Drugs for the treatment of menopausal symptoms

Susan R Davis† & Fiona Jane
Monash University, Alfred Hospital, Central Clinical School, Women’s Health Program, Commercial Road, Prahran, Victoria, Australia

Importance of the field: Over the last decade, the management of the menopause has attracted extensive public and professional debate and has become one of the most controversial areas in clinical practice.

Areas covered in this review: This review provides an overview of the field, primarily from a clinical practice perspective. However, as we have incorporated in this ‘big-picture’ snapshot of the field both conventional and complementary approaches to managing the menopause, it is not an exhaustive review of the literature.

What the reader will gain: By reviewing menopausal management from the perspective of practicing clinicians, we hope readers will gain insight into decision making processes appropriate for dealing with symptomatic women.

Take home message: Although most women do not require pharmacotherapy for menopausal symptoms, many are severely affected by estrogen deficiency at and beyond menopause and, for such women, hormone therapy is important if they are to retain an acceptable quality of life. This article considers the drug treatment of the symptomatic postmenopausal woman and the safety issues related to these medications.

Keywords: estrogen, HRT, menopause, progestogen


1. Introduction

Menopause is not only associated with symptoms that range from bothersome through to extremely distressing, it is also accompanied by hormonal changes that impact adversely on several non-reproductive systems. As the average life expectancy of women has increased from 18 years in 1000 BC [1] to beyond 80 years today, there has been a concomitant increase in the number of women who find menopausal symptoms intolerable.

2. Which menopausal symptoms merit treatment?

The menopausal transition begins with variation in menstrual cycle length and ends after 12 months of amenorrhea. The stages of the menopause have been classified according to a woman’s reported bleeding pattern supported by changes in pituitary follicle-stimulating hormone levels (FSH) [2]. The ‘perimenopause’, which means ‘about the menopause’, describes the time from which menses become irregular and FSH levels have increased through to 12 months after the last menstrual bleed. The term ‘postmenopause’ is applied to women who have not experienced a menstrual bleed for at least 12 months.

The most common symptoms experienced by women include vasomotor symptoms (hot flushes and night sweats) [3], arthralgia [4], urogenital atrophy (e.g., vaginal dryness, dyspareunia and sexual dysfunction, urinary tract infections,
Drugs for the treatment of menopausal symptoms

2.2 Menopause, the metabolic syndrome and cardiovascular disease risk

CVD is the leading cause of death and disability-adjusted life years globally in women [16]. The risk of acute coronary events for women increases exponentially with age and following the menopause. The large INTERHEART Study reported that the key components of the metabolic syndrome – abnormal lipids, abdominal obesity, and diabetes – are associated with population attributable risks (PAR) of 47.1%, 18.7%, and 19.1% for myocardial infarction in women [17]. There is evidence for favorable effects of endogenous estrogens on endothelial function [18-20] and lipids [21], and for postmenopausal estrogen therapy on lipids [22-24], body composition [25,26], and insulin sensitivity [27] with mixed effects on the CVD risk markers [high-sensitivity C-reactive protein (hsCRP), homocysteine, and interleukin-6 (IL-6)] [28]. Premature surgical menopause also doubles the risk of coronary artery disease in later life compared with natural menopause [29]. In addition, there is a stronger association between age at menopause and subclinical atherosclerosis than between age per se and subclinical atherosclerosis, further suggesting the importance of menopause on CVD risk [30].

Accumulation of abdominal fat is associated with an increase in risk for the development of insulin resistance (IR), hyperlipidaemia, and hypertension, and hence CVD [31,32]. The menopause is accompanied by a transition from a gynoid to an android pattern of body fat distribution and an increase in total body fat without a significant change in total percent body fat [33]. Increases are seen in both truncal and subcutaneous abdominal fat mass, with the greatest change seen in intra-abdominal fat mass. This has been reported to increase by as much as 20 to 44% [33,34]. The accumulation of central abdominal fat in women at this time is associated with a decline in circulating adiponectin. Adiponectin, an adipokine produced by fat, increases insulin sensitivity by promoting fat oxidation distally in liver and muscle. Low serum adiponectin levels are associated with IR and the metabolic syndrome such that the decline in adiponectin with intra-abdominal weight gain at menopause is believed to have an important role in the development of IR after menopause. Whether these metabolic changes are due to the abrupt decline in estrogen production at menopause or are a direct consequence of ageing merits consideration.

CVD increases exponentially with age and most CVD events occur in the postmenopausal age range [35]. In rodents, oophorectomy increases food intake and body and fat mass, and these effects are reversed by estrogen therapy. Mice rendered estrogen deficient by a targeted mutation in the aromatase gene, which is required for estrogen biosynthesis, are obese and insulin resistant. Similarly, the rare event of a mutation in the aromatase gene, and hence inability to biosynthesize estrogen, results in IR. T2DM, acanthosis nigricans, hepatic steatosis, and signs of precocious atherogenesis [11]. A key observation has been that treatment of a man with an aromatase gene mutation with estradiol resulted in an improvement of his acanthosis nigricans and hepatic steatosis,

