

Menopause

In England and Wales £57.2 million is spent annually on hormone replacement therapy (HRT) and local oestrogen preparations for urogenital atrophy (ePACT November 2016 to January 2017). Medicines optimisation projects in this area focus on selecting the most cost-effective product that is appropriate for the individual. Furthermore, therapy should be reviewed regularly and discontinued when appropriate for the individual.

This bulletin reviews the place in therapy of drug treatments for menopausal symptoms. It offers guidance and support materials for organisations considering reviewing the prescribing of these treatments as a medicines optimisation project.

Recommendations

- Do not use follicle stimulating hormone to diagnose menopause in women over 45 years of age.
- For vasomotor symptoms:
 - » HRT is generally the first line option. Offer HRT after a discussion of short term (up to five years) and longer-term benefits and risks (see 'Clinical effectiveness' section below).
 - » Do not routinely offer selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs) or clonidine as first line treatment for vasomotor symptoms alone.
 - » Where SSRIs and SNRIs are offered (unlicensed indication), a short term trial of one to two weeks may be adequate to assess the effect (three weeks for fluoxetine) for hot flushes.
 - » Clonidine is the only non-oestrogen based preparation that is licensed for menopausal flushing in the UK, but its use is limited by moderate efficacy and relatively high rate of adverse effects.
- Consider HRT for menopausal low mood, or cognitive behavioural therapy (CBT) for menopausal low mood or anxiety. There is no clear evidence that SSRIs/SNRIs ease low mood in menopausal women without a diagnosis of depression.
- For urogenital atrophy, offer vaginal oestrogen (including to those on systemic HRT) and continue for as long as needed to relieve symptoms.
- There is some evidence that products such as isoflavones, black cohosh and St John's wort may give some relief of symptoms. However the quality, purity and constituents of complementary therapies may be unknown, and there is a risk of (potentially serious) interactions with other medicines. The efficacy and safety of unregulated compounded bioidentical hormones are unknown.
- The lowest effective dose of HRT should be used for the shortest possible time. Treatment should be reviewed at three months to assess efficacy and tolerability. A review of therapy and discussion of an individual's risk:benefit ratio for continuing HRT should occur at least annually. Regular attempts to discontinue treatment should be made. For vasomotor symptoms, most women require two to five years of HRT, but some women may need longer.
- The risk of VTE is increased by oral HRT but not transdermal HRT, compared with baseline population risk. NICE recommend discussing this difference in risk with the patient and considering transdermal rather than oral HRT for women at increased risk of venous thromboembolism, including

those with a BMI over 30 kg/m². Refer those at high risk (for example, those with a strong family history of VTE or a hereditary thrombophilia) to a haematologist for assessment before considering HRT.

- Do not offer the SSRIs paroxetine and fluoxetine to women with breast cancer who are taking tamoxifen, as they may inhibit the metabolism of tamoxifen to an active metabolite.
- Refer to a specialist if symptoms do not improve, if ongoing adverse effects are a problem, or if uncertain about the most suitable treatment.
- Advise women with premature ovarian insufficiency to continue HRT or a combined oral contraceptive until at least the age of natural menopause (51 years).
- Offer women stopping HRT the choice of gradually reducing or immediately stopping treatment and discuss the pros and cons of each approach.
- Local formularies should support prescribers in selecting cost-effective products, where they are clinically appropriate and acceptable to the woman. Both oral and transdermal route options should be available on formularies.
- Women prescribed less suitable or disproportionately costly products for menopausal symptoms should be individually reviewed.
- Synthetic oestrogens such as ethinylestradiol are generally considered unsuitable for HRT, except in women with early ovarian failure, because of their greater metabolic impact. Ethinylestradiol is also comparatively costly.
- Use Ovestin® 0.1% cream in preference to Estriol 0.01% cream as they both deliver the same dose of 0.5mg estriol per application, but Estriol 0.01% cream is 12 times more costly than Ovestin® 0.1% cream.

