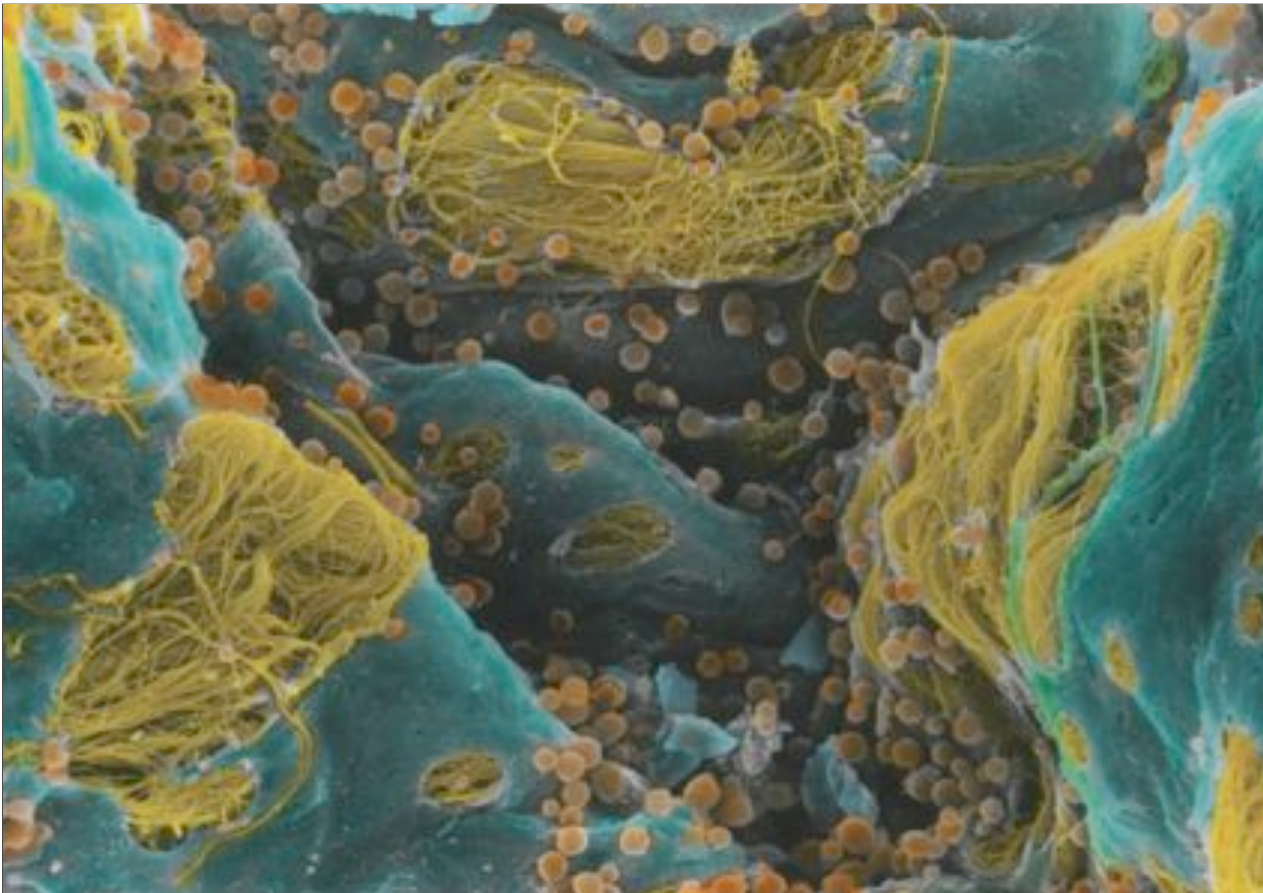


Current options in the treatment of menopausal symptoms

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Hormone replacement therapy remains the mainstay of menopausal symptom treatment despite continued debate over the risks and benefits. Our Drug review considers the properties and adverse events of the current treatment options, followed by sources of further information and an analysis of prescription data.

