How to Treat Quiz

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NEED TO KNOW

- PMDD is a real entity.
- PMDD is a severe, cyclical depressive disorder due to CNS impacts of gonadal hormone fluctuations.
- PMDD is not PMS and does not respond to lifestyle interventions alone.
- Gonadal hormones are an important treatment for PMDD.
- PMDD is a brain disorder, thus gynaecological surgery is not a key treatment.
- PMDD may be more common in women with early life trauma.

Premenstrual dysphoric disorder

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INTRODUCTION

UP to 80% of all women of reproductive age experience some physical, emotional or cognitive change associated with their menstrual cycle.[1] 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.[2] While PMS causes considerable regular 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 high morbidity and mortality.[3] 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".[4]

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.[5] 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.[6,7]

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.[8] 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 15 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.[9] The term 'premenstrual tension' was used until the 1950s when it was replaced by the term 'premenstrual syndrome' or PMS, which remains widely used today.[10] 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).[11] The condition's name was changed to premenstrual dysphoric disorder (PMDD) and included in the DSM-IV in 1994.[12] PMDD is recognised as a clear depressive disorder in DSM-5 with strict criteria for diagnosis.[13]

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 be unnecessarily pathologised.[14] It is further contended that a diagnosis of PMDD will lead to the 'medicalisation' and subsequently, marginalisation of women's premenstrual experiences.[15]

Arguments are still made that premenstrual mental health challenges are not biologically driven, but socially learned. For example, young women may be influenced by religious and cultural beliefs that menstruation is a 'dirty' time and that premenstrual changes are associated with negative physical and psychological effects.[16]

While the sociocultural theoretical debates continue, the very real suffering and the need for effective treatments for a significant number of women has driven neuroscience research and clinical practice.

DSM-5 SYMPTOMS AND SIGNS OF PMDD

TABLE 1 lists the diagnostic criteria of PMDD according to the DSM-5.[13]

Table 1. Diagnostic criteria for premenstrual dysphoric disorder

Feature	Detail
Timing of symptoms	A) In the majority of menstrual cycles, at least five symptoms must be present in the final week before the onset of menses, start to improve within a few days after the onset of menses, and become minimal or absent in the week post menses
Symptoms	B) One or more of the following symptoms must be present: 1) Marked affective lability (eg, mood swings, feeling suddenly sad or tearful, or increased sensitivity to rejection) 2) Marked irritability or anger or increased interpersonal conflicts 3) Markedly depressed mood, feelings of hopelessness, or self-deprecating thoughts 4) Marked anxiety, tension, and/or feelings of being keyed up or on edge C) 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 1) Decreased interest in usual activities 2) Subjective difficulty in concentration 3) Lethargy, easy fatigability, or marked lack of energy 4) Marked change in appetite; overeating or specific food cravings 5) Hypersomnia or insomnia 6) A sense of being overwhelmed or out of control 7) Physical symptoms such as breast tenderness or swelling; joint or muscle pain, a sensation of bloating or weight gain
Severity	D) The symptoms are associated with clinically significant distress or interference with work, school, usual social activities or relationships with others
Consider other psychiatric disorders	E) The disturbance is not merely an exacerbation of the symptoms of another disorder, such as major depressive disorder, panic disorder, persistent depressive disorder (dysthymia) or a personality disorder (although it may co-occur with any of these disorders)
Confirmation of the disorder	F) Criterion A should be confirmed by prospective daily ratings during at least two symptomatic cycles (although a provisional diagnosis may be made prior to this confirmation)
Exclude other medical explanations	G) The symptoms are not attributable to the physiological effects of a substance (eg, drug abuse, medication or other treatment) or another medical condition (eg, hyperthyroidism)

Source: DSM-5[13]

Clinical presentation

The symptoms detailed in the DSM-5 criteria particularly emphasise cyclicity, and confirmation of the disorder relies on two symptomatic cycles as a minimum validation for PMDD. A standardised rating scale — the Carolina Premenstrual Assessment Scoring System (C-PASS) — has been proposed to validate PMDD as a diagnosis.[17] The C-PASS is a standardised scoring system for making DSM-5 PMDD diagnoses 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, by eliminating diagnostician variability and sociocultural considerations raised around the DSM-5 diagnosis. This rating scale is available for clinical and community use in computerised and hard copy formats, and is an excellent objective measurement tool.