Background

Menopause

Menopause is a biological stage in a woman's life when menstruation ceases permanently due to the loss of ovarian follicular activity. It occurs with the final menstrual period and is usually diagnosed clinically after 12 months of amenorrhea (for women reaching menopause naturally). Perimenopause is the period before the menopause when the endocrinological, biological, and clinical features of approaching menopause commence. It is characterized by irregular cycles of ovulation and menstruation, and ends 12 months after the last menstrual period. Postmenopause is the time after a woman has not had a period for 12 consecutive months.¹

The average age of menopause in the UK is 51. However, this varies widely and one in 100 women experience premature ovarian insufficiency (menopause occurring before the age of 40 years). Premature ovarian insufficiency (POI) can occur naturally or as a result of medical or surgical treatment.²

Oestrogen depletion associated with menopause causes irregular periods and has many other effects on the body. The most common symptoms are hot flushes and night sweats. Other symptoms include mood changes, memory and concentration loss, vaginal dryness, a lack of interest in sex, headaches, and joint and muscle stiffness. Quality of life may be severely affected. Most women (eight out of ten) experience some symptoms, typically lasting about four years after the last period, but continuing for up to 12 years in about 10% of women.²

Treatments

Treatments for menopausal symptoms include HRT, non-hormonal treatments (e.g. some antidepressants and clonidine), and non-pharmacological treatments such as cognitive behavioural therapy (CBT). There has also been interest in a number of complementary and unregulated therapies for menopausal symptoms.²

The type of HRT most suited to a woman will depend on a variety of factors, including her symptoms, her stage in the menopausal process, and whether or not she has had a hysterectomy.³

Vaginal estrogen is available as creams, tablets and a vaginal ring. Systemic treatments are available as oral tablets, patches and gels (transdermal).⁴ They can be categorised as follows:

Oestrogen + progestogen – for women with a uterus. Oestrogen relieves typical menopausal symptoms such as hot flushes.³ Progestogens are added to reduce the increased risk of endometrial hyperplasia and cancer which occurs with unopposed oestrogen.¹

- Sequential (cyclical) combined HRT mimics the normal menstrual cycle. Oestrogen is taken every day and progestogen for 12 to 14 days, after which there is a withdrawal bleed.⁵ It is used in perimenopause and during the first year or two after menopause.³
- Continuous combined HRT contains continuous progestogen with the oestrogen, so there is no withdrawal bleed.¹ This type of HRT is thought to reduce the risk of endometrial cancer even more so than sequential combined HRT.³ It is for use in postmenopausal women and is not suitable for perimenopausal women or within 12 months of the last menstrual period.¹ Usually, women start on sequential combined HRT and change to continuous combined HRT later.⁵

Unopposed oestrogen - suitable for continuous use in women without a uterus. In women with previous endometriosis, endometrial foci may remain despite hysterectomy and the addition of a progestogen should be considered.⁶

Tibolone is a synthetic steroidal compound with oestrogenic, progestogenic, and androgenic activity. It is licensed for oestrogen deficiency symptoms in postmenopausal women, more than one year after menopause.¹ It is taken continuously and there is no withdrawal bleed.⁷

National guidance

In November 2015, NICE published guidance on the diagnosis and management of menopause. NICE noted that the advice and support available about treatments such as HRT is variable, and that prescriptions for HRT almost halved after the publication of the Women's Health Initiative study (2002) and the Million Women Study (2003). NICE state that these studies focused on the use of HRT in chronic disease prevention and potential long term risks rather than considering the benefits in terms of symptom relief. One of their aims in producing the guideline was to clarify the balance of benefits and risks of HRT use for both women and their healthcare providers.²

Premature ovarian insufficiency (POI)

In women under 40 years old, POI should be diagnosed based on menopausal symptoms, including no or infrequent periods (taking into account if woman has a uterus), and elevated follicle stimulating hormone (FSH) levels on two blood samples taken four to six weeks apart. If there is doubt about the diagnosis the woman should be referred to an appropriate specialist.

A choice of HRT or a combined oral contraceptive should be offered, unless contraindicated. Women should be advised of the importance of starting hormonal treatment with HRT or a combined oral contraceptive and continuing treatment until at least the age of natural menopause. It should be explained that the baseline population risk of diseases such as breast cancer and cardiovascular disease increases with age and is very low in women aged under 40 years.²

Menopause - diagnosis

NICE advise not to use an FSH test to diagnose menopause in women over 45 years of age (whereas it may be considered in women aged 45 years and less). FSH levels fluctuate considerably over short periods of time during the years leading up to the menopause, so FSH testing in this group does not improve management. If a woman is aged over 45 years and has not had a period for at least 12 months, or has vasomotor symptoms and irregular periods (or just symptoms if she doesn't have a uterus), this is

adequate information to diagnose menopause and perimenopause respectively. NICE state that this is an area where considerable savings could be made through disinvestment.²

Management

Women should be advised about lifestyle modifications to reduce menopausal symptoms. There is some evidence that women who are more active tend to suffer less from the symptoms of the menopause.⁸ Regular exercise and getting adequate sleep should be encouraged. Weight loss (if applicable), wearing lighter clothing, sleeping in a cooler room and avoiding possible triggers (such as spicy foods, caffeine, smoking, and alcohol) may help with hot flushes and night sweats.¹

The nature and severity of a woman's menopausal symptoms should be assessed, along with her expectations. This may include her reasons for consulting and if she would like treatment for her symptoms. Risk factors for cardiovascular disease and osteoporosis should also be assessed and managed.¹

Vasomotor symptoms

For vasomotor symptoms, the most effective treatment is considered to be HRT since symptoms occur at a time when oestrogen levels are dropping and 'replacement' leads to symptom relief¹ (see 'Clinical effectiveness' section below).

