A WOMAN has premenstrual syndrome (PMS) if she complains of recurrent psychological or somatic symptoms — and often both — occurring specifically during the luteal phase of the menstrual cycle (typically from day 14 to day 28) and resolving by the end of menstruation (typically day 5 of the cycle; see Figure 1, p444). These symptoms can be so severe that they disrupt normal functioning, quality of life and personal relationships.

**Symptoms**

The most commonly recognised symptoms of PMS include:

- Irritability
- Aggression
- Depression
- Tension
- Bloatedness and fluid retention (which are often reported as weight gain)
- Mastalgia

The degree and type of PMS symptoms can vary significantly between women. Only 5 per cent of women of reproductive age are symptom-free premenstrually (ie, in the two weeks before menstruation) — most have at least one premenstrual symptom. Severe, debilitating symptoms occur in about 5 per cent of these women. Serious related consequences of such symptoms include suicide and criminal activities, including child abuse. PMS of this severity is sometimes called “premenstrual dysphoric disorder” (PMDD) and defined in the American Psychiatric Association in its Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV; but see Panel 2 on p443).

**Possible mechanisms**

The definitive cause of PMS is not known and many theories have been proposed. It has been suggested that fluctuation in mood may be related to ovarian hormone imbalance. A link to hormone changes, particularly progesterone, seems likely because the temporal relationship between progesterone secretion and symptoms is so close. It is also likely that there is a hormone-related trigger factor. This could include abnormal metabolism of progesterone to its metabolites allopregnanolone and pregnanolone, which are neuroactive steroids with differential effects on anxiety-related symptoms. Investigations of these metabolites have shown that women with PMS have lower levels of allopregnanolone in the luteal phase and this deficiency may give rise to PMS.

**Diagnosis**

PMS is unusual in that women commonly present themselves with a self diagnosis of PMS, and...
it is the clinician’s role to determine the validity of this. In particular, women with unrelated psychiatric disorders often find it more acceptable to label their problems as PMS rather than suffer the stigma of depression. PMS must also be distinguished from premenstrual magnification, in which symptoms are present throughout the cycle, but are exacerbated premenstrually — underlying psychiatric or medical disorders can worsen in the luteal phase.

For practical clinical purposes, reliance is placed on the patient’s medical and symptom history, qualification of symptoms and the exclusion of certain specific disorders.

Symptoms must have occurred in at least four of the previous six cycles. Some women may have an additional underlying psychological disorder that coexists with PMS; others may actually have depression unrelated to their cycle. These patients are distinguished by the fact that their symptoms fail to resolve after menstruation.

Keeping a diary
Because there are no objective tests that can be used to confirm PMS, the diagnosis is made on the basis of daily symptom recording using various rating scales.

The symptoms should be recorded over two cycles using a symptoms diary. The Daily Record of Severity of Problems (DSRP) is a form recommended by the Royal College of Obstetricians and Gynaecologists (RCOG). It is mainly used in research and is not in general use outside the US.

Physical examination
Although physical examination of patients who may have PMS will make little contribution to diagnosis, the importance of opportunistic screening and the exclusion of disorders that can cause similar somatic symptoms, such as pelvic pain and abdominal bloating, justifies this practice. Reassurance that there is no breast, cervical or pelvic cancer is of particular value, and, of course, patients should not receive hormonal therapy (see later) without such an examination.

Blood tests
There is no objective measure, such as a biochemical test, to diagnose PMS or its severity. However, blood tests may be useful to exclude other disorders such as menopause, polycystic ovary syndrome, hyper- or hypothyroidism and anaemia.

Many disorders have been wrongly attributed to PMS. The key to diagnosis is the cyclicity of the symptoms. If these are not relieved by the end of menstruation, an alternative explanation must be sought. For example, non-cyclical breast pain may be due to an underlying condition such as a cyst.

Management
Basic management of PMS lies within the scope of primary care, and the need for specialist support or care will depend on severity of the problem, the experience of the clinician and the expectations of the patient. Panel 2 contains definitions for different grades of PMS but more research is needed to make these more robust.