<table>
<thead>
<tr>
<th>Article highlights.</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Many women are severely affected by estrogen deficiency at and beyond menopause. For such women, hormone therapy is an important way of retaining an acceptable quality of life.</td>
</tr>
<tr>
<td>• The most common menopausal symptoms experienced by women include vasomotor symptoms, arthralgia, urogenital atrophy and sleep disturbance.</td>
</tr>
<tr>
<td>• Estrogen insufficiency results in bone loss and increased osteoporotic fracture risk in postmenopausal women.</td>
</tr>
<tr>
<td>• The menopause is accompanied by a transition from a gynoid to an android body fat distribution and an increase in total body fat without a significant change in total percent body fat.</td>
</tr>
<tr>
<td>• There is a consensus that estrogen is the most effective therapy for the treatment of the main menopausal symptoms, with the current recommendation being that treatment should be restricted to women with significant symptoms and for the shortest period required.</td>
</tr>
</tbody>
</table>

This box summarizes key points contained in the article.

and urinary urgency) [5] and sleep disturbance [6] (as a separate issue to night sweats) (Table 1). These are all a result of loss of ovarian estrogen production. Vasomotor symptoms affect 80% of Caucasian women and are the most common reason women seek treatment [1]. The three forms of sleep disorder associated with menopause are: insomnia/depression, sleep disordered breathing, and fibromyalgia [6]. Other commonly reported symptoms include anxiety, mood lability, and cognitive changes. There is increasing evidence that depression is a menopausal symptom experienced by some women. Women with a history of depression are more likely to report depressed mood during the menopausal transition and are also likely to experience vasomotor symptoms [4].

A number of other health consequences of estrogen loss need to be considered, although these are not all thought to be an indication for hormone replacement treatment (HRT): bone loss, osteoporosis and increased fracture risk [7-11]; central weight gain and its association with cardiovascular disease (CVD), dyslipidaemia and type 2 diabetes mellitus (T2DM) [12].

2.1 Bone loss

Estrogen insufficiency results in bone loss and increased osteoporotic fracture risk in postmenopausal women [8-10], which can be prevented with estrogen therapy [7,11]. Available data indicate the menopause-related bone mineral density (BMD) decrement is very evident during the first year after menopause (lumbar spine: –8.1%/year; forearm: –3.4%/year) and decreases progressively according to a logarithmic function [9], usually settling at a rate of 1 – 2% per annum[11], with considerable interindividual variation. Estrogen therapy has been shown to reduce bone turnover, increase BMD and decrease vertebral fracture rates by up to 40% [7,14,15].
and improved his glycaemic control and the resolution of carotid plaques [11].

An important recent observation is the link between obesity, IR, and risk of breast cancer, indicating that factors produced by adipose tissue not only influence metabolic pathways involved in IR but also pathways involved in the development of breast cancer [36]. Thus, accumulation of intra-abdominal fat after menopause may contribute to the increase in risk of breast cancer, an estrogen-dependent malignancy, in the postmenopausal years, when circulating estradiol levels are low. In a prospective cohort study of non-diabetic women with early-stage breast cancer, women with the highest fasting insulin levels had three times the risk of recurrence and death than women with the lowest insulin levels [37]. Other studies have since indicated that the use of metformin is associated with decreased breast cancer risk [38].

Together, the available data provide strong evidence that the decline in estrogen production by the ovaries at menopause contributes to the increase in intra-abdominal fat and IR, which can be ameliorated with estrogen therapy. Furthermore, the development of IR after menopause not only has serious health implications in terms of increased risks of T2DM and CVD, but may also contribute to pathogenesis of breast cancer.

3. Pharmacotherapy for menopausal symptoms

3.1 Hormonal therapy
There is consensus that estrogen is the most effective therapy for the treatment of the main menopausal symptoms, with the current recommendation being that treatment should be restricted to women with significant symptoms and for the shortest period required [39]. This follows the release of the findings from the Women’s Health Initiative Study (WHI) [7,40] in 2002. The current available estrogens and progestogens and dosages are listed in Table 2. Specific dosage recommendations will vary on patient-specific needs.

3.2 Estrogen
It has been well recognized since the 1920s [1] that estrogen alleviates vasomotor symptoms and the other commonly reported symptoms of the menopause [41]. There is still some controversy as to whether systemic estrogen therapy relieves alleviates the symptoms of urinary incontinence. On the one hand, a meta-analysis supports the use of systemic estrogen for this purpose [42]; on the other hand, other data suggest that oral estrogen therapy may worsen urinary incontinence [43,44]. However, low-dose vaginal administration of estrogen is effective in alleviating vaginal atrophy and the symptom of vaginal dryness, and is safe and acceptable to women. Indeed, it is considered good practice to ensure a postmenopausal woman not on estrogen use vaginal estrogen for 2 weeks or more prior to undergoing a Papanicolaou (PAP) smear to minimize the chance of a non-diagnostic test.

The most widely used estrogen preparation in North America in postmenopausal women is oral conjugated equine estrogens (CEE). Other available oral estrogen preparations include synthetically derived piperazine estrone sulphate, estriol, micronized estradiol, and estradiol valerate (Table 2). Estradiol may also be given transdermally as a patch or gel and, more recently, as a skin spray. Other options include a slow-release percutaneous implant and an intranasal estradiol spray. Intravaginal estrogens include topical estradiol in the form of a ring or pessary, estriol in pessary or cream form, dienestrol, and conjugated estrogens in the form of creams.