- HRT is generally the first line option and should be offered after a discussion of short term (up to five years) and longer-term benefits and risks (see 'Benefits and risks' section below).
- Selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs) or clonidine should not be routinely offered as first line treatment for vasomotor symptoms alone.²

Psychological symptoms

For psychological symptoms NICE found limited evidence that low mood can be relieved by HRT and by psychological therapies, such as cognitive behavioural therapy (CBT). CBT also reduced anxiety compared with usual care.⁹ NICE therefore recommend considering HRT (for menopausal low mood) or CBT (for menopausal low mood or anxiety). It is emphasized that there is no clear evidence that SSRIs/SNRIs ease low mood in menopausal women without a diagnosis of depression.²

Altered sexual function

For altered sexual function NICE found limited evidence showing that testosterone increased the frequency of sexual episodes compared with placebo, although the majority of women included in these trials were surgically menopausal. Given the limited evidence and as testosterone does not have a UK marketing authorisation for this indication in women, it should only be offered as an option for improving low sexual desire when HRT is not effective.⁹ If offered, it should be prescribed by specialists¹⁰ after obtaining and documenting informed consent.²

Urogenital atrophy

For urogenital atrophy NICE found moderate to very low quality evidence suggesting that local oestrogens are effective in relieving symptoms in the short and long term (up to a year) and are safe.^{1,9} NICE recommend offering vaginal oestrogen (including to those on systemic HRT) and continuing for as long as needed to relieve symptoms. Adverse effects from vaginal oestrogen are very rare. Women should report unscheduled vaginal bleeding to their GP. Moisturisers and lubricants alone or in addition to vaginal oestrogen, can also be used to treat vaginal dryness.²

NICE also discuss the use of complementary and unregulated therapies. NICE state that there is some evidence that products such as isoflavones, black cohosh and St John's wort may give some relief of symptoms. However the quality, purity and constituents of complementary therapies may be unknown, and there is a risk of (potentially serious) interactions with other medicines. Furthermore, the efficacy and safety of unregulated compounded bioidentical hormones are unknown.² Other experts have strongly cautioned against the use of unlicensed bioidentical hormones.⁵

Monitoring

Treatment for short term menopausal symptoms should be reviewed at three months to assess efficacy and tolerability and then annually unless there are clinical indications for an earlier review. Women with a uterus should be made aware that unscheduled vaginal bleeding is a common adverse effect of HRT within the first three months of treatment. Women should report this at the three month review, or promptly if it occurs after the first three months.²

At reviews the importance of keeping up to date with nationally recommended health screening should be discussed. Health professionals should check for HRT side-effects, e.g. breast tenderness, nausea, headaches or bleeding. Blood pressure and weight should be checked. If appropriate, switching from cyclical HRT to continuous combined HRT should be considered. A review of an individual's risk:benefit ratio concerning HRT should occur at least annually.¹¹

Stopping HRT

The risks and benefits of HRT will change over time, so the question of when to stop should be considered regularly. Arbitrary limits should not be placed on the duration of usage of HRT. The British Menopause Society state that if symptoms persist, the benefits of HRT usually outweigh the risks.¹⁰ For vasomotor symptoms, most women require two to five years of HRT, but some women may need longer. This judgement should be made on a case-by-case basis with regular attempts to discontinue treatment. Symptoms may recur for a short time after stopping HRT.¹

Women stopping HRT should be offered the choice of gradually reducing or immediately stopping treatment. Gradual reduction may limit recurrence of symptoms in the short term, but gradually reducing or immediately stopping makes no difference to symptoms in the longer term.²

Vaginal oestrogen may be required long term. Regular attempts to stop treatment should be made. Symptoms may recur once treatment has stopped.¹

HRT should be discontinued in women who are diagnosed with breast cancer.¹²

Referral

Referral to a specialist should be made if symptoms do not improve or if ongoing adverse effects are a problem, or where there is uncertainty about the most suitable treatment.