However, 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, the very name of this condition deters clinicians from diagnosing PMDD if women present with irregular cycles or with different onset times for intermittent severe depression. Here, it is critical for clinicians to work in an empowering manner with their patients to elucidate a full history and listen to the woman's observations.

Key points underlining a clinical diagnosis of PMDD (but not necessarily strictly according to DSM-5 criteria) appear in box 1.

Above all, the patient will often detail her observations that about 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.[18]

By recognising that the patient's cyclical depression may be due to a different set of biological variables than those causing standard major depressive disorder, or bipolar affective disorder, we can consider different treatment options and validate our 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.[19] It is not surprising that some women experience depression, anxiety and other mental health issues associated with their menstrual cycles.[18] 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.

From both animal and human studies conducted to date, it appears that oestrogen is a 'protective' hormone and can improve psychotic symptoms as well as depression.[19,20]

Many of the author's patients have clicked their fingers to demonstrate the sudden onset and offset of this condition — a significant diagnostic clue.

Oestrogen directly influences the key neurotransmitters of serotonin and dopamine to achieve this positive effect. Thus, during low-oestrogen phases of the menstrual cycle (premenstrual phase and during the transition into menopause), depression and other adverse mental symptoms worsen. Progesterones can have the opposite effect. Susceptible women who use the progesterone-only contraceptive pill (the 'mini-pill') can experience worse depression, and there are certain types of progesterones in the combined oral contraceptive pill (COCP) that can be very depressive.[21]

Recent work regarding the cause of PMDD reveals that a breakdown product of progesterone, allopregnanolone (ALLO), is a critical stimulator of the GABA-A receptors. The GABA system can alleviate anxiety when stimulated. Benzodiazepines, such as diazepam, stimulate the GABA system and calm agitation.[22] Thus, ALLO is an 'anti-anxiety' hormone.

Box 1. Key clinical features in diagnosing PMDD

- A rapid, sudden onset of five of: Depression, irritability, anxiety, affect lability, decreased interest, difficulty concentrating, fatigue, feeling out of control, insomnia, change in appetite, breast tenderness or breast swelling; that interfere with usual activities — work, family, social life.
- A rapid, sudden offset of the above mood and associated symptoms after 7-10 days. This may coincide with menstrual bleeding, but in women with irregular, amenorrhoeic or medication-impacted cycles, the bleeding may not necessarily signal improvement in mood.
- An absence of new stressors or clear precipitating psychosocial factors causing depression.

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.[22]

Early life trauma and PMDD

Post-traumatic stress disorder (PTSD) often occurs as a result of repeated early life emotional neglect, invalidation 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.[23-25] 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.[25] The psychophysiological mechanisms linking PMDD and PTSD are currently not well investigated. However, several studies have found evidence of autonomic nervous system dysregulation both in patients with PMDD and with PTSD.[24]

Our research has shown that the hypothalamic-pituitary-adrenal (HPA) axis, a key mediator of stress, "initiates a series of neural and hormonal cascades that, in addition to other metabolic functions such as increasing blood sugar levels and suppressing immune function, serves to regulate the response to stress".[26] The metabolic feedback links between the HPA axis and the hypothalamic-pituitary-gonadal (HPG) axis may explain the relationship with HPA dysregulation in women who have cPTSD and also experience PMDD.[26] Furthermore, the autonomic nervous system dysregulation characteristic of cPTSD may be a risk factor for PMDD.[24]

While the 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 illness 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 PMDD include endometriosis, fibroids, menopause fibromyalgia, thyroid disorder, migraine, major depression, borderline personality disorder, bipolar affective disorder (type 2) and panic disorder.[27]

Investigations include blood tests measuring thyroid, liver and renal function as well as full blood examination, iron studies (for anaemia due to menorrhagia), clotting factors (before starting hormone therapy), vitamin B12, electrolytes and measures of the HPG axis. HPG measures include oestradiol, progesterone, FSH, LH, prolactin, testosterone, SHBG and DHEA, and are done to exclude menopause changes, polycystic ovarian syndrome (PCOS) or other hormonal abnormalities.