Making lifestyle adjustments, such as adopting a low glycaemic index diet and stress reduction, is good general advice and should be considered for all patients. Advice that pharmacists may give is outlined in Panel 3.

Approaches to drug treatment fall into two broad strategies:
1) Correction of any neuroendocrine anomaly
2) Suppression of ovulation

Prescribing decisions will be based on symptom severity and on the availability of support services. Advice can be ad hoc and many GPs may ask patients to purchase dietary supplements.

In most cases, a specialist is required if a woman is experiencing disruption of her family or professional life and previous treatment has failed. These women should, preferably, be seen in a multidisciplinary setting with a gynaecologist and input from a psychiatrist with a special interest in this field.

Note that marked placebo responses have been found in all randomised controlled trials of PMS treatments. The strength of the placebo effect may reflect the positive role of detailed history taking and a sympathetic approach. Many of the products prescribed for PMS are used off-licence.

Dietary supplements
Dietary supplements are popular because they are perceived to have fewer side effects than conventional medicines. Vitamin B12 (cyanocobalamin), isoflavones, calcium, magnesium and vitamin E have all been assessed in placebo-controlled trials. Results demonstrated beneficial effects with calcium, calcium with vitamin D, magnesium, vitamin E and isoflavones. Doses are generally based on recommended daily intake levels.

High-dose vitamin B6 (pyridoxine) may help in the treatment of premenstrual symptoms, particularly depression. However, doses above 200mg daily, have been reported to have neurotoxic effects14 so only doses up to 100mg daily (unlicensed indication) should be used. It has been suggested that B6 is involved with the production of serotonin in the brain and low serotonin levels cause depression. It is also thought that oestrogen may interfere with the body’s use of B6. Note that the safety of long-term supplementation with doses above 10mg daily has not been established.15

Herbal products
The fruit of the chaste tree (Vitex agnus castus L) contains a mixture

<table>
<thead>
<tr>
<th>PANEL 1: SYMPTOMS TO RECORD DAILY</th>
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<tbody>
<tr>
<td>Feeling depressed</td>
</tr>
<tr>
<td>Feeling anxious</td>
</tr>
<tr>
<td>Mood swings</td>
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<tr>
<td>Feeling angry or irritable</td>
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<tr>
<td>Loss of interest in usual activities</td>
</tr>
<tr>
<td>Difficulty concentrating</td>
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<tr>
<td>Feeling lethargic</td>
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<tr>
<td>Increased appetite, overeating or experiencing cravings</td>
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<tr>
<td>Problems with sleep (trouble falling asleep, or getting up)</td>
</tr>
<tr>
<td>Feeling overwhelmed or out of control</td>
</tr>
<tr>
<td>Breast tenderness, breast swelling, bloatedness, weight gain, headache or muscle aches</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>PANEL 2: GRADES OF PMS*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild Symptoms do not interfere with personal, social or professional life.</td>
</tr>
<tr>
<td>Moderate Symptoms interfere with personal, social and professional life but the woman is able to function and interact, albeit suboptimally.</td>
</tr>
<tr>
<td>Severe The woman is unable to interact personally, socially or professionally because of symptoms. She withdraws from social and professional activities.</td>
</tr>
</tbody>
</table>

Note that “premenstrual dysphoric disorder” is a term mainly used in research and is not in general use outside the US.

* Adapted from the Royal College of Obstetricians and Gynaecologists Green-top Guidelines
of iridoids and flavonoids and some compounds similar in structure to sex steroids. A multicentre randomised controlled study has shown agnus castus to be significantly more effective than placebo for most of the premenstrual symptoms assessed, except for bloating.14 On the basis of this current evidence, agnus castus fruit extract seems to be a potentially useful therapy for PMS, but no standard medicinal product is currently available in the UK.

Agnus castus has been reported to interact with dopaminergic drugs and with oestrogens and oestrogen antagonists.15 It is not recommended for use by women who are trying to conceive, pregnant or breastfeeding. Ginkgo biloba and pollen extract have both been shown to be beneficial in small scale studies, although further data are needed to support their use.8

Evening primrose oil, a source of gamma-linolenic acid, is popularly reputed to be a treatment for PMS. However, there is no good clinical proof that it works.14 Starflower oil is another source of gamma-linolenic acid requested by some compounds similar in structure to sex steroids.