Menopausal women with, or at high risk of, breast cancer should be referred to a healthcare professional with expertise in menopause.² HRT (including oestrogen/progestogen combination) should not be routinely offered to women with menopausal symptoms and a history of breast cancer. Tibolone or progestogens are not recommended for women with menopausal symptoms who have breast cancer.¹² Additionally, the SSRIs paroxetine and fluoxetine should not be offered to women with breast cancer who are taking tamoxifen,² as they may inhibit the metabolism of tamoxifen to an active metabolite.⁶

Clinical effectiveness

Vasomotor symptoms

NICE found strong evidence supporting transdermal oestradiol plus progestogen for reducing the frequency of hot flushes in women with a uterus. Although the evidence for oral oestrogen plus progestogen was weaker the Guideline Development Group (GDG) supported the use of both routes in clinical practice.⁹

NICE did not find SSRIs or SNRIs to be effective in relieving vasomotor symptoms, and they were found to be significantly worse in terms of high discontinuation rates compared with the other treatments. Therefore the GDG discouraged their first line use for this indication.⁹ The evidence for the use of antidepressants in the management of menopausal hot flushes has been summarised in UKMi Q&A 221. It states that limited evidence from a 2006 meta-analysis suggests that venlafaxine, paroxetine,

citalopram or fluoxetine are effective in reducing the frequency and severity of menopausal hot flushes. More recent reviews by the Endocrine Society and the International Menopause Society found evidence of efficacy with venlafaxine, desvenlafaxine (not available in the UK), paroxetine, citalopram, and escitalopram, but no significant reductions in hot flushes and inconsistent results with sertraline and fluoxetine. Antidepressants are unlicensed in the UK for the management of hot flushes.¹³

NICE focused on outcome data for frequency, rather than intensity, of vasomotor symptom. This impacted on the evaluation of non-hormonal treatments (such as clonidine) and non-pharmacological treatments (such as CBT), which were largely excluded from consideration.⁹ The evidence for non-hormonal alternatives to antidepressants in the management of menopausal hot flushes has been summarised in UKMi Q&A 222. Aside from antidepressants, the non-hormonal therapies most frequently considered as an alternative to HRT for menopausal hot flushes are clonidine and gabapentin. Methyldopa, octreotide and pregabalin have also been investigated. The data for all are limited and most studies have been short term.¹⁴ Specialist referral is therefore likely to be a more appropriate course of action than predominantly unlicensed treatments (with potentially problematic side-effects) in primary care. Clonidine is the only non-oestrogen based preparation that is licensed for menopausal flushing in the UK, but its use is limited by moderate efficacy and relatively high rate of adverse effects.¹⁴

A 2010 Cochrane review considered non-hormonal interventions for hot flushes in women with a history of breast cancer. Clonidine, SSRIs and SNRIs, gabapentin and relaxation therapy showed a mild to moderate effect on reducing hot flushes in women with a history of breast cancer.¹⁵

Long term benefits and risks of HRT

NICE collated evidence from randomised controlled trials and observational studies on different aspects of long term benefits and risks associated with HRT. The data for cardiovascular disease, breast cancer and fragility fractures were presented in risk tables. They can be accessed via the guideline (NG23) and can be used to facilitate the discussion between health professionals and women considering HRT therapy. When discussing risk it should be borne in mind that the individual's baseline risk will vary according to the presence of risk factors.

For venous thromboembolism (VTE) the risk is increased by oral HRT but not transdermal HRT, compared with baseline population risk. NICE recommend discussing this difference in risk with the patient and considering transdermal rather than oral HRT for menopausal women who are at increased risk of VTE, including those with a BMI over 30 kg/m². Those at high risk of VTE (for example, those with a strong family history of VTE or a hereditary thrombophilia) should be referred to a haematologist for assessment before considering HRT.²

For cardiovascular disease, HRT does not increase risk when started in women aged less than 60 years, nor does it affect the risk of dying from cardiovascular disease. Oestrogen alone is associated with no, or reduced, risk of coronary heart disease. Combined oestrogen and progestogen is associated with little or no increase in the risk of coronary heart disease. Oral (but not transdermal) oestrogen is associated with a small increase in the risk of stroke, but it should be noted that the baseline population risk of stroke in women aged under 60 years is very low.² NICE advise that the presence of cardiovascular risk factors is not a contraindication to HRT as long as they are optimally managed.