Much confusion currently 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 This review describes the treatment options currently used to treat 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 per cent. 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



CPD questions available for this article. See page 25

- 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, after full discussion

Table 1. Indications for nonoral HRT

full-time workloads with home life, the onset of such symptoms can have a huge detrimental effect.

Therapeutic approaches

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.

Any therapy used to control menopausal symptoms should be reduced and then stopped every few years to assess whether or not it is still required.

HRT

Many placebo-controlled trials have demonstrated the significant benefits of HRT – including low-dose preparations – in controlling menopausal symptoms, particularly vasomotor symptoms. This is particularly important since symptom control is currently seen as the main indication for HRT. Trials have shown a 77 per cent reduction in frequency of hot flushes for HRT relative to placebo. Symptom severity was also significantly reduced compared with placebo.³

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 flush.

Type of HRT

The appropriate type of HRT is chosen according to whether or not she has had a hysterectomy (generally

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); the woman’s menopausal status (perimenopausal women should be offered sequential therapy using daily oestrogen and cyclical progestogen, while postmenopausal women can be offered continuous combined therapy using daily oestrogen and daily progestogen); her preference for type of treatment (oral or nonoral, see Table 1); and past medical history and current medication.

The dosages chosen should be the lowest that are effective, and dosage should be titrated against symptom control.

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 every two to three years.

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, so that bone protection can be offered as well as symptom control.⁴ The merits

- check compliance
- allow 3-6 months on therapy to ensure full effect
- inadequate oestrogen dosage – increase dose or change from oral to nonoral route
- poor absorption due to bowel disorder – change to nonoral route
- drug interactions, eg barbiturates, phenytoin, carbamazepine – increase oral dose or change to nonoral route
- poor patch adhesion – change delivery system
- incorrect diagnosis – review indications, consider thyroid dysfunction
- unrealistic expectations – counsel

Table 2. Causes of poor symptom control with HRT and suggested management

Side-effects	Management
<p><i>Oestrogenic</i> eg breast tenderness/enlargement; leg cramps; bloating; nausea; headache</p>	<p><i>Breast symptoms:</i> try evening primrose oil (though not now licensed for use); reduce oestrogen dose, particularly in older patients</p> <p><i>GI symptoms:</i> take with food; change route of administration; change type of oral oestrogen</p>
<p><i>Progestogenic</i> eg PMS-type symptoms; breast tenderness; lower abdominal pain; backache; depressed mood; acne/greasy skin; headache</p>	<p>change progestogen (testosterone derived: norethisterone/norgestrel/levonorgestrel; progesterone derived: medroxyprogesterone/dydrogesterone/drospirenone); change route of administration; offer tailor-made combination (remember recommended dose and duration for endometrial protection); if post-menopausal, consider change to continuous combined or tibolone (avoids symptoms related to progestogen fluctuation)</p>

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

of long-term use should be assessed for each individual at regular intervals, ideally annually.

Other benefits of HRT

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 are at risk of, osteoporosis and have menopausal symptoms. Lower doses than previously thought have been shown to be effective,⁵ but treatment may require to be lifelong⁶

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, improved balance and reduction in falls, improved dentition and reduced risk of cataracts and macular degeneration.

Side-effects of HRT

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

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 of HRT

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 of the order of an extra two cases per 10 000 women per year.⁷ From the WHI trial, the risk was an extra 0.69 cases per 1000 women per year in the oestrogen-only group, and an extra 1.8 cases per 1000 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 previous or family history of VTE.

There is some evidence that transdermal oestrogen may not confer the same increased risk and can be considered in women at risk who have good indications for HRT, even where thrombophilia exists.^{8,9}

Breast cancer It is now well accepted that long-term HRT use (over five years) confers a small increased risk of breast cancer similar to that of a late natural menopause, and the figures generally quoted are those from the Collaborative Group on Hormonal Factors in Breast Cancer (see Table 4).¹⁰

From both the WHI trial and Million Women study, it appears that oestrogen-only HRT carries less risk of breast cancer than oestrogen combined with progestogen. The WHI trial in particular demonstrated no increased risk with oestrogen-only taken for up to seven years.¹¹

In the combined HRT arm of the WHI trial, the increased risk was only seen in women who had taken HRT before the trial (see Table 5), as well as then taking it for the five years of the trial, suggesting that combined HRT may need to be taken for more than five years after the age of 50 before conferring an increased risk. By five years after stopping HRT, the risk returns to baseline.

