disorder of the reproductive organs. There is no single clear theory that explains exactly which hormones trigger specific neurochemicals – or why only some women experience PMDD. However, we know that some women are susceptible to mood changes with very small swings in gonadal hormones due to changes in the activity of central neurotransmitters (GABA, serotonin and dopamine) that influence mood and behaviour. At the same time, many of the physical symptoms (breast tenderness, bloating, headaches, constipation) are the direct effects of gonadal hormones, so that overall, both mind and body are affected.

Many of the author’s patients have clicked their fingers to demonstrate the sudden onset and offset of this condition – a significant diagnostic clue. Such as diazepam, stimulate the GABA system and calm agitation. Thus, ALLO is an ‘anti-anxiety’ hormone. Like oestrogen, the levels of progesterone and its metabolite, ALLO, fall in the premenstrual phase. Women with PMDD are often agitated and anxious as well as depressed; a newer theory proposes that their brain chemistry is not reacting normally to ALLO, resulting in anxiety. This is an area that is under investigation, with new drugs that have an impact on ALLO being developed and tested. 25

Early life trauma and PMDD Post-traumatic stress disorder (PTSD) often occurs as a result of repeated early life emotional neglect, invalidization or abuse, or physical/sexual abuse. Complex PTSD (CPTSD) is a good descriptor for PTSD caused by early life trauma and it is often comorbid with PMDD. 26 However, it is unclear whether this relationship is driven by the trauma that may lead to PTSD, or if PTSD is uniquely associated with PMDD. The psychopharmacological mechanisms that lead to PMDD are currently not well investigated. However, several studies have found evidence of autonomic nervous system dysregulation by investigating associations with PMDD and with PTSD. 27

Our research has shown that the hypothalamic-pituitary-gonadal (HPG) axis may mediate the stress responses of the neuropeptide system (such as increasing blood sugar levels and suppressing immune function, as well as negative stress responses). 28 The metabolic feedback links between the HPA axis and the hypothalamic-pituitary-gonadal (HPG) axis may explain the relationship with HPA dysfunction in women who have CPTSD and also evidence for PTSD. Furthermore, the autonomic nervous system dysregulation characteristic of CPTSD may be a risk factor for PMDD. 29 On the other hand, mechanisms linking early life trauma or repeated traumatic events and PMDD remain unclear – it is important for clinicians to take a detailed developmental history from their patients with PMDD, to better understand their illnesses and management context.

INVESTIGATIONS

There are no specific laboratory investigations for PMDD. However, it is important to perform tests for three reasons: firstly, to rule out other causes for PMDD symptoms; secondly, to obtain general health baseline measures prior to starting treatment; and thirdly, to monitor general health once treatment is ongoing.

Possible differential diagnoses for premenstrual symptoms include fibroids, menopause fibromyalgia, thyroid disorder, migraine, major depression, borderline personality disorder, bipolar disorder (type 1 and 2) and panic disorder. 30 Investigations include blood tests measuring thyroid function as well as full blood examination, iron studies (for anaemia due to menorrhagia), clotting factors (for starting hormone therapy), vitamin B12, electrolytes and measures of the HPG axis. HPG measurements include estradiol, progesterone, FSH, LH, prolactin, testosterone, SHBG and DHEA, and are done to exclude menopause changes, polycystic ovary syndrome or other hormonal abnormalities.

The HPG axis investigations are not a test for PMDD itself, but these investigations need to be done for the patient’s health status, age, lifestyle and risk factors. Gynaecological investigations include a routine cervical screening test and special investigations for endometriosis. 31-33 Laboratory tests and symptoms are present. If the patient is to receive hormone treatments, perform routine breast-health screening with breast ultrasound or mammogram, and cardiovascular health screening according to the patient’s age and risk factors.

MANAGEMENT

UNDERSTANDING the body-mind connections in PMDD is critical to

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<th>Feature</th>
<th>Detail</th>
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<tr>
<td>Timing of symptoms</td>
<td>In the majority of menstrual cycles, at least five symptoms must be present in the final week before the onset of symptoms, start to improve within a few days after the onset of symptoms, and become minimal or absent in the week post menstruation.</td>
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<td>Symptoms</td>
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<td>A) One or more of the following symptoms must be present:</td>
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<td>1) Decreased interest in usual activities</td>
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<td>2) Marked irritability or anger or increased interpersonal conflicts</td>
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<td>3) Markedly depressed mood or loss of interest in nearly all activities</td>
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<td>4) Marked anxiety, tension, and/or feelings of being keyed up or on edge</td>
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<td>5) One (or more) of the following symptoms must additionally be present to reach a total of five symptoms when combined with symptoms from Criterion B above:</td>
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<td>6) A sense of being overwhelmed or out of control</td>
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<td>7) Physical symptoms such as breast tenderness or swelling, pain or muscle pain, sensation of bloating or tightness</td>
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<td>Severity</td>
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<td>D) The symptoms are associated with clinically significant distress or interference with work, school, usual social activities or relationships with others</td>
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<td>Consider other psychiatric disorders</td>
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<td>F) Criterion A should be confirmed by prospective daily ratings during at least two menstrual cycles (although a provisional diagnosis may be made prior to this confirmation)</td>
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<td>Exclude other medical explanations</td>
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<td>G) The symptoms are not attributable to the physiological effects of a substance (e.g. drug abuse, medication or other treatment) or another medical condition (e.g. hypothyroidism)</td>
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Table 1. Diagnostic criteria for premenstrual dysphoric disorder
There is no single clear theory that explains exactly which hormones trigger specific chemicals — or why only some women experience PMDD.