For breast cancer, around the age of natural menopause, oestrogen alone is associated with little or no change in the risk of breast cancer. Combined oestrogen and progestogen can be associated with an increase in the risk of breast cancer. Any increase in the risk is related to treatment duration and reduces after stopping HRT.² Women's Health Concern* have produced a factsheet to illustrate the risks of breast cancer with HRT in context with other breast cancer risk factors, such as smoking, drinking alcohol and obesity, available via https://thebms.org.uk/_wprs/wp-content/uploads/2016/04/WHC-Understanding-Risk-of-Breast-Cancer-160516.pdf¹⁶

For osteoporosis, the risk of fragility fracture is decreased while taking HRT. This benefit is maintained

during treatment but decreases once treatment stops.²

Neither oral nor transdermal HRT are associated with an increased risk of developing type 2 diabetes.²

The likelihood of HRT affecting their risk of dementia is unknown.²

There is limited evidence suggesting that HRT may improve muscle mass and strength.²

NICE did not discuss ovarian cancer risk with HRT. A 2015 meta-analysis of 52 epidemiological studies found an increased risk of ovarian cancer in women currently using HRT compared to women who have never used HRT (RR 1.43, 95% CI 1.31-1.56). Risk declined the longer ago use had ceased, although about ten years after stopping long-duration therapy there was still an excess of cases. Application of the relative risks to age-specific ovarian cancer incidence in England suggested that five years of HRT use, starting at around 50 years old, would result in about one additional case per 1000 users. For ten years of HRT use from about 50 years old, one additional case per 600 users was estimated.¹⁷

When evaluating data about the long term effects of HRT, the age that HRT treatment is commenced should be considered. The women in the WHI study were generally older (average age 63.2 years, two-thirds > 60 years) than the cohort of women for whom HRT is normally recommended in the UK. The absolute risk of conditions such as stroke, heart disease and breast cancer increases with age.¹⁸

Current advice to offer HRT for menopausal symptoms means that it is likely to be initiated in younger women than in the WHI study (average age of menopause in the UK is 51 years²). Furthermore, the Medicines and Healthcare products Regulatory Agency (MHRA) advise that HRT be used at the lowest effective dose for the shortest possible time.¹⁹ The MHRA also advise regular health check-ups and reassessment of the continued need for HRT at least annually.²⁰ Therefore contemporary HRT use in the UK is likely to differ considerably from its use in the WHI study.

Other prescribing considerations

HRT

- For symptom control, start with a low dose preparation. Older women may be less tolerant of oestrogen and need to start (and are usually maintained) on a lower dose. Younger women may require higher doses to remain symptom-free. Tailor the dose to the symptoms.¹
- Synthetic oestrogens such as ethinylestradiol are generally considered unsuitable for HRT, except in women with early ovarian failure, because of their greater metabolic impact. Oestrogens found in normal physiology are preferred.¹ Prescribing of ethinylestradiol for menopausal symptoms should therefore be reviewed. Ethinylestradiol is also disproportionately costly compared with other available oestrogens for HRT (see 'Costs' section below).
- HRT is available with a range of types of progestogen. Changing to a product with a different progestogen component may be required if progestogenic side effects occur.²¹ The Mirena® intrauterine system is an alternative option for endometrial protection (licensed for four years use for this indication).²²
- It is preferable for the oestrogen and progestogen to be in one combined form (for example in one tablet) because the adverse effects of the progestogen may lead to poor compliance if given separately. If oestrogen and progestogen are given separately, an explanation about the endometrial protective effect of progestogens is important to ensure compliance.¹
- HRT is not a contraceptive. Peri- and post menopausal women should be advised in accordance with the Faculty of Sexual & Reproductive Healthcare on contraception for women aged over 40 years.²
- Combination packs of HRT incur multiple prescription charges.⁴ A prepayment certificate may be appropriate for some patients. Further information can be found here: <http://www.nhs.uk/nhsengland/healthcosts/pages/ppc.aspx>

- Angeliq® contains estradiol and drospirenone (a progestogen with anti-aldosterone activity). As well as reducing menopausal symptoms, Angeliq® has been shown to reduce blood pressure and weight, compared with placebo. However the modest differences were of arguable clinical significance and do not justify selection of the product on this basis.²³ The Scottish Medicines Consortium do not recommend Angeliq® for use in NHS Scotland as comparative data versus other low dose continuous combined treatments are lacking and the cost-effectiveness has not been demonstrated and there are cheaper alternatives.²⁴
- Duavive® is a relatively new HRT product that contains conjugated oestrogens and bazedoxifene (a selective oestrogen receptor modulator) and is currently the most costly HRT product available.²⁵ NICE has published an Evidence Summary (ES3) on this product. Duavive® has been shown to reduce the average daily number of moderate and severe hot flushes in the short term. Some beneficial effects on vulvar or vaginal atrophy compared with placebo have also been demonstrated (NB. the recommended first line treatment for urogenital atrophy is vaginal oestrogen). The lack of active comparator makes it difficult to establish effectiveness compared with existing treatments. Furthermore, the current data do not allow for assessment of whether the incidence of rare but important adverse events including cardiovascular or cerebrovascular events, VTE or certain cancers are increased in women taking Duavive® compared with placebo, or other treatments.²⁶

