The menopause: benefits and risks of available treatments

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Menopausal symptoms affect many women, but debate continues over the role of hormone replacement therapy (HRT) in their management. This review provides a summary of the current treatment options for menopause management and considers their benefits and risks.

Much confusion still exists surrounding menopause management and the role of hormone replacement therapy (HRT), fuelled by publication of the much-debated Women’s Health Initiative (WHI) trial1 and the Million Women Study,2 along with reviews of both these publications.3–7 The NICE guideline Menopause: Diagnosis and Management (NG23),8 published in November 2015, should help to allay some confusion.

This review describes the treatment options currently used to manage menopausal symptoms, highlighting their risks, benefits and side-effects, in addition to suggesting a management protocol.

Menopausal symptoms
Menopausal symptoms are estimated to affect two-thirds of women and are described as distressing in 10–20%. The classic menopausal symptoms include hot flushes and night sweats, but many other symptoms – such as sleep disturbance, joint aches, irritability, mood changes, lack of confidence and genitourinary problems – have also been associated with the hormonal changes of the menopause. For many women leading extremely busy lives, balancing full-time workloads with home life, the onset of such symptoms can have a huge detrimental effect.

There exists a large variation in both duration and severity of symptoms and neither can be predicted; many confounding factors contribute to their presence and severity. Regular exercise, a healthy diet and reducing smoking, alcohol, caffeine and stress can all help to reduce symptoms to some extent and should always be encouraged, but for many women prescribed or ‘over-the-counter’ preparations will be required. For any therapy used to control menopausal symptoms, consideration should be given to having a trial off treatment occasionally to assess whether or not treatment is still required.

Menopause and lowered plasma oestrogen are also associated with physiological changes that may present with no symptoms, at least in the short term. These include decreased bone density and altered lipid and glucose metabolism.
Hormone replacement therapy
Symptom control is currently seen as the main indication for HRT, but evidence of benefit has been shown for some of the other changes associated with the menopause. Many placebo-controlled trials have demonstrated the significant benefits of HRT – including low-dose preparations – in controlling menopausal symptoms, particularly vasomotor symptoms; trials have shown up to 100% reduction in frequency of hot flushes relative to placebo. Symptom severity was also significantly reduced compared with placebo. It is believed that restoration of oestrogen levels allows improved functioning of the ‘thermostat’ located in the hypothalamus, although much uncertainty still exists around the cause of hot flushes.

There is good evidence that HRT reduces bone density loss by up to 30% after menopause with reduced fracture risk, and this benefit continues for the duration of HRT use but will decrease on stopping treatment.

Choice of therapy
The appropriate type of HRT is chosen according to whether or not a woman has had a hysterectomy, her menopausal status, her preference, and her personal and family history. For example:

- Women who have had a hysterectomy are offered oestrogen-only therapy while nonhysterectomised women are offered oestrogen with the addition of progestogen to reduce the risk of endometrial hyperplasia and cancer.
- Perimenopausal women should be offered sequential therapy using daily oestrogen and cyclical progestogen.
- Postmenopausal women can be offered continuous combined therapy using daily oestrogen and daily progestogen.

The woman’s previous medical history, her family history and use of any current medication will influence her choice of, and eligibility for, treatment, and her choice will also be influenced by her preference for an oral/transdermal/intrauterine/vaginal route of administration, or a combination of routes (such as a Mirena intrauterine delivery system (IUS) and a transdermal oestrogen patch). Indications for non-oral HRT are shown in Table 1. Transdermal administration of oestrogen has evidence of greater safety where a thrombotic risk exists. The dosages chosen should be the lowest that are effective, and dosage should be titrated against symptom control.

Duavive is a tissue-selective oestrogen complex combining conjugated oestrogens and the selective estrogen-receptor modulator (SERM) bazedoxifene. The SERM prevents oestrogenic stimulation of the endometrium in place of a progestogen. Duavive is licensed for the treatment of oestrogen deficiency symptoms in postmenopausal women with a uterus for whom treatment with a progestin-containing therapy is inappropriate.

NICE recommends “an individualised approach at all stages of diagnosis, investigation and management of menopause”, and that women should be informed about nonhormonal and nonpharmaceutical management of menopausal symptoms.

Duration of use
Since duration of symptoms cannot be predicted, neither can the duration of treatment. Most women in the UK taking HRT for symptom relief use it for less than five years; usual practice is to try reducing and then stopping HRT. Reducing HRT dose gradually may reduce symptom recurrence in the short term but will have no overall effect on symptoms long term. Ongoing therapy may be chosen if symptoms persist when treatment is withdrawn, but the risks of long-term treatment must be discussed so that women can make an informed decision. For some women with persistent severe symptoms, long-term therapy may be indicated if it is thought that the benefits outweigh the risks.