The HPG axis investigations are not a test for PMDD itself. Other investigations need to be done per the patient's health status, age, lifestyle and risk factors. Gynaecological investigations include a routine cervical screening test and special investigations for endometriosis if clinical symptoms and signs 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

develop effective strategies to manage those women with significant depression and other physical issues every month. As mentioned, gonadal hormones have potent central effects and there is a valid biological basis to explain the relationship between menstrual (and menopausal) phases and mental health.

Management options need to include the holistic consideration of all aspects of the woman's life including her current physical health, work, relationships, previous traumas and daily demands.

In the author's experience, many women experiencing PMDD require hormone treatment and other strategies to assist them to improve their quality of life. Clinical experience suggests that women are more likely to try hormone strategies initially compared with psychotropic medications; the latter have associated stigma and side effects, as well as withdrawal symptoms when ceased.

Concomitant psychotherapy is critical for women with PMDD and the nature of this therapy depends on the woman's history, current social context and psychological insight. Healthy eating, regular exercise, a good sleep pattern, limited alcohol intake, no cigarette smoking and no illicit drug use are all part of a healthy lifestyle approach required to manage PMDD. Importantly, address interpersonal violence or bullying in the woman's domestic or workplace environment urgently to ensure her safety and promote her self-esteem.

The staged/tiered treatment model appears in table 2.

Table 2. Staged treatment of PMDD

Tier	Treatment
1	Complementary treatments: Exercise, primrose oil, CBT, vitamin B6, magnesium, can be useful for PMS but not PMDD Combined oral contraceptive pill (COCP): Taken continuously for three or more cycles (without placebo pills). Newer generation COCPs (Zoely, Yaz, Diane) are more effective than the older COCPs, but differential depressive responses can occur in individual women COCP (continuous) plus antidepressant (intermittent SSRI or SNRI or agomelatine)
2	COCP plus oestradiol patches (25 or 50 or 100µg) plus antidepressant (intermittent SSRI or agomelatine) Oestradiol patches (50 or 100µg) plus micronised progesterone (100mg or 200mg [day 17-28], orally or vaginally) plus antidepressant (intermittent SSRI or SNRI or agomelatine) Oestradiol patches (100µg) plus micronised progesterone (100mg or 20 mg [day 17-28], orally or vaginally) plus higher dose SSRIs or SNRIs continuously eg, citalopram/escitalopram 20-40mg, venlafaxine
3	GnRH analogues plus add-back HRT (continuous combined oestrogen plus progesterone [eg, 50-100µg oestradiol patches or 2-4 doses of oestradiol gel combined with micronised progesterone 100mg/day] or tibolone 2.5mg/day
4	Surgery plus HRT

Adapted from the RCOG UK treatment guidelines[27]

Current evidence for the staged treatment guidelines

COMPLEMENTARY THERAPIES

To date, there is limited evidence for the efficacy of complementary treatments for PMDD. While physical symptoms may respond, trials of evening primrose oil showed minimal response in the depressive symptoms of PMDD.[27] Interestingly, a systematic review into herbal remedies for PMS supported the use of *Vitex agnus-castus* (also known as chasteberry) but evidence is contradictory for calcium, vitamin B6 and gingko biloba.[27]

There are not enough published controlled trials to comment on the efficacy of saffron, curcumin, lemon balm, wheatgerm and isoflavones in PMDD.[27] A trial of St John's Wort in mild PMS showed significant improvements in behavioural and physical symptoms but no impact on mood or pain-related symptoms.[28] St John's Wort interacts with other medications; in particular it should not be used concurrently with SSRIs and it can render low-dose COCPs ineffective. Exercise is thought to have some benefit for milder PMS symptoms.[29]

COMBINED ORAL CONTRACEPTIVES

Studies investigating the efficacy of the COCP use to alleviate premenstrual mood symptoms have had mixed results.[30,31] Joffe and colleagues compared premenstrual symptoms in women before first oral contraceptive pill (OCP) use with symptoms experienced while using an OCP.[30] Of the 658 women studied, 12.3% reported an improvement in mood, while 16.3% reported a deterioration. This suggests that the OCP does not necessarily influence mood symptoms. Note that the type of OCP (that is, mono-/triphasic, high/low dose) was not factored into the analysis. However, considering the women in the study were aged 36-44, it is likely they were taking higher-dose OCPs.