SSRIs and venlafaxine for hot flushes

- Relief of symptoms is thought to be achieved at lower doses and more rapidly compared with the management of depression. A short term trial of one to two weeks may be adequate to assess the effect of an SSRI (three weeks for fluoxetine) or venlafaxine for hot flushes.
- A low dosage of antidepressant should be used initially, which should be titrated according to effect. The most appropriate dosage and duration of treatment has not been established.
- The Royal College of Obstetricians and Gynaecologists suggests that the most convincing data available are for venlafaxine at a dose of 37.5mg twice daily.¹³

Costs

There is a significant difference in cost between different HRT preparations. See appendix 1 for the following tables which list HRT preparations in ascending cost order:

Table 1. Sequential combined hormone replacement therapy products

Table 2a. Continuous combined hormone replacement therapy products

Table 2b. Other continuous therapies with oestrogenic and progestogenic or selective oestrogen receptor modulating (SERM) activity

Table 3. Unopposed oestrogen hormone replacement therapy products

Table 4. Local oestrogens for urogenital atrophy

- Patches and transdermal gels are generally more expensive than tablets.
- Ethinylestradiol has a high cost (£200 per pack⁴) and is not the most clinically suitable oestrogen for menopausal symptoms (see 'Other prescribing considerations').¹
- Estriol 0.01% cream is 12 times more expensive than Ovestin 0.1% cream.⁴ Both products deliver the same estriol dose per application.
 - » Ovestin 0.1% cream contains 0.5mg estriol per 0.5 g application²⁷
 - » Estriol 0.01% cream contains 0.5mg estriol per 5 ml application²⁸

Savings

In England and Wales £57.2 million* is spent annually on HRT and local oestrogen preparations for urogenital atrophy (ePACT November 2016 to January 2017). It seems likely that savings could be made by:

- Ensuring women are commenced on cost-effective products, where they are clinically appropriate and acceptable to the woman. Local formularies can support this. The need to individualise treatment will mean that the 1st or 2nd formulary choice product may not be suitable for all women.
- Using the lowest effective dose for the shortest possible time. Review of therapy and discussion of an individual's risk:benefit ratio for continuing HRT should occur at least annually. Regular attempts to discontinue treatment should be made.
- Reviewing those prescribed higher cost products for menopausal symptoms, notably ethinylestradiol tablets and estriol 0.01% cream.

*This figure includes approximately £4 million on ethinylestradiol, which is used for other indications, including palliative treatment of prostate cancer.⁴

Table 5. Potential cost savings for HRT and local oestrogens for urogenital atrophy (November 2016 to January 2017)

Annual savings for a 10% reduction in prescribing (this is a conservative estimate)	£5.7 million (this equates to £9,351 per 100,000 patients)
Annual saving if 80% of estriol 0.01% cream prescribing was for Ovestin 0.1% cream instead	£5.3 million (this equates to £8,610 per 100,000 patients)

It is possible that implementation of the latest NICE guidance on management of menopause could result in an increase in prescribing and spend on HRT overall. However the potential to make savings by medicines optimisation, whilst maintaining or increasing the quality of care, remain.

Summary

Most women approaching menopause experience some symptoms, such as hot flushes and night sweats. Menopausal symptoms typically last for about four years after the last period, but in some women continue for much longer. Quality of life may be severely affected.² Women should be supported to make informed choices about the management of their menopausal symptoms. To do this, health professionals need an evidence-based and up-to-date understanding of both the benefits and risks of HRT, as well as other treatments. Where HRT is chosen it should be individualised and reviewed regularly, so that the lowest effective dose is used for the shortest possible time.¹⁹

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*Women's Health Concern is the patient arm of the British Menopause Society. They are a charity and receive corporate sponsorship from the pharmaceutical industry.