The physiology of endogenous estrogen is important to our understanding of the metabolism of exogenous estrogen and the potential risks of different estrogen formulations and routes of administration. In postmenopausal women, estrone sulphate is the main circulating estrogen, being produced extragonadally, primarily in fat tissue [45]. Circulating levels of estrone sulphate in postmenopausal women are 10–25 times greater than estrone or estradiol [46]. Estrone sulphate has a long plasma half-life and slow clearance rate, and thus acts as a reservoir for the formation of estradiol and estrone in target tissues [47]. Furthermore, in their unsulphated forms, estradiol and estrone are partly bound to sex-hormone-binding globulin (SHBG) and variations in the plasma level of SHBG impact significantly on the amount of free or bioavailable estradiol to a greater extent than estrone as well as on bioavailable testosterone [48]. This has significant therapeutic implications. Oral CEE and other oral estrogen preparations may result in up to 10-fold higher levels of circulating estrone sulphate than transdermally administered estradiol at comparable or even higher doses [47,49]. Not only do estrogen-sensitive target tissues such as breast and endometrium have high capacity to metabolize estrone sulphate through to estradiol, but estradiol can also be synthesized in these sites from androgens and act locally at these sites as a paracrine or even intracrine factor [45]. These are mechanisms by which concentrations of estrone and estradiol in breast cancer tissue are several-fold greater than circulating levels [50]. Orally administered estrogen therapy also increases SHBG to a greater extent than non-orally administered estrogens [51]. Thus, it would seem that the prescription of oral estrogen therapy should be at the lowest available dose to minimize levels of

Table 1. Estimated prevalence of menopausal symptoms [40].

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Pre-menopause</th>
<th>Peri-menopause</th>
<th>Post-menopause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hot flashes and night sweats</td>
<td>14 - 51%</td>
<td>35 - 50%</td>
<td>30 - 80%</td>
</tr>
<tr>
<td>Vaginal dryness</td>
<td>4 - 22%</td>
<td>7 - 39%</td>
<td>17 - 30%</td>
</tr>
<tr>
<td>Sleep disturbance</td>
<td>16 - 42%</td>
<td>39 - 47%</td>
<td>35 - 60%</td>
</tr>
<tr>
<td>Mood symptoms</td>
<td>8 - 37%</td>
<td>11 - 21%</td>
<td>8 - 38%</td>
</tr>
<tr>
<td>Urinary symptoms</td>
<td>10 - 36%</td>
<td>11 - 21%</td>
<td>8 - 38%</td>
</tr>
</tbody>
</table>

Table 2. Specific dosage preparations and routes of administration.

<table>
<thead>
<tr>
<th>Estrogen Form</th>
<th>Dosage</th>
<th>Route of Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrone sulphate</td>
<td>0.05 - 0.5 mg</td>
<td>Oral, transdermal, patch</td>
</tr>
<tr>
<td>Micronized estradiol</td>
<td>0.25 - 0.5 mg</td>
<td>Oral, transdermal, patch</td>
</tr>
<tr>
<td>Estradiol valerate</td>
<td>0.4 - 2 mg</td>
<td>Oral, transdermal, patch</td>
</tr>
<tr>
<td>PAP</td>
<td>0.625 - 1.25 mg</td>
<td>Intranasal, intravaginal</td>
</tr>
<tr>
<td>Estriol in pessary</td>
<td>0.25 - 0.5 mg</td>
<td>Intravaginal, topical</td>
</tr>
<tr>
<td>Estriol in cream form</td>
<td>0.25 - 0.5 mg</td>
<td>Intravaginal, topical</td>
</tr>
<tr>
<td>Dienestrol</td>
<td>0.625 - 1.25 mg</td>
<td>Intravaginal, topical</td>
</tr>
</tbody>
</table>

For personal use only.
Drugs for the treatment of menopausal symptoms

Table 2. Commonly used doses of estrogen and progestogen therapy.

<table>
<thead>
<tr>
<th>Dosage</th>
<th>High</th>
<th>Standard</th>
<th>Low</th>
<th>Ultra-low</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Estrogens</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral conjugated equine estrogens</td>
<td>1.25 mg</td>
<td>0.625 mg</td>
<td>0.3 mg</td>
<td></td>
</tr>
<tr>
<td>Oral micronized 17β-estradiol</td>
<td>4.0 mg</td>
<td>2.0 mg</td>
<td>1.0 mg</td>
<td>0.5 mg</td>
</tr>
<tr>
<td>Oral estradiol valerate</td>
<td>2.0 mg</td>
<td>1.0 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral piperazine estrone sulphate</td>
<td>1.25 mg</td>
<td>0.625 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transdermal 17β-estradiol patch</td>
<td>100 µg</td>
<td>50 µg</td>
<td>25 µg</td>
<td>14 µg*</td>
</tr>
<tr>
<td>Subcutaneous implant estradiol</td>
<td>100 mg</td>
<td>50 mg</td>
<td>20 mg</td>
<td></td>
</tr>
<tr>
<td><strong>Vaginal</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estriol</td>
<td>1 mg/g</td>
<td></td>
<td>0.5 mg</td>
<td>10 µg</td>
</tr>
<tr>
<td>ESTRADIOL</td>
<td>25 µg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transdermal estradiol gel</td>
<td>1 mg/1 g</td>
<td>150 µg/actuation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasal spray estradiol hemihydrate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Oral progestogens</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Norethisterone acetate</td>
<td>1 mg</td>
<td>0.5 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medroxyprogesterone acetate</td>
<td>10 mg</td>
<td>2.5 – 5 mg</td>
<td>1.5 mg</td>
<td></td>
</tr>
<tr>
<td>Drospirenone</td>
<td>2 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dydrogesterone</td>
<td>10 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Micronized progesterone</td>
<td>200 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral tibolone</td>
<td>2.5 mg</td>
<td></td>
<td>1.25 mg</td>
<td></td>
</tr>
<tr>
<td>LEVONORGESTROL intrauterine device</td>
<td>Releases levonorgestrol</td>
<td>20 µg/24 h</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*14 µg 17β-estradiol is indicated only for prevention of osteoporosis.

