5.2 *Who are the key health professionals to manage women with severe PMS?*

Women with severe PMS may benefit from being managed by a multidisciplinary team comprising a general practitioner, a general gynaecologist or a gynaecologist with a special interest in PMS, a mental health professional (psychiatrist, clinical psychologist or counsellor) and a dietician. ✓

While this set-up is desirable, it is not widely available or implemented within the National Health Service (NHS). There are specialist clinics within tertiary centres to which patients can be referred. However, it is likely that the general practitioner will remain key in facilitating potential treatments. A multidisciplinary team can offer women an individualised management plan utilising a range of treatments, such as cognitive behavioural therapy (CBT) and lifestyle interventions.[11]

6. How is PMS managed?

6.1 *Are complementary therapies efficacious in treating PMS?*

Women with PMS should be informed that there is conflicting evidence to support the use of some complementary medicines. C

An integrated holistic approach should be used when treating women with PMS. ✓

Interactions with conventional medicines should be considered. ✓

Although there is limited evidence to support the use of complementary therapies, some women with PMS may benefit from a holistic approach.[12] This is particularly important for women in whom hormonal therapy is contraindicated. It is important to evaluate evidence carefully for PMS as there is a 36–43% placebo response.[13,14]

Evidence level 1–

Table 1 summarises current research into the benefits of selected complementary therapies for the treatment of PMS.

Unsaturated fatty acids, as contained in evening primrose oil, have been shown in one prospective randomised trial[15] to improve menstrual symptoms compared with placebo at both 1 g/day and 2 g/day dosages. There was no measurable change in cholesterol levels.

Dante et al.[16] conducted a systematic review into herbal remedies for PMS. Four of the trials, including almost 600 women, supported the use of *Vitex agnus castus* L. (also known as chasteberry). However, this study concluded that there were inadequate safety data to support its use.

Whelan et al.[17] conducted a systematic review of 29 randomised controlled trials (RCTs). Two of these studies (n = 499) revealed consistent evidence for calcium in alleviating both physical and psychological symptoms of PMS. The evidence for both vitamin B6 and *Vitex* was contradictory in this review and therefore advice could not be given for either. Due to the lack of power, reliable recommendations cannot be provided.

Table 1. Summary of evidence for selected complementary therapies

Complementary therapy	Benefit	Types of studies	Numbers in the study	Note
Exercise[22–25]	Some benefit	Nonrandomised and randomised	72 (4 published studies)	High quality studies recommended.
Reflexology[26]	Some benefit	Randomised	35	
Vitamin B6[27–39]	Mixed results	Double-blind Randomised Cross-over	1067 (13 published studies)	Peripheral neuropathy with high doses (most studies performed using higher doses). Department of Health restricts the daily dose to 10 mg.
Magnesium[37,40,41]	Mixed results	Double-blind Randomised Cross-over	153 (3 published studies)	Used in premenstrual phase.
Multivitamins[42–45]	Unknown	–	400 (several published studies)	Unclear which are the active ingredients.
Calcium/ vitamin D[46,47]	Yes	Double-blind Randomised Cross-over	499 (2 published studies)	
Isoflavones[48,49]	Mixed results	Double-blind Randomised Cross-over	72 (2 published studies)	May benefit menstrual migraine.
Vitex agnus castus L.[19,39,50–54]	Yes	Double-blind Randomised	923 (7 published studies)	There is no standardised preparation.
St John's Wort[20,21,55,56]	Mixed results	Double-blind Placebo-controlled	401 (4 published studies)	May benefit physical and behavioural symptoms. Many withdrew from one study due to adverse effects. Significant interactions with conventional medicines. The British National Formulary advises avoid concomitant use with SSRIs.
Ginkgo biloba[57,58]	Some benefit	Double-blind Placebo-controlled	233 (2 published studies)	
Saffron[59]	Yes	Double-blind Placebo-controlled	47	Further data before recommendation.
Evening primrose oil[15,60–63]	Some benefit	Double-blind Placebo-controlled Cross-over	215 (4 published studies)	May benefit women with cyclical breast symptoms.