Additional PrescQIPP resources



Briefing

Available here: <https://www.prescqipp.info/category/365-menopause>



Data pack

Available here:

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Appendix 1: Tables

Table 1. Sequential combined hormone replacement therapy products (listed in ascending order of cost, MIMS January 2017)

Brand	Form	Oestrogen (daily dose)	Progestogen (daily dose)	Cost per 28 days
Prempac-C* 0.625mg/0.15mg	tablets	Conjugated oestrogens (0.625mg)	Norgestrel (0.15mg)	£2.08
Prempac-C* 1.25mg/0.15mg	tablets	Conjugated oestrogens (1.25mg)	Norgestrel (0.15mg)	£2.47
Elleste Duet 1mg	tablets	Estradiol (1mg)	Norethisterone acetate (1mg)	£3.07
Elleste Duet 2mg	tablets	Estradiol (2mg)	Norethisterone acetate (1mg)	£3.07
Clinorette	tablets	Estradiol (2mg)	Norethisterone (1mg)	£3.08
Cyclo-progynova	tablets	Estradiol valerate (2mg)	Norgestrel (500 microgram)	£3.11
Trisequens	tablets	Estradiol (2mg and 1mg)	Norethisterone acetate (1mg)	£3.70
Novofem	tablets	Estradiol (1mg)	Norethisterone acetate (1mg)	£3.81
Femoston 1/10	tablets	Estradiol (1mg)	Dydrogesterone (10mg)	£5.39
Femoston 2/10	tablets	Estradiol (2mg)	Dydrogesterone (10mg)	£5.39
Tridestra	tablets	Estradiol valerate (2mg)	Medroxyprogesterone acetate (20mg)	£6.30
Evorel Sequi	patches	Estradiol hemihydrate (50 microgram)	Norethisterone acetate (170 microgram)	£11.09
FemSeven Sequi	patches	Estradiol (50 microgram)	Levonorgestrel (10 microgram)	£12.51

*Note: Prempac-C tablets (both strengths) are being discontinued by the manufacturer. (Personal communication, Pfizer Ltd, 09/02/17).

Table 2a. Continuous combined hormone replacement therapy products ((listed in ascending order of cost, according to MIMS January 2017 unless otherwise indicated)

Brand	Form	Oestrogen (daily dose)	Progestogen (daily dose)	Cost per 28 days
Premique Low Dose	Tablets	Conjugated oestrogens (300 microgram)	Medroxyprogesterone acetate (1.5mg)	£2.17
Premique*	Tablets	Conjugated oestrogens (625 microgram)	Medroxyprogesterone acetate (5mg)	£3.54 (Drug Tariff Jan 2017)
Kliofem	Tablets	Estradiol (2mg)	Norethisterone acetate (1mg)	£3.81
Kliovance	Tablets	Estradiol (1mg)	Norethisterone acetate (500 microgram)	£4.40
Elleste Duet Conti	Tablets	Estradiol (2mg)	Norethisterone acetate (1mg)	£5.67
Nouvelle Continuous	Tablets	Estradiol hemihydrate (2mg)	Norethisterone acetate (1mg)	£6.33
Indivina 1mg/2.5mg	Tablets	Estradiol valerate (1mg)	Medroxyprogesterone acetate (2.5mg)	£6.86
Indivina 1mg/5mg	Tablets	Estradiol valerate (1mg)	Medroxyprogesterone acetate (5mg)	£6.86
Indivina 2mg/5mg	Tablets	Estradiol valerate (2mg)	Medroxyprogesterone acetate (5mg)	£6.86
Femoston-Conti	Tablets	Estradiol (1mg)	Dydrogesterone (5mg)	£8.14
Angeliq	Tablets	Estradiol (1mg)	Drospirenone (2mg)	£10.63
Evorel Conti	Patches	Estradiol hemihydrate (50 microgram)	Norethisterone acetate (170 microgram)	£12.40
FemSeven Conti	Patches	Estradiol (50 microgram)	Levonorgestrel (7 microgram)	£14.71

*Note: Premique 0.625mg/5mg tablets are being discontinued by the manufacturer. Premique Low Dose tablets will continue to be available. (Personal communication, Pfizer Ltd, 09/02/17)

Table 2b. Other continuous therapies with oestrogenic and progestogenic or selective oestrogen receptor modulating (SERM) activity (listed in ascending order of cost, MIMS January 2017)

Brand	Form	Active ingredients (daily dose)	Cost per 28 days
Livial	Tablets	Tibolone* (2.5mg)	£10.36
Duavive	Tablets	Conjugated oestrogens (0.45mg) Bazedoxifene† (20mg)	£15.00

*Tibolone is a synthetic steroidal compound with oestrogenic, progestogenic, and androgenic activity.

†Bazedoxifene is a selective oestrogen receptor modulator.