Emphasis is moving away from there being a set time limit on duration of use: HRT should be continued for as long as the woman feels that the benefits outweigh the risks. For women with a premature menopause, it is still believed that HRT should be offered until the average menopause age of 52 years at least, so that bone protection can be offered as well as symptom control. The merits of long-term use should be assessed for each individual at regular intervals, ideally annually.

Causes of poor symptom control and how they are managed are outlined in Table 2.

| • Individual preference |
| • Poor symptom control with oral HRT |
| • Side-effects with oral therapy such as nausea |
| • Bowel disorder that may affect absorption of oral therapy |
| • History of migraine (when steadier hormone levels achieved with a patch may be beneficial) |
| • Lactose sensitivity (all oral preparations of HRT contain lactose) |
| • History of gallstones |
| • Current use of drugs such as antiepileptic medication that may interfere with the breakdown of oral HRT |
| • Variable hypertension |
| • High triglyceride levels |
| • Risk factors for venous thromboembolism, including BMI >30, after full discussion |

Table 1. Indications for non-oral HRT

Table 2. Causes of poor symptom control with HRT and suggested management
Oestrogenic, eg breast tenderness/enlargement, leg cramps, bloating, nausea, headache

Breast symptoms: try evening primrose oil (though not now licensed for use); reduce oestrogen dose, particularly in older patients
GI symptoms: take with food; change route of administration; change type of oral oestrogen

Progestogenic, eg PMS-type symptoms, breast tenderness, lower abdominal pain, backache, depressed mood, acne/greasy skin, headache
Change progestogen (testosterone derived: norethisterone/norgestrel/levonorgestrel; progestosterone derived: medroxyprogestrone/dydrogesterone/drospirenone); change route of administration; offer tailor-made combination (remember recommended dose and duration for endometrial protection); if postmenopausal, consider change to continuous combined therapy or tibolone (avoids symptoms related to progestogen fluctuation)

Table 3. Oestrogenic and progestogenic side-effects and their management

Other benefits
The WHI trial confirmed that HRT reduces the risk of fractures of both the spine and hip. This is particularly important in young menopausal women and in those older women who have, or who are at risk of, osteoporosis and have menopausal symptoms. Lower doses than previously thought have been shown to be effective, but treatment may need to be lifelong.

Recent data suggest that early use of HRT after menopause is beneficial in prevention of cardiovascular disease, although the evidence remains conflicting. Some case-control cohort studies and the WHI trial have shown that HRT confers a reduced risk of colorectal cancer, but insufficient evidence exists for this to be seen as a primary indication for its use. Other possible benefits include improved wound healing, balance, muscle health and dexterity, and reduced risk of cataracts and macular degeneration.

Side-effects
Side-effects commonly occur in the first month or two following commencement of HRT (see Table 3) and may be due to both oestrogen and progestogen, but they usually settle by the third month of treatment. If this is not the case, the type or route of oestrogen or progestogen should be changed. In nonhysterectomised women, irregular bleeding in the first few months may occur. Further assessment should be arranged if the bleeding on sequential therapy becomes heavier, prolonged or irregular, and if bleeding persists beyond six months or occurs after a spell of amenorrhoea on continuous combined therapy.

Risks
Venous thromboembolism Studies have consistently demonstrated a two-fold increased risk of venous thromboembolism (VTE) with use of HRT, the initial figure reporting an increase in the order of an extra two cases per 10,000 women per year. In the WHI trial, the risk was an extra 6.9 cases per 10,000 women per year in the oestrogen-only group, and an extra 18 cases per 10,000 women per year in the combined HRT group. The greatest risk appears to be within the first year of use and is particularly relevant to women who have other risk factors, including obesity or previous or family history of VTE.

Transdermal oestrogen does not confer the same increased risk. NICE confirms that the risk of VTE with transdermal oestrogen is no different from population baseline risk, should be offered for women with a BMI >30, and can be considered in women at risk who have good indications for HRT, even where thrombophilia exists.

Breast cancer It is now well accepted that long-term HRT use (over five years) is associated with a small increased risk of breast cancer similar to that of a late natural menopause, and the figures from the Collaborative Group on Hormonal Factors in Breast Cancer may still be quoted (see Tables 4 and 5).