Table 1. (Continued)

Complementary therapy	Benefit	Types of studies	Numbers in the study	Note
Acupuncture[64–73]	Some benefit	Case–control	235 (10 published studies)	High risk of bias. Further data before recommendation.
Lemon balm[74]	Some benefit	Double-blind Placebo-controlled	100 (1 published study)	PMS severity quantified by PSST. Further data before recommendation.
Curcumin[75]	Some benefit	Double-blind Placebo-controlled	70 (1 published study)	PMS severity quantified by an unvalidated symptom score. Further data before recommendation.
Wheat germ[76]	Some benefit	Triple-blind Placebo-controlled	84 (1 published study)	PMS severity quantified by an unvalidated symptom score. Further data before recommendation.

A systematic review[18] focusing on the use of *Vitex* illustrated that in four out of five discrete placebo-controlled trials and two comparator trials, *Vitex* was superior to placebo, pyridoxine and magnesium in the treatment of PMS. In another study, it appeared comparable to fluoxetine for PMDD.[16] The safety of *Vitex* is described as excellent, with adverse effects being infrequent and mild.[18,19] Studies have shown a dose dependent treatment response; however, due to the variability in quality and content of preparations a dosage range to treat PMS cannot be recommended.

RCTs including St John's Wort (*Hypericum perforatum*) show conflicting results. A trial[20] including 36 women with mild PMS showed significant improvements in physical and behavioural symptoms but no improvement in mood or pain-related symptoms. Another trial[21] including 125 women found no evidence of benefit but felt that this may be attributable to low statistical power. St John's Wort interacts with other medications, in particular it should not be used concurrently with SSRIs and can render low dose COCs ineffective.

Evidence level 1–

6.2 *Is there a role for CBT and other psychological counselling techniques?*

When treating women with severe PMS, CBT should be considered routinely as a treatment option.

A

Hunter et al.[77] conducted a randomised trial comparing fluoxetine, CBT and the combination of fluoxetine and CBT for the treatment of PMDD. After a 6-month treatment period, all three treatment groups showed evidence of benefit, which was similar for each group, with fluoxetine combined with CBT no more effective than the two component therapies used separately. Fluoxetine showed quicker improvements; however at follow-up CBT was associated with better maintenance of treatment effects compared with fluoxetine.

Evidence level 1+

A meta-analysis identified five RCTs testing CBT against a control intervention. The evidence was poor due to a high risk of bias but demonstrated a significant reduction in depression, anxiety and behavioural problems. If CBT proves successful to a patient it would avoid pharmacotherapy and potential adverse effects.[78]

Evidence level 1–

6.3 *Hormonal medical management of PMS*

6.3.1 What is the role of cycle-modifying agents in managing PMS?

6.3.1.1 Which COC has the best evidence for managing PMS, including regimens delivering ethinylestradiol?

When treating women with PMS, drospirenone-containing COCs may represent effective treatment for PMS and should be considered as a first-line pharmaceutical intervention. B

Despite the combined pill's ability to suppress ovulation, studies initially illustrated no benefit in the treatment of PMS.[79] This may be attributed to the progestogens in second-generation pills (levonorgestrel or norethisterone) regenerating PMS-type symptoms. Further research has therefore been directed towards new combined contraceptives, in particular those containing the antimineralocorticoid and antiandrogenic progestogen, such as drospirenone. Evidence level 2+

A Cochrane review[80] involving five RCTs and 1920 participants looked into the effectiveness of drospirenone (3 mg) and ethinylestradiol COCs against placebo or an alternative COC, where the progestogen was substituted for desogestrel (150 micrograms) or levonorgestrel (150 micrograms). This concluded that, when compared with placebo, drospirenone-containing oral contraceptives used for 3 months did reduce the severity of symptoms for those with PMDD (mean difference −7.92; 95% CI −11.16 to −4.67). The severity of symptoms was rated using validated questionnaires and where nonvalidated tools were used the original data were analysed. Evidence level 1−

A double-blind, placebo-controlled, cross-over trial[81] of 64 subjects showed drospirenone 3 mg and ethinylestradiol 20 micrograms to be effective for treating PMDD, based upon DRSP chart scoring. The mean decrease from baseline scoring was −12.47 (95% CI −18.28 to −6.66, $P < 0.001$). Participants were allocated to their initial treatment arm for three cycles and swapped to the alternative treatment arm after one cycle treatment-free.