It has been suggested that newer, low-dose OCPs have more positive effects on mood and that monophasic OCPs could help stabilise mood more effectively than triphasic pills.[32,33] Recent trials using a combination OCP (drospirenone and ethinyl oestradiol) have shown improved mood symptoms in women with PMDD.[34,35]

For example, Pearlstein and colleagues examined the effects of a low-dose OCP (drospirenone 3mg/ethinyl oestradiol 20µg) for the treatment of PMDD in a double-blind, placebo-controlled, crossover study.[35] Subjects (n=64) were treated with the monophasic OCP or placebo for three months, with a one-month washout period before switching treatment regimens. Treatment response occurred in 62% of the active-treatment group and 32% of the placebo group.

There is no single clear theory that explains exactly which hormones trigger specific chemicals — or why only some women experience PMDD.

Despite these results suggesting that certain OCPs might improve mood, future studies to investigate the dose and dose regimen are required to clarify the role of OCPs in the treatment of PMS/PMDD. Newer pills that include 17-beta oestradiol 1.5mg + nomegestrol acetate 2.5mg or combinations of estetrol (E4) + drospirenone appear promising in clinical practice for the treatment of PMDD but are yet to be trialled for this indication.

Continuous COCP therapy compared with 21/7 dosing showed that a 168-day extended regimen of drospirenone 3mg and ethinyl oestradiol 30µg led to a significant decrease in premenstrual-type symptoms compared with a standard 21/7-day regimen.[36] Phase II of this trial extended the continuous use of this COCP for a total of 364 days. Menstrual symptoms were recorded on DRSP charts. The results concluded that mood, headache and pelvic pain scores improved compared with a 21/7-day regimen. Most women reported a high level of satisfaction.

ANTIDEPRESSANTS

Studies suggest that 60-70% of women respond to SSRIs while approximately 30% of women respond to placebo.[37] SSRIs may be taken continuously (every day of the menstrual cycle), during the luteal phase, using an intermittent dosing approach (from ovulation to the first day of menses), or from symptom onset (from the day that symptoms start during the luteal phase to the first day of menses).

Fluoxetine, sertraline, and paroxetine (both continuous and luteal-phase administration) are approved by the FDA for the treatment of PMDD. SNRIs are commonly associated with significant withdrawal symptoms, so are more difficult to use in an intermittent fashion. If the woman is stabilised on an SNRI, then continuous use of this is better with respect to withdrawal symptoms. More recently, agomelatine appears to be a useful antidepressant for PMDD with decreased side effects on intermittent use and increased efficacy in treating sleep disturbances.[38]

OESTRADIOL AND PROGESTERONE TREATMENTS

Percutaneous oestradiol together with cyclical progestogen has been shown to be effective in the management of the physical and psychological symptoms of PMDD. Percutaneous preparations provide sufficient oestradiol levels to suppress ovarian activity. Trials have demonstrated that 17b-oestradiol combined with cyclical progestogens are effective in the management of severe symptoms of PMS.[39,40] When treating women with percutaneous oestradiol, also prescribe treatment with oral or vaginal progesterone to prevent endometrial hyperplasia. Increased frequency of breast screening is needed in women receiving hormone treatment.

Micronised oral progesterone (100 or 200mg) has fewer androgenic and unwanted adverse effects compared with the progestogens norethisterone and levonorgestrel. Progesterone may act as a diuretic and central nervous system anxiolytic, which in theory could alleviate the symptoms of PMS, although there is currently little evidence to demonstrate this.[41] Micronised progesterone can also be administered vaginally, which may be better tolerated as it avoids first-pass hepatic metabolism. Vaginally administered progesterone also avoids the formation of psychoactive metabolites such as ALLO.[42] The new ALLO modulators that are currently being trialled for future treatment of PMDD are of great interest.[22]

GNRH ANALOGUES

Gonadotropin releasing hormone (GnRH) analogues are highly effective in treating severe PMDD. They should usually be reserved for women with the most severe symptoms and are not routinely recommended unless they are used to aid diagnosis or treat particularly severe cases. This is because of their effects on bone mineral density. GnRH analogues suppress ovarian steroid production and thus result in a dramatic improvement or complete cessation of symptoms in patients with core premenstrual dysphorias.