Cognitive behavioural therapy
Cognitive behavioural therapy has been shown to provide better results with maintenance of benefit over 12 months of follow up, compared with fluoxetine.17 However, this therapy is intensive, involving weekly sessions, and not widely available on the NHS.

GP referrals can be made if a CBT service has been commissioned.

Alternative approaches
Massage, relaxation and aromatherapy are popular, where benefit is likely to outweigh any possible harm, although studies have shown inconclusive results.10 Advice about graded exercise (ie, activity that starts slow and increased over time) is useful for general health. However there is no evidence for or against a specific benefit in PMS. Self monitoring and self regulation compared with peer support groups with professional guidance have been studied. The latter intervention was reported to be effective,18 with a 75 per cent reduction in severity of PMS.

SSRIs
Selective serotonin reuptake inhibitors are now regarded as first-line therapy for severe PMS.8 These medicines should be initiated in a multidisciplinary setting with psychiatrist availability. Around 30–40 per cent of patients fail to respond to SSRIs.

There have been various trials for the use of SSRIs for PMS.19 Drugs most commonly studied were fluoxetine and sertraline, followed by citalopram, paroxetine, clomipramine and fluvoxamine. Some studies compared different dose levels and others included

Further reading
- “Premenstrual syndrome, management” from the Royal College of Obstetricians and Gynaecologists (December 2007) reviews the diagnosis and management PMS, in particular, the evidence for pharmacological and non-pharmacological treatments. It is available at www.rcog.org.uk.
- Treatment guidelines for premenstrual syndrome (available to purchase from the National Association for Premenstrual Syndrome).

Hormonal methods
Clinicians have sought various strategies to suppress ovulation because it appears to act as a PMS trigger. Most women with PMS have no underlying endocrine disorder.

Combined oral contraceptives
The observation that symptoms of PMS are present in the post-ovulatory phase of the menstrual cycle, and the fact that they disappear with spontaneous ovulation, strongly suggest that any therapy which suppresses ovulation should relieve PMS. The combined oral contraceptive pill (COCP) has been popular because it is cheap and suitable for long-term use. However, although some studies have shown a reduction in the prevalence and severity of PMS, others have failed to show any difference in cyclical symptoms between COCP users and non-users.22 This is probably due to the fact that the progestogens used in second generation pills were either levonorgestrel or norethisterone — C19 testosterone analogues which can cause PMS-like symptoms. The COCP Yasmin contains an antimineralocorticoid and anti-androgenic progestogen, drospirenone. A systemic review of five RCTs23 including a total of 1,500 women compared a combined pill containing drospirenone with placebo or other COCPs — one with desogestrel and the other with levonorgestrel. Pils containing drospirenone, a spironolactone analogue, were significantly more effective than placebo over a three-month treatment period. Both 30μg and 20μg doses of ethinylestradiol were included in the COCPs studied in this trial.
Overall, this evidence suggests that a trial of therapy with a low dose COCP is appropriate for women with no contraindication to its use, and that pills containing third-generation progestogens are more effective than those containing second-generation progestogens.

Transdermal estradiol Percutaneous estradiol, either as an implant or as a patch, has been used in combination with cyclical progestogens for the management of physical and psychological symptoms of severe PMS. A dose of 200μg/24h estradiol patch twice weekly was found to be more effective than placebo in an initial study. Subsequently, a lower dose of 100μg/24h twice weekly was found to be as effective in reducing symptom levels in severe premenstrual syndrome and this dose was better tolerated.21 These limited data support the role of transdermal estradiol for the relief of PMS, although information on its long-term safety in relation to breast and endometrial cancer and cardiovascular risk is lacking. Its use with the levonorgestrel-releasing intrauterine system for endometrial protection can be considered.