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.

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Years of HRT	No. cases of breast cancer/1000 women aged 50-70	No. extra cases/1000 women
0	45	0
>5	47	2
>10	51	6
>15	57	12

Table 4. Duration of HRT use and associated breast cancer risk⁸

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).¹²

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 Estrogen/progestin Replacement Study (HERS)¹³ and WHI trial¹ have shown 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 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 a trend towards a reduced risk.

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 cardiovascular effect, 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.

HRT should currently not be used as the principal therapy for either primary or secondary prevention of cardiovascular disease¹⁴ or for the prevention of Alzheimer’s, though the debate continues. It appears that there is a window of opportunity whereby HRT commenced within the first 10 years of the menopause is very unlikely to be harmful to the cardiovascular system and may yet prove to be beneficial, but if commenced later when atherosclerosis is already established 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 shown was one extra case per 2500 women taking HRT for five years.

Risks vs benefits

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

- generally for women with menopause aged <50, the benefits of HRT far outweigh the risks and HRT should be offered
- for women aged between 50 and 60 with menopausal symptoms, the benefits of HRT outweigh the risks
- for women aged >60, the benefits of HRT equal the risks and treatment should be individualised
- for women aged >70, the risks tend to outweigh the benefits.¹⁵

Contraindications to HRT

Contraindications to the use of HRT include:

- pregnancy
- undiagnosed abnormal vaginal bleeding – this should be investigated before commencing HRT
- active recent VTE or MI
- 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 nonoral route. Interactions can also occur with cimetidine, erythromycin, ketoconazole (Nizoral) 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

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

Table 5. Absolute risk of breast cancer with HRT

- 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 best type of therapy for patient, *eg* consider changing from sequential to continuous combined therapy when known to be postmenopausal
- discuss 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-treatment every two years or so to assess if treatment is still required
- check blood pressure
- encourage breast awareness
- cervical smear three- or five-yearly depending on local recommendations
- pelvic examination – only if clinically indicated.

Overall, despite the highly publicised and often overestimated risks, the benefits of HRT outweigh these risks for many women when used appropriately for its licensed indications.

Clonidine

Clonidine is a centrally active α_2 -agonist that has been shown to reduce hot flushes in some – but not all – trials.¹⁶ It is often used as a first-line treatment in a dose of two or three 25µg tablets twice daily.

Side-effects include difficulty in sleeping, dry mouth, dizziness, constipation and sedation. Interaction may occur with antihypertensives.

SSRIs and SNRIs

The belief that a variety of chemical reactions involving serotonin, noradrenaline and dopamine are instrumental in initiation of the flush has led to trials of drugs that selectively inhibit the reuptake of serotonin and noradrenaline.

Venlafaxine, a selective inhibitor of both serotonin and noradrenaline reuptake, in doses of 37.5mg, 75mg or 150mg daily, reduced flushes by 37, 61 and 61 per cent compared to placebo reduction of 27 per cent.¹⁷ The usual starting dose 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.

Previous advice from the CSM stated that ‘because of concerns about cardiotoxicity and toxicity in overdose, treatment with venlafaxine should only be initiated by specialist mental health practitioners and there should be arrangements in place for continuing

<i>Side-effects</i> persistent side-effects following logical therapy changes as per side-effect management (see Table 3)
<i>Poor symptom control</i> inadequate control despite logical changes in HRT as per poor symptom control (see Table 2)
<i>Bleeding problems</i> 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
<i>Complex medical history</i>
<i>Past history of hormone-dependent cancer</i> <i>eg</i> breast or endometrial
<i>Patient request</i>

Table 6. Specialist referral for patients on HRT

supervision of the patient. Venlafaxine should not be used in patients with heart disease.’ However, after further investigation, these restrictions have now been lifted.