A meta-analysis of seven trials identified 71 women on active treatment. GnRH analogue therapy did not result in elimination of premenstrual symptoms, but the lack of efficacy was in part because of diagnostic difficulties rather than a limitation of the therapy.[43]

When treating women with severe PMS using GnRH analogues for more than six months, add-back hormone therapy should be used. Add-back hormone therapy includes continuous combined HRT or tibolone and is important to maintain healthy bone mineral density.[43]

SURGERY AND HORMONE THERAPY

Most cases of severe PMDD can be successfully treated with medical management. However, hysterectomy with bilateral oophorectomy can be justified in women where medical management is unsuccessful, where long-term GnRH analogue treatment is required, or if gynaecological comorbidities indicate hysterectomy.[44] Advise women being surgically treated for PMDD to use HRT, particularly if they are younger than 45. Following hysterectomy, oestrogen-only replacement can be used. The avoidance of progestogen prevents reintroduction of PMDD-type adverse effects. Consider testosterone replacement, as the ovaries produce 50% of the body's testosterone and deficiency may result in distressing low libido (hypoactive sexual desire disorder).[45]

CASE STUDY

SARAH, 35, is a secondary school teacher and a talented artist. She is referred to a Women's Mental Health Clinic following a suicide attempt.

She says: "About every month I feel suddenly depressed — for no reason, and then I get overwhelmed by incredible tiredness and brain fog. I just can't do my work, can't be bothered talking to my partner or doing anything — even brushing my hair seems too hard. And then after about a week or 10 days, I suddenly feel fine. Usually, I feel better when I start to have a period. This started in my teens and keeps happening. I feel like I am only alive for part of each month — it's horrible."

Eight years earlier Sarah had consulted a psychiatrist who diagnosed bipolar affective disorder — type 2. The diagnosis was based on Sarah's history of cyclical depression while in between episodes, she described herself as "Great, well-able to produce meaningful paintings and teach art to years 11 and 12. When I am feeling good, I get lots done like cleaning the house, planning lessons, baking and preparing everything I can as a kind of 'stocking up' for when I get depressed and just can't do anything". This was interpreted as a hypomanic episode.

When Sarah tried to discuss her observations that her depression was cyclical and related to her menstrual periods, this was dismissed as irrelevant.

She was treated with a combination of lithium carbonate 750mg twice daily, quetiapine 600mg at night and fluoxetine 40mg daily. She was admitted to a psychiatry ward on three occasions for medication stabilisation.

Sarah gained 20kg, her BMI increased to 30kg/m^2 and her menstrual cycle became more irregular. She became hypothyroid and was treated with 50µg thyroxine daily. She continued to experience depression in a cyclical fashion.

She developed a tremor in both hands, and this interfered with her ability to paint, depriving her of an important creative aspect of her life. Her frequent work absences led to the loss of a valued teaching job she had enjoyed for six years. A five-year intimate relationship ended because her partner could not cope with her depression and associated symptoms.

It was at this stage Sarah attempted suicide during an episode of depression.

Sarah's history reveals she was born in a metropolitan suburb. Her parents split up when she was two and her mother found a new partner when Sarah was five. She had no further contact with her biological father.

Her stepfather was physically violent towards Sarah, her two stepbrothers and her mother. Sarah also experienced verbal abuse from her stepbrothers. She discovered that school was a haven for her, particularly art classes, and eventually left home to attend university, completing a teaching degree majoring in fine art.

Sarah was involved in emotionally abusive intimate relationships at ages 19 and 22. She was referred for therapy with a clinical psychologist and came to understand the extent of her early life trauma and the impact it had on her quality of life as an adult.

At 27, she met Michael, and they planned a life together. They both wanted children, but because of her ▸

◂ diagnosis of bipolar affective disorder and the psychotropic drugs, her GP and psychiatrist advised against a pregnancy. After five years of recurrent, worsening depression and hospitalisations, the couple separated.

Sarah's history prompts further exploration of the cyclical nature of her depression. She had kept records of her cycles with mood charts and a pattern of monthly sudden onset 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.

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

A working diagnosis of PMDD is made and Sarah is started on the COCP, 'Zoely' (1.5mg 17 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 tremor 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 25µg 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 ensure optimal outcomes.