circulating estrone sulphate and SHBG. Consistent with this, lower doses of oral micronized estradiol are associated with equivalent symptom relief as higher-dose combinations but lower rates of mastalgia and vaginal bleeding [52].

Although oral estrogen therapy is associated with a more favorable cholesterol profile (reduction in low-density lipoprotein cholesterol and increased high-density lipoprotein cholesterol) it is also associated with increased levels of triglycerides [22]. Oral estrogen therapy is consistently associated with a 2- to 3-fold increase in the risk of venous thromboembolic disease (VTE) [40,53]. This risk is increased further after major surgery or hospital admission. Increasing age and higher body mass index (BMI) are additional risk factors. However, for women aged 50 – 59 years who have a BMI of < 25 kg/m², the rate of VTE in the WHI study was similar to that noted for the control group.

Non-oral estrogen administration results in a more physiological balance between estradiol and estrone and is unlikely to affect SHBG. Transdermal patches or gels deliver estradiol to the general venous circulation at a continuous rate. Local skin reactions to the patches occur in about 5% of women who use matrix (estrogen in adhesive) patches. The incidence of skin irritation diminishes when women rotate the application site. Percutaneous gel preparations are convenient and have been available in France for over 20 years. A transdermal skin spray has been approved for use in the US as a new alternative to a transdermal patch. The dose can be titrated and skin reactions are uncommon [54]. Estradiol pellets (implants) containing pure crystalline 17β-estradiol have been available for over 50 years. They are inserted subcutaneously into the anterior abdominal wall or buttock. Pellets are difficult to remove and may continue to release estradiol for a long time after insertion. Thus, implantation should not be repeated until the serum estradiol levels have fallen to a value similar to that seen in a premenopausal women during the early to mid phase of the menstrual cycle. Vaginal rings are a sustained delivery system composed of a biologically inert liquid polymer matrix with pure crystalline estradiol that maintain adequate estradiol levels. Transdermal estradiol does not appear to increase the risk of VTE [55], although this has not been evaluated in a large randomized controlled trial.

Vaginal estrogens have been used for treatment of vaginal dryness and atrophy. At low doses, local application can reverse menopausal vaginal changes and there is little to no significant absorption into the circulation. The most popular vaginal options include a vaginal tablet that delivers 25 µg estradiol per dose or estriol cream or pessary. The standard recommendation is that a woman such preparations two to three times per week.

Osteoporotic fracture is a major cause of morbidity and mortality in aging women. It has been estimated that 40% of white American woman aged 50 years will experience an osteoporotic fracture in their life [56]. The prevalence, pathophysiology, and diagnosis of osteoporosis have recently...
been reviewed in detail [56]. The institution of an appropriate lifestyle, including weight-bearing exercise and adequate calcium and vitamin D intake, is fundamental to preventing and managing bone loss [56]. Estrogen therapy increases BMD and reduces vertebral and non-vertebral fractures in postmenopausal women [57]. Of note, estrogen is the only therapy to date demonstrated to reduce fracture risk in women unselected for osteoporosis [56].

3.3 Progestogen therapy

The addition of a progestogen to estrogen for a postmenopausal woman with an intact uterus is required to protect against endometrial hyperplasia and endometrial carcinoma. The progestogen is usually administered for 14 days per month for the first 12 – 24 months after menopause resulting in a cyclical menstrual loss [58]. After that, progestogen is usually taken continuously such that menstrual bleeding does not occur. Epidemiological data indicate elevated rates of endometrial hyperplasia and cancer amongst women supposedly on adequate cyclical regimens [59], indicating that, in reality, compliance is poor, or that endometrial protection is inadequate, or both. By contrast, continuous combined estrogen–progestogen regimens have not been associated with an increased rate of endometrial cancer.