Another double-blind RCT[82] of 450 participants comparing the same contraceptive pill with placebo also supported its use in PMDD. Evidence level 1+

This oral contraceptive is now available on the NHS in the UK; it is licensed in Europe and the USA for PMDD but only in women requiring oral contraception.

6.3.1.2 What is the optimum COC pill regimen, e.g. continuous, cyclical or flexible?

When treating women with PMS, emerging data suggest use of the contraceptive pill continuously rather than cyclically. ✓

Continuous therapy would seem appropriate; there are some data to support this. Phase I of a study[83] showed that a 168-day extended regimen of drospirenone 3 mg and ethinylestradiol 30 micrograms led to a significant decrease in premenstrual-type symptoms compared with a standard 21/7-day regimen. Phase II of this trial extended the continuous use of this COC for a total of 364 days. Menstrual symptoms were recorded using DRSP charts. The results concluded that mood, headache and pelvic pain scores improved Evidence level 2−

when compared with a 21/7-day regimen. There was a high level of satisfaction, with most women continuing on this regimen 6 months on from the 364-day trial.[84] This trial used a preparation that is currently available in the UK as a 24/4-day regimen containing ethinylestradiol 20 micrograms and drospirenone 3 mg; however, phase II of the study supports continuous use and this may be considered for off-label usage.

Evidence level 2−

6.3.2 How efficacious is percutaneous estradiol?

Percutaneous estradiol combined with cyclical progestogens has been shown to be effective for the management of physical and psychological symptoms of severe PMS.

A

When treating women with PMS, alternative barrier or intrauterine methods of contraception should be used when estradiol is used to suppress ovulation.

✓

Percutaneous preparations give sufficient estradiol levels to suppress ovarian activity. A placebo-controlled trial demonstrated that implants of 17β-estradiol combined with cyclical progestogens are effective for the management of severe PMS symptoms. Administered as a 100-mg implant, this proved to be highly effective when compared with placebo.[85] Both implants and patches have been evaluated in controlled trials but gels have not. Implants are available in the UK but are unlicensed for use in PMS.

In a randomised, double-blind, placebo-controlled trial of 20 women with cross-over at 3 months, transdermal estradiol patches (200 micrograms) were assessed and found to be highly effective.[86] Significant improvements occurred after changing to active treatment, proven by the use of symptom questionnaires. There was concern that estradiol 200 micrograms twice weekly was still too high a dose to be used as long-term therapy. A subsequent randomised study[87] showed that 100-microgram estradiol patches twice weekly were as effective as 200 micrograms in reducing symptom levels in severe PMS and this dosage was better tolerated.[88]

Evidence level 1+

Although doses are usually sufficient to suppress ovulation, contraceptive efficacy has not been demonstrated and so should not be relied upon; additional contraceptive measures should be adopted. It is also important to ensure appropriate endometrial protection (see section 6.3.4).

6.3.3 How can the return of PMS symptoms be avoided during estrogen therapy with progestogenic protection?

When using transdermal estrogen to treat women with PMS, the lowest possible dose of progesterone or progestogen is recommended to minimise progestogenic adverse effects.

A

Women should be informed that low levels of levonorgestrel released by the LNG-IUS 52 mg can initially produce PMS-type adverse effects (as well as bleeding problems).

✓

Micronised progesterone is theoretically less likely to reintroduce PMS-like symptoms and should therefore be considered as first line for progestogenic opposition rather than progestogens.

✓