RESOURCES

- **Carolina Premenstrual Assessment Scoring System** www.med.unc.edu/psych/wmd/files/2018/07/CPASSWorksheet.pdf

- **Daily Record of Severity of Problems** www.aafp.org/afp/2011/1015/afp20111015p918-fig1.pdf

References on request from howtotreat@adg.com.au

How to Treat Quiz.

PREMENSTRUAL DYSPHORIC DISORDER

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1. **Which THREE statements regarding premenstrual dysphoric disorder are correct?**
   - **a** Women experience both physical symptoms, and irritability and dysphoria.
   - **b** The condition affects about 2-8% of the reproductive female population.
   - **c** The conditions 'premenstrual syndrome' and 'premenstrual dysphoric disorder' are synonymous.
   - **d** It is a severe, debilitating depression with high morbidity and mortality.

2. **Which TWO statements regarding the clinical presentation PMDD are correct?**
   - **a** The Carolina Premenstrual Assessment Scoring System (C-PASS)-17 has been proposed to validate PMDD as a diagnosis.
   - **b** The DSM-5 criteria emphasise symptomatology, and confirmation of the disorder relies on three symptomatic cycles as a minimum validation for PMDD.
   - **c** An increased rate of suicide has not been described in women with PMDD.
   - **d** Note all details of suicidal ideation, plans and attempts.

3. **Which THREE are key features for the diagnosis of PMDD?**
   - **a** An absence of new stressors or clear precipitating psychosocial factors causing depression.
   - **b** A rapid, sudden onset of five symptoms that interfere with usual activities.
   - **c** Onset of symptoms must be related to the exact premenstrual (luteal) phase of a regular cycle.
   - **d** A rapid, sudden offset of the above mood and associated symptoms after 7-10 days.

4. **Which TWO statements regarding the causes of PMDD are correct?**
   - **a** The link between gonadal hormones and brain chemistry is tenuous.
   - **b** Some women are susceptible to mood changes with very small swings in gonadal hormones.
   - **c** Many of the physical symptoms are the direct effect of gonadal hormones.
   - **d** During high oestrogen phases of the menstrual cycle, depression and other adverse mental symptoms worsen.

5. **Which THREE statements regarding early life trauma and PMDD are correct?**
   - **a** There is a clear link between early trauma and PMDD.
   - **b** Complex PTSD (cPTSD) is often comorbid with PMDD.
   - **c** A detailed developmental history in patients with PMDD may help understand the patient's illness and management context.
   - **d** The metabolic feedback links between the HPA and HPG axes may explain the relationship between HPA dysregulation in women with cPTSD who also experience PMDD.

6. **Which TWO are differential diagnoses for PMDD?**
   - **a** Pregnancy.
   - **b** Major depression.
   - **c** Endometrial cancer.
   - **d** Thyroid disorders.

7. **Which THREE are appropriate investigations in a patient with suspected PMDD?**
   - **a** FBC, UEC, TFTs, LFTs, iron studies, clotting factors and B12.
   - **b** Routine cervical screening test.
   - **c** Measures of the HPG axis.
   - **d** CT brain.

8. **Which THREE may be appropriate medications in PMDD?**
   - **a** Combined oral contraceptive pill.
   - **b** High dose oil of evening primrose.
   - **c** Combined oral contraceptive pill plus antidepressant.
   - **d** GnRH analogues plus add-back HRT.

9. **Which THREE statements regarding the management of PMDD are correct?**
   - **a** There is no difference in the improvement in mood symptoms between the older and newer COCPs.
   - **b** Many women experiencing PMDD require hormone treatment and other strategies to assist them to improve their quality of life.
   - **c** A staged/tiered treatment model may be required.
   - **d** SNRIs are commonly associated with significant withdrawal symptoms, so are more difficult to use in an intermittent fashion.

10. **Which THREE statements regarding the management of PMDD are correct?**
    - **a** Agomelatine appears to be a useful antidepressant for PMDD, with decreased side effects from intermittent use.
    - **b** GnRH analogues are highly effective in treating severe PMDD and are indicated as first-line therapy.
    - **c** Increased frequency of breast screening is needed in women receiving hormone treatment.
    - **d** Hysterectomy with bilateral oophorectomy can be justified in women where medical management is unsuccessful.

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