As in the case of estrogen, the route of administration and dose remain controversial and in need of clarification. Oral administration of progesterone is convenient; however, the oral micronized form is rapidly metabolized and inactivated in the liver. High doses must therefore be administered to achieve adequate circulating blood levels. Synthetic progestogens are more resistant to hepatic metabolism. Hence lower doses can be used to achieve the desired endometrial effect. However, there is up to a 10-fold variation in the bioavailability of the various progestogens following oral administration [60]. Side effects are reported by a small but significant number of women with both progesterone and synthetic progestin therapy. Natural micronized progesterone taken orally may induce sedation and undesirable hypnotic effects and synthetic progestogens may cause adverse mood effects in some women. Intramuscular progesterone administration results in predictable circulating levels but the injection is painful and inconvenient. The vaginal route results in therapeutic levels in the endometrium. Vaginal gels and tablets of micronized progesterone are commonly used in in vitro fertilization protocols. Transvaginal progesterone used in an alternate-day regimen for 12 days has been shown to be effective as part of a cyclic regimen. But, long term, this route of administration is inconvenient and unsatisfactory for most women. A vaginal levonorgestrel-impregnated intrauterine device is available in some countries and in appropriate circumstances is an excellent option for progestogen effects to be achieved in the endometrium with minimization of systemic side effects. However, the use of the levonorgestrel intrauterine device may carry a breast cancer risk either when used alone or with estrogen [61].

3.4 Other safety issues

For many years hormone replacement therapy (HRT) as estrogen (E) or estrogen plus progestin (EP), was considered an effective and safe therapy for peri- and postmenopausal women. However, the WHI studies generated data that raised substantial safety concerns internationally [7,40]. Subsequent detailed analysis of WHI data combined with other published data indicates an increased risk of breast cancer in EP users and much less risk in E-only users. Oral EP is associated with an increase in breast density and thus a reduction in the sensitivity of mammography for breast cancer. The risk of HRT appears to be tempered by body mass [62]. Thus, the risk appears to be greatest in lean women and least in overweight-obese women. It has been proposed that the reduction in HRT use since the WHI studies were published has resulted in a substantial reduction in breast cancer rates [63,64]. Most recently, Sprague et al. have reported that the change in hormone therapy use accounted for a decline of only about 3% in breast cancer cases, indicating 4% of risk being caused by a factor as yet unidentified [65].

The use of E/EP does not appear to influence CVD or stroke risk in women < 60 years [66]. Women who commence EP therapy within the first 10 years of menopause did not have a risk of CVD that differed from placebo [67]. A potential cardioprotective effect of EP in women treated in early menopause appeared to emerge after 6 years of treatment in the WHI Study [67]; however, these findings need to be considered with caution. Parenteral estrogen therapy is associated with a reduction in central abdominal fat, as described above [25,26]. The treatment of postmenopausal women with oral EP or E has been associated with a significant decline in IR over the first year of therapy, which does not persist in follow-up at 3 and 6 years [68,69]. Oral EP therapy has also been associated with a significant reduction in the cumulative incidence of treated diabetes [hazard ratio (HR) 0.79, 95% confidence interval (CI) 0.67 – 0.93, p = 0.004] [69], although a significant effect was not seen for E alone versus placebo in the Women’s Health Initiative randomized controlled trial [68]. Of note, in women with the metabolic syndrome, oral E therapy may worsen IR with transdermal E being the preferred mode of administration [70].

Observational studies [71-73] that indicate that the progestogen, dydrogesterone, added to estrogen achieves the benefits of relieving menopausal symptoms and minimizes the cardiovascular, VTEs and breast cancer effects as seen in the WHI study, if HRT is commenced around the time of menopause.

3.5 Androgen therapy

Testosterone levels decline in women prior to menopause and do not appear to change across menopause [74,75]. A thorough review of androgen therapy is beyond the scope of this article; however, there are data to indicate that such therapy may play a role in the management of disorders of sexual desire and arousal in women at midlife.

A Cochrane Review of studies of the use of testosterone in postmenopausal women for low libido up to 2007 concluded...
Drugs for the treatment of menopausal symptoms

that there are benefits in terms of improved sexual function with the addition of testosterone to standard postmenopausal hormone therapy (HT) [76]. Subsequent large, randomized controlled trials (RCTs) in both surgically menopausal [77-79] and naturally menopausal women [80], for whom the frequency of satisfactory sexual events was the primary endpoint, demonstrate that treatment with the transdermal testosterone patch, which delivers 300 µg testosterone per day (but not the patch delivering 450 µg per day) significantly increased the number of self-reported sexually satisfying events per month when compared with placebo. These studies also demonstrated significant improvements in desire, arousal, responsiveness, orgasm, pleasure and satisfaction.

An analysis of data from a number of these studies combined indicates that women with a SHBG level > 160 nmol/l or taking CEE are unlikely to benefit from testosterone therapy [81]. The former is because testosterone binds to SHBG with high affinity such that having an elevated SHBG results in a very low free or bioavailable testosterone. The interaction between CEE therapy and exogenous testosterone is unclear, but it may be that a component of CEE interferes with the binding of testosterone to the androgen receptor in addition to increasing SHBG.