Much evidence now exists to suggest that oestrogen-only HRT carries little or no change in the risk of breast cancer. Combined HRT carries a small increase in risk over background but may need to be taken for more than five years after the age of 50 years before conferring an increased risk. By five years after stopping HRT, the risk returns to baseline.

The NICE guideline NG23 stresses that baseline breast cancer risk for women of menopausal age varies and will be influenced by underlying risk factors such as family history and lifestyle. Any role of HRT is believed to be as a promoter of breast cancer cells rather than an initiator.

Endometrial cancer Oestrogen-only therapy given to women with an intact uterus increases the risk of endometrial hyperplasia and cancer. Oestrogen combined with cyclical progestogen (sequential HRT) or long-cycle HRT reduces this risk but does not eliminate it. Sequential HRT given for over five years does confer a small increased risk of endometrial cancer but no increased risk appears to apply to oestrogen combined with continuous progestogen (continuous combined therapy).

Questionable risks/benefits
For many years, HRT was thought to be cardioprotective with observational studies showing reduced risks of coronary artery disease and stroke in users. However, both the Heart and

<table>
<thead>
<tr>
<th>Years of HRT</th>
<th>No. cases of breast cancer/1000 women aged 50–70 years</th>
<th>No. extra cases/1000 women</th>
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<tr>
<td>0</td>
<td>45</td>
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</tr>
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<td>&gt;5</td>
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<td>&gt;15</td>
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Table 4. Duration of HRT use and associated breast cancer risk
Estrogen/progestin Replacement Study (HERS)\(^1\) and the WHI trial\(^1\) showed early increased risks of cardiovascular events, though these were small and transient and only occurred in the WHI trial in women who were taking combined HRT and who were 20 years or more postmenopausal.

In the WHI trial, women who were less than 10 years postmenopausal when starting combined HRT, and hysterectomised women taking oestrogen only, showed no increased risk of coronary heart disease during the trial, and indeed showed a trend towards a reduced risk.

In general, HRT does not increase cardiovascular disease risk when started in women aged under 60 years and does not affect the risk of dying from cardiovascular disease.\(^8\) In fact in women under 60 years, oestrogen reduces coronary heart disease and all-cause mortality; oestrogen and progestogen both appear to be cardioprotective.\(^2\)

Both oestrogen-only and combined HRT were shown to be associated with a small increased risk of ischaemic stroke in the WHI trial but, again, only in older women. It is possible that lower doses than were used in the WHI trial may confer some protection. It appears that the dose, type and route of HRT used are important in conferring cardiovascular effects, as is the timing of commencement of therapy.

Debate also surrounds the role of HRT in the development of Alzheimer’s disease, with some studies showing a reduction in risk in HRT users while the WHI trial showed an increased risk, but only in older women. International Menopause Society (IMS) guidance states that HRT initiated midlife is associated with reduced risk of Alzheimer’s disease and dementia. HRT is not currently recommended as the principal therapy for either primary or secondary prevention of cardiovascular disease\(^2\) or for the prevention of Alzheimer’s but the debate continues.

It appears that there is a window of opportunity for beneficial effects when HRT is commenced early, as reported by a randomised controlled trial with 10 years of follow-up, which suggested that women receiving HRT within 10 years of menopause or before the age of 60 years had a significantly reduced risk of mortality, heart failure or myocardial infarction, with no apparent increase in risk of cancer, stroke or blood clot.\(^2\) If commenced later when atherosclerosis is already established, it is thought that HRT may cause further harm in a small number of women.

Some studies have suggested a possible link between long-term HRT use and a small increased risk of ovarian cancer, but most studies have been inconclusive. The WHI trial demonstrated no increased risk of ovarian cancer in the HRT group while, despite much alarm being caused by data from the Million Women Study, the increased risk of serous or endometrioid ovarian cancer shown was one extra case per 2500 women taking HRT for five years.

**Summary of benefits versus risks**

HRT benefits versus risks can be summarised according to age of menopause:

- Generally for women with menopause aged <50 years, the benefits of HRT far outweigh the risks and HRT should be offered

**Table 5. Absolute risk of breast cancer with HRT\(^1,17\)**

<table>
<thead>
<tr>
<th>Source of data</th>
<th>Extra cases/1000 for 5 years’ HRT</th>
</tr>
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<tr>
<td>Collaborative group 1997</td>
<td>+2</td>
</tr>
<tr>
<td>WHI oestrogen</td>
<td>0 (-0.76/1000/year)</td>
</tr>
<tr>
<td>WHI combined HRT</td>
<td>+4, but only if HRT taken before trial</td>
</tr>
</tbody>
</table>

- For women aged between 50 and 60 years with menopausal symptoms, the benefits of HRT outweigh the risks
- For women aged >60 years, the benefits of HRT equal the risks, except for women with persistent troublesome symptoms, and treatment should be individualised
- For women aged >70 years, the risks may outweigh the benefits, except for women with persistent troublesome symptoms.\(^2\)

**Contraindications**

Contraindications to the use of HRT include:

- Pregnancy
- Undiagnosed abnormal vaginal bleeding – this should be investigated before commencing HRT
- Active recent venous thromboembolism or myocardial infarction
- Breast or endometrial cancer
- Active liver disease with abnormal liver function tests.