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Table 3. Unopposed oestrogen hormone replacement therapy products (listed in ascending order of cost, MIMS January 2017)

Brand	Form	Oestrogen (daily dose)	Cost per 28 days
Premarin 1.25mg	Tablets	Conjugated oestrogens (1.25mg)	£1.19
Premarin 625 microgram	Tablets	Conjugated oestrogens (625 microgram)	£1.34
Bedol	Tablets	Estradiol (2mg)	£1.69
Elleste Solo 1mg	Tablets	Estradiol (1mg)	£1.69
Elleste Solo 2mg	Tablets	Estradiol (2mg)	£1.69
Premarin 300 microgram	Tablets	Conjugated oestrogens (300 microgram)	£2.02
Zumenon 1mg	Tablets	Estradiol (1mg)	£2.30
Zumenon 2mg	Tablets	Estradiol (2mg)	£2.30
Progynova 1mg	Tablets	Estradiol valerate 1mg	£2.43
Progynova 2mg	Tablets	Estradiol valerate 2mg	£2.43
Evorel 25	Patches	Estradiol (25 microgram)	£3.42
Evorel 50	Patches	Estradiol (50 microgram)	£3.88
Evorel 75	Patches	Estradiol (75 microgram)	£4.12
Oestrogel	Gel	Estradiol (2.5g or 5g of estradiol 0.06%) w/v gel applied daily)	£4.20-£8.40
Evorel 100	Patches	Estradiol (100 microgram)	£4.28
Sandrena 0.5mg	Gel	Estradiol (0.5mg - 1.5mg applied daily)	£5.08*
Elleste Solo MX 40 microgram	Patches	Estradiol (40 microgram)	£5.19
Estraderm MX 25	Patches	Estradiol (25 microgram)	£5.49
Estraderm MX 50	Patches	Estradiol (50 microgram)	£5.49
Sandrena 1mg	Gel	Estradiol (0.5mg - 1.5mg applied daily)	£5.85† - £10.93§

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Brand	Form	Oestrogen (daily dose)	Cost per 28 days
Elleste Solo MX 80 microgram	Patches	Estradiol (80 microgram)	£5.99
Estradot 25 microgram/24 hrs	Patches	Estradiol (25 microgram)	£5.99
Estradot 37.5 microgram/24 hrs	Patches	Estradiol (37.5 microgram)	£6.00
Femseven 50	Patches	Estradiol (50 microgram)	£6.01
Estradot 50 microgram/24 hrs	Patches	Estradiol (50 microgram)	£6.02
Progynova TS 50 microgram/24 hrs	Patches	Estradiol (50 microgram)	£6.30
Estraderm MX 75	Patches	Estradiol (75 microgram)	£6.42
Estraderm MX 100	Patches	Estradiol (100 microgram)	£6.66
Progynova TS 100 microgram/24 hrs	Patches	Estradiol (100 microgram)	£6.90
Femseven 75	Patches	Estradiol (75 microgram)	£6.98
Estradot 75 microgram/24 hrs	Patches	Estradiol (75 microgram)	£7.00
Estradot 100 microgram/24 hrs	Patches	Estradiol (100 microgram)	£7.27
Femseven 100	Patches	Estradiol (100 microgram)	£7.28
Ethinylestradiol 10 microgram	Tablets	Ethinylestradiol (10 microgram)	£200 (21 tablets)
Ethinylestradiol 50 microgram	Tablets	Ethinylestradiol (50 microgram)	£200 (21 tablets)
Ethinylestradiol 1mg	Tablets	Ethinylestradiol (1mg)	£200 (28 tablets)

Sandrena price for *0.5mg daily dose, †1mg daily dose (as 1 x 1mg sachet), §1.5mg daily dose (0.5mg sachet + 1mg sachet)

Table 4. Local oestrogens for urogenital atrophy (listed in ascending order of cost, MIMS January 2017)

Brand	Form	oestrogen, daily dose	Cost per 28 days
Ovestin 0.1% cream	Cream and applicator	1 applicator full contains estriol 0.5mg. Dose: Initially 0.5mg estriol (one applicator full) per day. After 2-3 weeks frequency is reduced to twice a week.	£1.19 (twice a week dose)
Vagifem 10 microgram vaginal tablets	Vaginal tablets and applicator	1 vaginal tablet contains estradiol (as hemihydrate) 10 microgram. Dose: Initially 10 microgram estradiol (one vaginal tablet) daily. After two weeks frequency is reduced to twice a week.	£5.57 - £19.51
Estring	Vaginal ring	Estradiol (as hemihydrate), 7.5mg/24 hrs Dose: One ring to be inserted and left in the vagina continuously for 90 days and then removed and replaced by a new ring.	£9.78
Estriol 0.01% w/w cream (generic)	Cream and applicator	1 applicator full contains estriol 0.5mg. Dose: Initially 0.5mg estriol (one applicator full) per day. After restoration of the vaginal mucosa has been achieved frequency is reduced to twice a week.	£14.21 (twice a week dose)