The link between postmenopausal estrogen–progestogen use and breast cancer has created a level of concern regarding the use of testosterone in women. Testosterone has been widely used by women as an unapproved therapy for decades. There is no evidence from studies of premenopausal women and postmenopausal women using systemic estrogen treated with testosterone for up to 24 months, or studies of women with chronic androgen excess due to polycystic ovarian syndrome, that elevated testosterone levels – even above what is considered physiologically normal – are associated with altered breast cancer risk [82,83]. Primate and human studies suggest that testosterone might in fact protect the breast from estrogen-induced breast-cell proliferation [84-86]. However, this is an area of considerable controversy, which needs to be addressed in post-marketing surveillance research. There is also no evidence that in women without insulin resistance, testosterone adversely affects CVD risk [87]. However, uncertainty as to the consequences of restoring testosterone levels to those of premenopausal women in women who are many years past menopause remains. Now that testosterone patch therapy (Intrinsa®) has been approved for surgically menopausal women with hypoactive sexual desire disorder despite estrogen therapy (other than CEE) in Europe, these data will eventually be forthcoming from post-marketing-surveillance studies of women in the community.

3.6 Tibolone

Tibolone is a synthetic steroid possessing a 3-keto group with a 7α methyl group. It is in widespread use in Europe and Asia-Pacific countries as an alternative to conventional estrogen or estrogen/progestogen therapy. It has been described as a pro-drug as, following ingestion, it is quickly metabolized in the gastrointestinal tract to two estrogenic metabolites 3α and 3β which then circulate predominantly in their sulfated inactive forms [88]. These metabolites only become estrogenically active when desulfated by the sulfatase enzyme in target tissues. Tibolone itself and its 3β metabolite may also be converted to a Δ4-isomer by the enzyme 3β-hydroxysteroid dehydrogenase (HSD) isomerase [88]. The Δ4-isomer can bind and transactivate the progesterone receptor and the androgen receptor, such that in the endometrium tibolone exerts a predominantly progestagenic effect [88]. Tibolone alleviates postmenopausal vasomotor symptoms [89] without stimulating the endometrium [90]. Hence, a progestogen is not required and cyclical bleeding is not induced. In addition to having weak androgenic effects, tibolone significantly lowers SHBG, and increases circulating free testosterone further adding to its androgenicity [91]. The incidence of breast tenderness after treatment with tibolone is low [90] and mammographic density does not increase with tibolone, unlike with traditional oral HT [92]. In osteoporotic women over the age of 60 years, tibolone significantly reduces the incidence of vertebral and non-vertebral fractures and is associated with a reduced risk of breast cancer (RH 0.32; 95% CI 0.13 – 0.80; p = 0.02) and colon cancer (RH 0.31; 95% CI 0.10 – 0.96; p = 0.04) [93]. Tibolone has been associated with an increased risk of stroke in older women but this has not been observed in multiple RCTs of younger women [94,95]. Tibolone also does not increase the risk of venous thromboembolic disease or coronary heart disease events [93,96]. There have been conflicting reports in the literature about the endometrial safety of tibolone. In a large RCT comparing tibolone 1.25 and 2.5 mg with CEE/medroxyprogesterone acetate (MPA), tibolone did not induce endometrial hyperplasia or carcinoma in postmenopausal women; it is also associated with a better vaginal bleeding profile than CEE/MPA [94]. In addition, rates of break-through bleeding after commencement of tibolone are low [97]. Tibolone improves sexual well-being in postmenopausal women presenting with low libido with greater improvements in desire arousal and satisfaction and receptiveness than seen for transdermal estrogen–progestin therapy [95].

3.7 Dehydroepiandrosterone

Dehydroepiandrosterone (DHEA) and its sulphate ester, DHEAS, are the most abundant circulating sex steroid hormones in women. Maximal values of circulating DHEAS are achieved between the ages of 20 and 30 years. Thereafter, serum DHEA and DHEAS decline steadily [98-100], resulting in widespread speculation that the age-related decline in these C19 steroids results in loss of well-being, deterioration in cognition, and lowered libido [101]. It has been proposed that restoration of serum DHEA to the levels found in young people may be beneficial [101]. A number of studies of DHEA therapy have been published but the results are inconsistent. Large, randomized trials in postmenopausal women do not support the use of oral DHEA for sexual function, metabolic
parameters, well-being or menopausal symptoms [102-104]. A recent review of the literature concluded that evidence to support either benefit or safety of DHEA supplementation for otherwise healthy perimenopausal or postmenopausal women is lacking and that further research into the use of DHEA is warranted [105].

3.8 Non-hormonal treatments

3.8.1 Clonidine

Women who flush appear to have greater sympathetic nervous system activity and the drug clonidine, a centrally acting α-adrenergic antihypertensive, may act by elevating the ‘flush threshold’. Clonidine 50 – 150 μg twice daily has been used for many years to alleviate hot flushes with limited effectiveness [106]. Some women experience side effects at very low doses (dry mouth) [107]. Generally, most women do not find clonidine useful.

3.8.2 Gabapentin

Gabapentin was developed for the treatment of epilepsy. It is also used for neurogenic pain, restless-leg syndrome, essential tremor, bipolar disorder and migraine prevention. However, doses of 300 – 900 mg at night have been shown to be efficacious in reducing the frequency and severity of hot flushes [108-110]. More somatic complaints were reported with gabapentin than with estrogen or placebo; however, it still represents a non-hormonal alternative to estrogen for some women.