**Interactions**

Interactions may occur with anticonvulsants, which may increase the breakdown of oral oestrogen leading to inadequate symptom control; this is managed by increasing the oral dose or by using a non-oral route. Interactions can also occur with cimetidine, erythromycin, ketoconazole and St John’s wort.

**Recommended review**

After commencement or change of HRT, women should be reviewed after three months to:

- Assess effect of therapy
- Enquire about side-effects and bleeding pattern
- Check blood pressure and weight.

Thereafter, when settled on therapy, a review should be arranged at least annually to:

- Check effectiveness of therapy and presence of side-effects
- Review the best type of therapy for the patient, eg consider changing from sequential to continuous combined therapy when the patient is known to be postmenopausal
- Discuss the pros and cons of continuing HRT, in particular discussing the increased risk of breast cancer with long-term HRT, which should be weighed against the benefits. To facilitate decision-making, patients should be advised to have a trial off HRT occasionally to assess if treatment is still required
- Check blood pressure
- Encourage breast awareness
- Conduct cervical screening every three or five years, depend-
Side-effects
Persistent side-effects following logical therapy changes as per side-effect management (see Table 3)

Poor symptom control
Inadequate control despite logical changes in HRT as per poor symptom control management (see Table 2)

Bleeding problems
Sequential therapy: change in pattern of bleeding including increased duration, frequency and/or heaviness and irregular bleeding
Continuous combined therapy or tibolone: if still bleeding after 6 months of therapy or if bleeding occurs after a spell of amenorrhoea

Complex medical history

Past history of hormone-dependent cancer
eg breast or endometrial cancer

Patient request

Table 6. Specialist referral for patients on HRT

- Assess need for a pelvic examination – only if clinically indicated.

Overall, despite the highly publicised and often overestimated risks, the benefits of HRT outweigh the risks for many women when used appropriately for its licensed indications. Table 6 summarises when specialist referral for patients on HRT is indicated.

Non-HRT treatment options

Clonidine
Clonidine is a centrally active alpha₂-agonist that has been shown to reduce hot flushes in some – but not all – trials. It is often used as a first-line treatment at a dosage of two or three 25μg tablets twice daily. Side-effects include difficulty in sleeping, dry mouth, dizziness, constipation and sedation. Interaction may occur with antihypertensive drugs.

SSRIs and SNRIs
The belief that a variety of processes involving serotonin, noradrenaline and dopamine are instrumental in initiation of the hot flush has led to trials of drugs that selectively inhibit the reuptake of serotonin and noradrenaline. In a randomised controlled trial, venlafaxine, a selective inhibitor of both serotoninin and noradrenaline reuptake (SNRI), at dosages of 37.5mg, 75mg or 150mg daily reduced flushes by 37%, 61% and 61% compared with a placebo reduction of 27%. The usual starting dosage of venlafaxine is 37.5mg daily with a gradual increase in dose to reduce the risk of side-effects, which include mouth dryness, dizziness, insomnia, agitation and confusion. The SSRI paroxetine 12.5–25mg daily has been shown to produce a 50% reduction in flushes, and fluoxetine 20mg daily has also been reported as achieving a 60% reduction.

Interactions may occur with monoamine oxidase inhibitors (MAOIs), CNS-active drugs, warfarin and tamoxifen, with an increased risk of breast cancer recurrence shown in women taking tamoxifen and paroxetine. NICE recommends that fluoxetine or paroxetine should not be taken with tamoxifen.

NICE does not recommend either clonidine or SSRIs/SNRIs as first-line management of menopausal symptoms. While HRT may improve low mood arising during menopause, there is no evidence that SSRIs/SNRIs will improve mood in women where no diagnosis of depression has been made.8

Progestogens
Megestrol acetate, a synthetic progestogen, has been shown to reduce hot flushes by 85% compared with a placebo effect of 21% when given at a dosage of 20–80mg daily. A transient increase in hot flushes has been noted in the first two weeks of therapy. There is a possibility of adrenal suppression since megestrol acetate has glucocorticoid activity, leading to adrenal insufficiency after discontinuation. In addition, problems exist with the availability of megestrol so it is rarely used.