Clinical findings suggest that women are more likely to try hormone strategies initially to improve their quality of life. Clinical experience suggests that women are more likely to try hormone strategies initially compared with psychotropic med-

ications; the latter have associated side effects and as such are not typically recommended.

Concomitantly, the woman’s domestic or workplace environment and psychosocial stressors are critical for women with PMDD and should usually be addressed during treatment. Factors such as school or workplace burnout, family issues, and a lack of social support can have a significant impact on the course of the disease and may require interventions beyond the treatment of the symptom clusters.

There is growing evidence that the efficacy of hormone therapies varies between individuals. Some women may experience improvements in symptoms within a few weeks or months, while others may require several months of treatment to see a significant reduction in symptoms. Age, baseline symptom severity, and individual biological and psychological factors may influence the response to hormonal therapy.

Possible hormonal therapies for women with PMDD include:  
- The use of a continuous combined oral contraceptive pill (COCP) to prevent ovulation, which can help reduce premenstrual symptoms. COCPs are often prescribed for PMDD and can be used as monotherapy or in combination with other medications.  
- The use of a progesteroneonly contraceptive, such as a progesterone implant or intrauterine device (IUD), which can reduce symptoms by preventing ovulation.  
- The use of a gonadotropin-releasing hormone (GnRH) antagonist, which can block the release of hormones necessary for ovulation and menstrual cycle symptoms.  
- The use of a selective estrogen receptor modulator (SERM), such as raloxifene or tamoxifen, which can reduce symptoms by altering the effects of estrogen on target tissues.  
- The use of a selective serotonin reuptake inhibitor (SSRI), such as citalopram or escitalopram, which can improve mood and reduce symptoms by altering the effects of serotonin on the brain.  
- The use of a combination of a COCP and a SERM or a GnRH antagonist, which can provide additional benefits over the use of either medication alone.  

These therapies may be used as monotherapy or in combination with other medications, depending on the individual's response and the severity of their symptoms. Regular assessment of symptomatology and periodic adjustment of the treatment regimen may be necessary to ensure optimal management.

For some women, alternative therapies such as herbal medicine, exercise, and nutrition may also be beneficial. These interventions should be discussed with a healthcare provider to ensure safe and effective treatment.

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The new ALLO modulators that are currently being trialled for future treatment of PMDD are of great interest.

...and offset of depression emerged. Although the timing of her depression was not always precisely in the premenstrual week, since her periods were irregular, the sudden onset and then offset after 7–10 days was apparent.

A working diagnosis of PMDD is made and Sarah is started on the COCP, Zoely® (1.5mg t: beta estradiol plus 2.5mg nomegestrol acetate), taken continuously. The lithium is gradually decreased over eight weeks and ceased, as is the quetiapine, although this takes six months. Sarah’s temor improves once the lithium is stopped, and she begins painting again. The resumption of an important creative activity spurs on a great improvement in her depression. Sarah engages in psychotherapy and continues to make good progress. She still has some depression every month so 25g of transdermal oestradiol is added to her existing treatment of fluoxetine 40mg daily.

Twelve months later, Sarah is doing very well. She has lost 13kg and is painting and teaching art. She has very mild depressive symptoms each month and copes with these in therapy.

She is physically healthy and undergoes her required health screening. She is not in an intimate relationship but has discussed her desire to have a baby; it will be important to assist her planning for this goal.

Sarah’s symptoms are typical of PMDD but were not recognised as such for 15 years. As a result, Sarah lost jobs, friendships and intimate relationships as well as experiencing side effects of many psychotropic medications — with little respite from the relentless severe cyclical depression. Sarah’s story is a reminder that PMDD is a real entity and the impact of reproductive hormones on mental health is critical in many women. Her case also underlines the importance of listening carefully to our patients, whose observations often hold the key to optimising their diagnosis and management.

CONCLUSION

PMDD is a real disease entity that appears to be due to the impact of fluctuations in gonadal hormones in the brain. Approximately 2–8% of women of reproductive age experience significant cyclical depression that requires management, including the use of gonadal hormone treatments.

Early consideration of PMDD as a key diagnosis for cyclical depression may prevent a number of adverse effects of ineffective psychotropic medications and poor psychosocial outcomes for the patient. A holistic management approach in collaboration with the woman is critical to ensuring optimal outcomes.

RESOURCES

• Carolina Premenstrual Assessment Scoring System

• Daily Record of Severity of Problems

References on request from howtotreat@adg.com.au