3.8.3 Serotonin reuptake inhibitors

Selective serotonin reuptake inhibitors (SSRIs) have been studied as alternatives to estrogen to reduce hot flushes and improve mood disorders in women unable to use hormone therapy. Studies of venlafaxine [111,112], a serotonin–noradrenergic reuptake inhibitor (SNRI), and paroxetine, an SSRI [113], indicate a moderate reduction in vasomotor symptoms with doses of 37.5 – 75 mg and 12.5 – 25 mg per day, respectively. Both therapies may cause nausea and insomnia. In addition, venlafaxine may cause dry mouth, constipation and decreased appetite whereas paroxetine may cause headaches. Of note, paroxetine should not be used in combination with tamoxifen as it may impair conversion of tamoxifen to its active metabolite, endoxifen, by inhibiting the liver enzyme CYP2D6 (P4502D6) [113].

The vasomotor effect appears to be independent of the effect on mood, with relief from hot flushes occurring in the first week whereas the antidepressant effect manifests after 6 – 8 weeks. The lowest effective dose should be used and when ceasing the drug the dose should be tapered. Female sexual dysfunction (FSD) is frequently reported by women using SSRI therapy and venlafaxine [114,115].

The overall incidence of antidepressant-related FSD has been reported as being as high as 56.9% at doses used to treat depression [115]. Whether the lower doses used for vasomotor symptoms results in a similar incidence of FSD is not known.

3.8.4 Phytoestrogens

Plant constituents with a phenol structure similar to estrogen are known as phyto (plant) estrogens. These compounds, found in a wide variety of edible plants, may display both estrogenic and anti-estrogenic effects. Earlier epidemiological studies, primarily comparing Asian and Western populations, were interpreted as indicating that consumption of a phytoestrogen-rich diet may ameliorate estrogen deficiency symptoms in postmenopausal women, and may protect against breast cancer, bone loss and CVD [116]. Consequently there was a movement towards increased consumption of phytoestrogen-rich foods and tablet formulations of concentrated isoflavone extracts were heavily promoted.

Phytoestrogens do not simply mimic the effects of human steroidal estrogen but exhibit both similar and divergent actions. The ultimate actions of these compounds in specific cells is determined by many factors including the relative levels of the estrogen receptors ERα and ERβ and the diverse mix of co-activators and co-repressors present in any given cell type. Effects vary according to the phytoestrogen studied, cell line, tissue, species and response being evaluated.

Systematic reviews of intervention studies questions the validity of the proposed benefits of phytoestrogen supplementation, with little data in postmenopausal women to support a role for phytoestrogens as an alternative for conventional HT [117,118]. Meanwhile the effects of phytoestrogens on the breast remain unclear.

3.8.5 Black cohosh

Black cohosh (Cimicifuga racemosa, also known as Actaea racemosa) is North American native plant. It has common usage internationally for the treatment postmenopausal vasomotor symptoms. The results of randomized controlled trials do not support black cohosh as an effective treatment for postmenopausal hot flushes [106]. There have been a number of case reports linking black cohosh to acute hepatitis requiring liver transplant a few weeks of week of treatment [119]. Women considering the use of black cohosh should have their liver function assessed biochemically before starting this herb and periodically during treatment [120]. Safety beyond 6 months is unknown as are the clinical effects of black cohosh on the breast.

3.8.6 Individually compounded hormone therapy: ‘bio-identical’ therapy

‘Bio-identical’ hormonal preparations are said by some to provide an individually tailored combination of estradiol, estrone and estriol. For the estrogen doses commonly given in these preparations, no studies have been conducted to establish the lowest effective dose to treat symptoms, or the required dose of progesterone (progestosterone) to be used for endometrial protection. There is insufficient evidence that transdermal (skin) or buccally absorbed progesterone will protect the lining of the uterus from conditions such as uterine cancer. This has culminated in cases of endometrial cancers being reported amongst users of such therapy [121]. Compounded
Drugs for the treatment of menopausal symptoms

Estrogen creams, lozenges, or troches, are also sometimes combined with testosterone or DHEA or each of these is sometimes prescribed alone.

Again, there is no evidence that any of the suggested doses of compounded preparations are safe or effective and the use of these preparations may carry the same risk–benefit ratio as commercially available estrogen/progesterone therapies [122]. There is no published data on these products, yet some of the compounding pharmacies have issued documents recommending various doses and equivalent doses to Food and Drug Administration approved estrogen therapies. Evidence for many of these recommendations is lacking.

4. New frontiers

4.1 Estrogen and estrogen agonists/antagonists

Estrogen and estrogen agonists/antagonists (EAAs) are compounds that exhibit selective estrogenic and anti-estrogenic activities in differing tissues as a result of their binding to the ERs. Our understanding of the consequences of the interactions between various ligands (such as EAAs) with α and β has been enhanced by the crystal structures of α and β ligand-binding domains (LBD) complexed with several ligands. Although agonists and antagonists bind at the same site within the core of the LBD, each induces specific conformations in the transactivation domain, known as AF-2. The effect of each ligand on the positioning of helix 12 provides a structural mechanism by which an estrogen receptor ligand may act as an agonist or antagonist. The binding of estradiol to the LBD places helix 12 in an agonist position such that co-activators can bind the complex and transcription is activated. EAAs such as tamoxifen and raloxifene in vitro distinctly place helix 12 in an antagonist position [125]. Raloxifene exhibits estrogen agonist activity on bone and lipids, and antagonist activity on breast and the endometrium. Raloxifene prevents vertebral fractures in postmenopausal, osteoporotic women [124]. Like oral estrogen, raloxifene increases the risk of VTE [124]. However, raloxifene reduces the risk of invasive breast cancer [125]. Unfortunately, both tamoxifen and raloxifene have the tendency to cause rather than alleviate hotflushes and vaginal dryness. Raloxifene has been associated with an increased risk of fatal stroke in women at high risk of stroke [126].