A new SNRI, desvenlafaxine, may become available in the near future and will be licensed for nonhormonal treatment of menopausal vasomotor symptoms.

Paroxetine 12.5-25mg daily has been shown to produce a 50 per cent reduction in flushes, and fluoxetine 20mg daily has also been reported as achieving a 60 per cent reduction.

Interactions common to these SSRIs may occur with MAOIs, CNS-active drugs, warfarin and tamoxifen, with an increased risk of breast cancer recurrence shown in women taking tamoxifen and paroxetine.

Progestogens

Megestrol acetate, a synthetic progestogen, has been shown to reduce hot flushes by 85 per cent compared to a placebo effect of 21 per cent when given in a dose of 20-80mg daily.¹⁸ 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.

Other progestogens shown to be effective include medroxyprogesterone acetate 20-100mg daily¹⁹ and norethisterone 5-10mg daily.²⁰

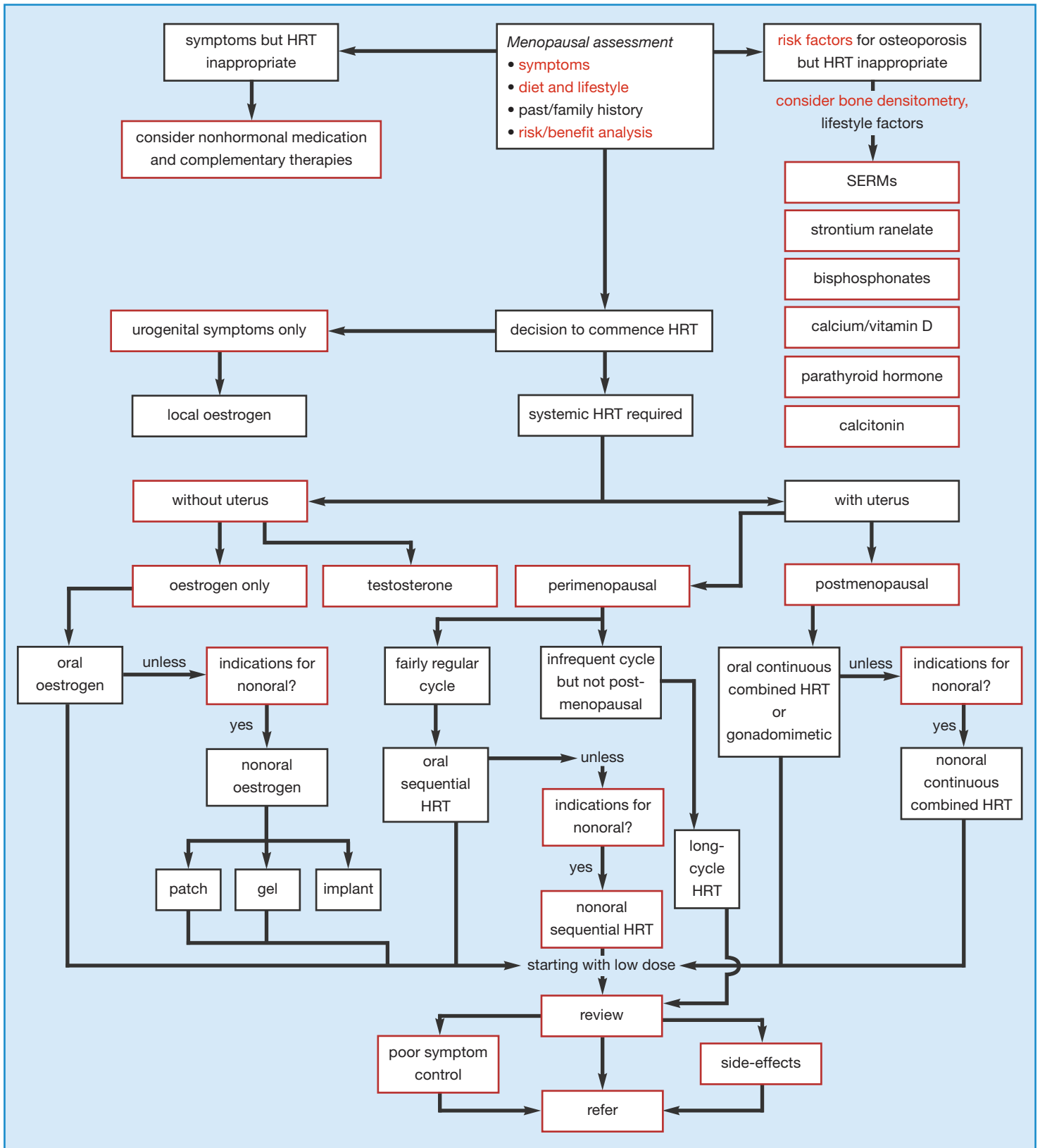


Figure 1. Menopause management flowchart. Reproduced with permission from www.menopausematters.co.uk/tree.php. The online version is interactive; clicking on the red boxes/red text leads to further information

It has been stated that progestogens used in fairly high dose may confer an increased risk of VTE,²¹ 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 in doses of 300-1600mg daily has been shown in a randomised, placebo-controlled study to reduce flushes by 45 per cent.²² 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 implants and patches are available and have been shown to be helpful in the management of libido problems.^{23,24}

Alternative therapies

Approximately one-third of the adult population in the UK has been reported as ever having used herbal remedies. Usage of complementary therapies is more common in women, particularly for menopausal symptoms, either because of contraindications to conventional HRT or as complementary treatment.

Evening primrose/starflower oil, a rich source of gamma-linolenic 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 oil, red clover and certain vegetables; currently, there is promising but limited evidence regarding their effectiveness and safety.^{25,26}

Many other products are commonly used but evidence of their effectiveness is lacking and some evidence exists of possible harmful effects. Therefore randomised controlled trials are required, and regulation needs to be worldwide.²⁷

Treatment of genitourinary symptoms

More than 50 per cent of menopausal women suffer from atrophic genitourinary symptoms such as dys-