Other progestogens shown to be effective include medroxy-progesterone acetate 20–100mg daily, and norethisterone 5–10mg daily. Norethisterone used at high dosages may confer an increased risk of VTE, and weight gain is a common progestogenic side-effect. Safety with regard to breast disease remains undetermined.

Gabapentin
Gabapentin, a gamma-aminobutyric acid (GABA) analogue, used at dosages of 300–1600mg daily has been shown in a randomised, placebo-controlled study to reduce hot flushes by 45%. Gabapentin may be beneficial for the symptoms of aches, pains and paraesthesia that many menopausal women experience. Interaction may occur with antacids and side-effects include dizziness, fatigue, tremor, ataxia, arthralgia and weight increase. Side-effects can be reduced by gradually increasing the dose.

It should be noted that HRT and clonidine are the only prescribed therapies that are currently licensed for the treatment of menopausal vasomotor symptoms.

Androgens
Sexual function may be improved with oestrogen replacement but in younger women, eg following oophorectomy, testosterone replacement may also be required. Testosterone preparations have been shown to be helpful in the management of libido problems and NICE recommends use of testosterone for sexual dysfunction if HRT does not provide sufficient benefit. However, unfortunately patches are no longer available for prescription and licensing restrictions limit prescribing of other formulations.

Alternative therapies
Approximately one-third of the adult population in the UK has been reported as ever having used herbal remedies. Use of complementary therapies is more common in women, particularly for menopausal symptoms, either because of real or perceived contraindications to conventional HRT or as complementary treatment.
Evening primrose/starflower oil, a rich source of gamolenic acid, has been used for breast tenderness and mood swings. It seems to be less successful in the treatment of hot flushes. Phytoestrogens – naturally occurring compounds with weak oestrogenic activity – are commonly found in soya, linseed (flaxseed) oil, red clover and certain vegetables; currently, there is promising but limited evidence regarding their effectiveness and safety.\(^{32,33}\)

Many other products are commonly used, including unregulated compounded bioidentical hormones, but evidence of their effectiveness is lacking and some evidence exists of possible harmful effects. Therefore randomised controlled trials are required, and worldwide regulation is needed.\(^{34}\) There is some evidence that isoflavones or black cohosh may relieve vasomotor symptoms, but the NICE guideline on the menopause (NG23) recommends that women are informed that multiple variable preparations are available and their safety is uncertain; there have also been reports of interactions with other medication.\(^{8}\)

**Treatment of genitourinary symptoms**

More than 50% of menopausal women suffer from atrophic genitourinary symptoms such as dyspareunia, cystitis-like symptoms and pruritus. Systemic HRT does alleviate these symptoms but topical replacement is often required as systemic therapy may be insufficient, undesired or contraindicated.

Locally delivered, low-dose natural oestrogens are available in vaginal tablet, ring or cream form. Long-term maintenance replacement is often required leading to the theoretical concern of endometrial stimulation. Reassuringly, serum oestradiol levels are unaltered during vaginal estradiol tablet or ring application, and epidemiological data so far have not shown any increased risk of endometrial neoplasia with long-term use.\(^{35}\)

Annual review is recommended and endometrial assessment is indicated if postmenopausal bleeding occurs. Urinary frequency and urgency, urge incontinence and nocturia are all improved by local vaginal oestrogens as long as therapy is continued, again with no reported negative effects.\(^{36}\)

Alternatively, nonhormonal lubrication has been shown to be of benefit, especially for dyspareunia and irritation.\(^{37}\) Nonhormonal vaginal moisturisers are now available on prescription, which can be used for general comfort, not just for lubrication during intercourse.

**Conclusion**

Menopausal symptoms affect many women and are said to be distressing in 10–20%. Management should include consideration of diet, lifestyle, past and family medical history, and current medication. Figure 1 provides a flowchart summarising menopause management. HRT is currently the most effective treatment available for control of symptoms, and when used appropriately with individualisation of treatment, at the lowest effective dose and with regular review, the benefits are likely to outweigh the risks. Other therapies have been shown to be effective and can be considered, but are not without risks and side-effects. Provision of accurate information is essential to enable women to make informed choices and take an active part in the management of their menopause.
Figure 1. Menopause management flowchart. Reproduced with permission from: www.menopausematters.co.uk/tree.php. The online version is interactive; clicking on the red boxes/red text leads to further information.
References

Declaration of interests
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