GnRH analogues Gonadotrophin-releasing hormone (GnRH) analogues (eg, nafarelin and goserelin) have been successfully used to suppress ovarian steroid production, and should eliminate PMS if symptoms are triggered by ovulation. A meta-analysis of studies comparing a GnRH agonist with placebo has shown a reduction in both physical and behavioural symptoms.22 However, oestrogen should also be prescribed (hormonal add-back) if treatment is long term.

GnRH analogues are effective in the management of severe PMS, but the cost and potentially long-term nature of treatment when used with hormonal add-back should limit its use to women with severe symptoms that are socially disruptive and resistant to other forms of treatment. GnRH analogues can offer a useful means of further assessment of the pattern and nature of cyclical symptoms where the diagnosis is unclear or oophorectomy is considered.

Danazol Cycle suppression may be achieved using danazol, an androgenic steroid. A dose of 200mg/day in a crossover study showed clinically significant improvement compared with placebo.23 However, the side effects (eg, acne, fatigue) and metabolic sequelae (eg, insulin resistance) limit its usefulness for long-term management of PMS.

Progestosterone Based on the unfounded assumption that PMS is secondary to a progestosterone deficiency, there has been widespread use of luteal-phase progestogen supplements. A systematic review assessed 14 RCTs of progesterone and four of progestogens in PMS.24 Overall the results demonstrated no difference compared with placebo. Results with progestogens were difficult to interpret due to the small number of studies, but, overall, odds ratios were marginally in favour of progestogens for both physical and behavioural symptoms. Drop out from the studies due to side effects, however, was high.

The evidence base does not support the use of either progesterone or progestogens in the management of PMS when given during the luteal phase only. The continuous use of progestogens in ovulation suppressive doses may be beneficial but there is insufficient evidence to support this fully. Until recently in the UK natural progesterone was only available in the form of vaginal or rectal creams and pessaries so synthetic progestogens were used where tablets were required. However, these progestogens were linked to PMS-like side effects. Progestrone capsules are now available although they have not been tested for PMS.

Surgery Hysterectomy with bilateral oophorectomy stops the ovarian cycle, but is rarely justified. For example, in women undergoing hysterectomy for other indications, a history of PMS is not a sufficient indication for concurrent oophorectomy without careful assessment. Unless there are other reasons for hysterectomy, laparoscopic oophorectomy offers a less invasive surgical approach.

Role for pharmacists PMS remains, to this day, a poorly diagnosed and inadequately managed condition despite there being a wide range of therapies with proven efficacy, particularly for severe symptoms. Pharmacists can play a part in helping women to manage PMS by:

* Advising those who suspect they may be suffering from PMS to complete a diary (eg, the Daily Record of Severity of Problems) for two months and then see their GP for further evaluation.
* Providing advice on lifestyle adjustments and on the use of dietary supplements.
* Offering immediate treatment of symptoms over the counter (eg, analgesics for breast tenderness with pain).
* Referring women with PMS to support and self-help groups (see Signposting), or running such groups in a community setting.
* Referring women to a registered psychologist trained in providing CBT (many will take self referrals or referrals from health professionals on a private basis).

Specialist support groups

The National Association for Premenstrual Syndrome (www.pms.org.uk) is an advocacy group that aims to promote the interest of PMS sufferers. Members of the group are given access to personal advice and other information. (There is a fee for joining.)

Signposting

* Patient information leaflets on PMS are available from www.rcog.org.uk and www.patient.co.uk.
* The National Association for Premenstrual Syndrome (www.pms.org.uk) is an advocacy group that aims to promote the interest of PMS sufferers. Members of the group are given access to personal advice and other information. (There is a fee for joining.)

**PRACTICE POINTS**

Reading is only one way to undertake CPD and the regulator will expect to see various approaches in a pharmacist’s CPD portfolio.

1. Visit www.pmdd.factsforhealth.org, download the Daily Record of Severity Problems form and make sure you can explain how to use it.
2. Read the patient information leaflets on PMS cited in Signposting. Which do you prefer?
3. Find out more about agnus castus: look up its other reputed uses.

Consider making this activity one of your nine CPD entries this year.

**References available online.**