- management should include discussion of diet, lifestyle, current medication and past and family history
- HRT is the most effective treatment for menopausal symptoms
- risks must be balanced against benefits
- treatment must be individualised
- start with low-dose therapy
- regular review recommended with ongoing discussions of risk/benefit balance
- nonhormonal therapies shown to be effective but not without side-effects/risks

Table 7. Key points

pareunia, 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 tablet, ring, cream or pessary form. Long-term maintenance replacement is often required leading to the theoretical concern of endometrial stimulation. Reassuringly, serum oestradiol levels are unaltered during vaginal oestradiol tablet or ring application, and epidemiological data so far have not shown any increased risk of endometrial neoplasia with long-term use.²⁸

Annual review is recommended and endometrial assessment is indicated if postmenopausal bleeding occurs. Alternatively, nonhormonal lubrication has been shown to be of benefit, especially for dyspareunia and irritation.²⁹ Nonhormonal vaginal moisturisers are now available on prescription – Replens, Sylk, and Repadina – 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 per cent. Management should include consideration of diet, lifestyle, past and family history and current medication.

HRT is currently the most effective treatment available for control of symptoms, and when used appropriately with individualisation of treatment, use of the lowest effective dose and 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.

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Resources

Guidelines

Hormone replacement therapy. BMS Consensus Statement. British Menopause Society. 2008. www.thebms.org.uk/statementpreview.php?id=1.

Menopause – management. NHS Clinical Knowledge Summaries. www.cks.nhs.uk/menopause.

Websites/organisations

Amarant Trust. Helpline: 01293 413000 (11am-6pm Mon-Fri). Website: www.amarantmenopausetrust.org.uk.

British Menopause Society. Tel: 01628 890199; e-mail: admin@thebms.org.uk; website: www.thebms.org.uk.

The Daisy Network Premature Menopause Support Group. Website: www.daisynetwork.org.uk.

European Menopause and Andropause Society. Website: <http://emas.obgyn.net>.

International Menopause Society. Tel: 01524 221190; e-mail: jwright.ims@btoopenworld.com; website: www.imsociety.org.

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Further reading

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