Preliminary evidence suggests that raloxifene can be combined with estrogen therapy [127] and further studies looking at EAA–estradiol combinations are underway. Of the newer EAAs in development, bazedoxifene has been found to be effective in preventing and treating postmenopausal osteoporosis, without adverse effects on the endometrium or breast [128]. By contrast, lasofoxifene reduces fracture breast cancer risk but has been associated with an increased incidence of vaginal bleeding, endometrial thickening, and endometrial polyps [128]. A combination of bazedoxifene and CEE has been reported to improve sexual function and quality-of-life measures over 12 weeks in postmenopausal women with vulvar/vaginal atrophy [129].

In summary, as for all drugs, the use of HT is associated with risks. These risks vary according to each individual’s background risk profile and the risk:benefit ratio is therefore a balance between symptom severity and risk profile. Although the standard recommendation is for use of the smallest dose for the shortest duration, in reality there are women who have persistent severe symptoms who elect to have longer-term therapy. The development safer options, such as more selective estrogenic compounds that are safe for the breast and endometrium, or centrally acting non-hormonal therapies for vasomotor symptoms is hopefully where future research will take this field.

5. Expert opinion

Clinical studies of menopausal therapy published over the last decade have provided more questions than answers and instilled in the community widespread suspicion of approved hormonal therapies. This has fuelled the increasing use of treatments considered ‘natural’ and hormonal therapies marketed as ‘bio-identical’.

Nonetheless, estrogen therapy, with or without concomitant progestogen, remains an important therapeutic option for women experiencing significant menopausal symptoms. When put into appropriate perspective, the reported risks of postmenopausal hormone therapy, approved by national drug regulating agencies, are small, such that for most early menopausal symptomatic women the benefits are likely to outweigh the risks.

The general recommendation is that risk should be in the context of the extent of symptomatology and risk profile of each woman considering treatment. Although doctors are advised to assess each woman’s risk profile, there is little evidence – with the exception of high thrombotic risk or fracture risk – that a given profile indicates greater risk or benefit with hormone therapy.

In general, non-oral estrogen therapy is preferable to oral therapy, with tibolone being an excellent option in countries in which this therapy is available. Duration of use depends on the duration and severity of symptoms with many symptomatic women choosing to continue hormone therapy long term while fully cognizant of potential risks.

Clinical trials of low dose therapy, novel delivery modes and exploration of new selective estrogen receptor modulators (SERMs), alone or in combination with estrogen are required, as are longer term studies of androgen therapy.

Declaration of interest

SR Davis is a consultant to Procter & Gamble Pharmaceuticals, Boehringer Ingelheim and Acrux Pty Ltd, has research grant support from Bayer Schering, BioSante, AstraZeneca, Procter & Gamble and has received honoraria as a speaker from Organon-Australia (now Pfizer). F Jane has received research support from Bayer Schering and Biosante USA.
Bibliography

12. Lobo RA. Metabolic syndrome after menopause and the role of hormones. Maturitas 2008;60:10-8
15. Seeman E. Osteoporosis: trials and tribulations. 1997;103:74s-87s
33. Lee CG, Carr MC, Murdoch SJ, et al. Adipokines, inflammation, and visceral adiposity across the
Drugs for the treatment of menopausal symptoms

52. Stadberg E, Mattsson LA, Uvebrant M. 17 beta-estradiol and norethisterone acetate in low doses as continuous combined hormone replacement therapy. Maturitas 1996;23(1):31
61. Lyytinen HK, Dyba T, Ylikorkala O, Pukkala E. A case-control study on hormone therapy as a risk factor for breast cancer in Finland: intrauterine system carries a risk as well. Int J Cancer 2009;126(2):483-9
63. Canfell K, Banks E, Moa AM, Beral V. Decrease in breast cancer incidence following a rapid fall in use of hormone
replacement therapy in Australia. MJA 2008;188(11):641-4


Drugs for the treatment of menopausal symptoms


120. Chow EC, Teo M, Ring JA, Chen JW. Liver failure associated with the use of herbal preparations containing black cohosh. Med J Aust 2003;179:390-1

121. Chow EC, Teo M, Ring JA, Chen JW. Liver failure associated with the use of herbal preparations containing black cohosh. Med J Aust 2003;179(4):244-5


Affiliation
Susan R Davis MMMS FRACP PhD† &
Fiona Jane MBBS
†Author for correspondence
Monash University,
Alfred Hospital,
Central Clinical School,
Women’s Health Program,
Commercial Road, Prahran,
Victoria 3181, Australia
Tel: +61 3 9903 0827; Fax: +61 3 9903 0828;
E-mail: susan.davis@med.monash.edu.au