Menopause: new therapies

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ABSTRACT

- The risk–benefit ratio of traditional postmenopausal hormone therapy is considered by many to be unacceptable.
- Low-dose oestrogen–progestin therapy (oral or non-oral and continuous or pulsatile) may have a better risk–benefit ratio, but this remains unproven.
- Steroids with selective tissue activation, such as tibolone, alleviate symptoms and protect against bone loss, but long-term safety data are lacking.
- Selective oestrogen receptor modulators (SERMs), such as raloxifene, prevent bone loss when used alone, and may soon be combined with oestradiol to treat symptoms and prevent osteoporotic fracture. Effects of SERMs on the cardiovascular system are currently being evaluated.

MJA 2003; 178: 634–637

FEWER THAN 25% OF WOMEN experience a symptom-free menopausal transition, and over 25% suffer severe symptoms,[1] most commonly vasomotor events. Non-pharmaceutical approaches, such as paced respiration, have been shown to reduce the severity and frequency of vasomotor symptoms but are of no use in preventing symptoms that disturb sleep.[2] A multitude of over-the-counter preparations are used by menopausal women for symptom relief, but are of varying quality,[3] and some have been shown to be no better than placebo for symptom management.[4,5] Of concern is the potential for side effects, with several cases of acute hepatitis reported after use of black cohosh and other common herbal remedies.[6]

Postmenopausal oestrogen therapy effectively alleviates menopause symptoms, prevents osteoporotic fractures and possibly reduces the risk of bowel cancer. However, there are justifiable concerns about the safety of available regimens. Oestrogen given alone to women with an intact uterus significantly increases uterine cancer risk,[7] while oral oestrogen–progestin regimens used for more than 5 years have been reported to increase breast cancer risk.[8-11] The latter regimens have also been associated with increased risk of venous thromboembolic and cardiovascular events.[8,12]

In an attempt to avoid adverse consequences of hormone therapy, the trend is towards low-dose regimens, new routes of administration and the use of novel synthetic steroids, such as tibolone. The possibility of combining oestrogen with a selective oestrogen receptor modulator (SERM) in place of a progestin is under evaluation. These potential options are the subject of this review. The role of androgens in postmenopausal regimens is also under evaluation but is not discussed here.

Oestrogen therapy

The most commonly prescribed postmenopausal therapies are oral conjugated equine oestrogen, with or without medroxyprogesterone acetate, and various oestradiol–norethisterone preparations. Irrespective of which of these is used, traditional doses achieve high levels of circulating oestrone sulfate.[13,14] This oestrogen has a long plasma half-life and slow clearance rate and thus acts as a reservoir for the formation of oestradiol and oestrone in target tissues.[13] Oestrogen-sensitive tissues, such as breast and endometrium, have a high capacity to metabolise oestrone sulfate through to oestradiol, and this may be a prime mechanism by which concentrations of oestrone and oestradiol are raised several-fold in breast cancer tissue compared with circulating levels.[15] Standard doses of oral oestrogen also substantially increase sex hormone binding globulin,[16,17] thereby significantly reducing unbound testosterone.[18] Testosterone is both antiproliferative and apoptotic in human breast cancer cell lines,[19] and exogenous testosterone opposes the epithelial proliferation induced by oestrogen–progestin therapy in mammalian breast tissue.[19,20] Hence, a reduction in bioavailable testosterone may contribute to the increase in breast cancer risk reported with oral oestrogen–progestin therapy.

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Low-dose oral oestrogen

Low-dose oral oestrogen preparations result in lower circulating oestrogen levels and less increase in sex hormone binding globulin, with symptom relief comparable to that of higher-dose therapy.[21] A new low-dose regimen (conjugated equine oestrogen, 0.45 mg; and medroxyprogesterone acetate, 1.5 mg daily) induces favourable changes in lipids, lipoproteins and haemostatic factors.[22] Whether it will also result in lower risk of cardiovascular events and breast cancer remains to be seen.

Parenteral oestrogen

Transdermal administration of oestradiol avoids the increases in oestrone sulfate and sex hormone binding globulin that occur with oral therapy, and the consequent reduction in free testosterone.[13,23] Standard-dose transdermal regimens produce little or no change in circulating lipids, coagulation parameters or C-reactive protein lev-

els,[24,25] while maintaining favourable effects on vascular endothelium. Although this suggests that parenteral therapy has a neutral cardiovascular profile, this has not yet been clearly established in randomised trials.[26]

Approved parenteral oestradiol preparations include patches, a gel, implants, vaginal preparations and, most recently, a nasal spray. Each of these has undergone extensive pharmacokinetic testing to establish the lowest effective dose and the dose of progestin to protect the endometrium, as well as pharmacovigilance to detect adverse effects. Various preparations are available for transbuccal absorption but cannot be routinely recommended until pharmacokinetic and safety data are available.

Intranasal oestradiol is now available on prescription in Australia. This form of administration takes advantage of the highly vascular nasal mucosa, with a single spray in each nostril resulting in a peak level of oestradiol after about 10–30 minutes, returning to 10% of the peak value by 2 hours.[27] Like other parenteral oestrogen therapies, intranasal oestradiol does not increase sex hormone binding globulin and does not result in a high oestradiol to oestrone ratio.[28] It has been shown to have clinical therapeutic equivalence to oral and transdermal oestradiol, and to be associated with significantly lower reporting of mastalgia.[28] Intranasal oestradiol also increases bone mineral density of the lumbar spine, but fracture data are not yet available.[29] A nasal spray combining oestradiol and norethisterone is currently undergoing clinical trial.

Tibolone and tissue-specific steroid activation

Tibolone is another more recent postmenopausal therapeutic alternative. The hormonal effects of this synthetic steroid depend on its metabolism and activation in peripheral tissues. It is not a selective oestrogen receptor modulator (see below). The parent compound has been described as a pro-drug, as it is quickly metabolised in the gastrointestinal tract to two oestrogenic metabolites, 3α and 3β, which then circulate predominantly in their inactive forms.[30] These metabolites become oestrogenically active only when desulfated in target tissues. The global effect of tibolone would thus be expected to be oestrogenic. However, tibolone itself and its 3β metabolite may be converted to a Δ4-isomer,[31] which can bind to and transactivate the progesterone receptor.[30]

Tibolone has the following effects:

- It alleviates postmenopausal vasomotor symptoms[32-34] without stimulating the endometrium, where its effects are predominantly progestogenic[35]. Hence, it does not need to be combined with a progestin, and cyclical bleeding is not induced.
- Tibolone normalises vaginal cell maturation and alleviates symptomatic atrophic vaginitis;[36,37] women treated with tibolone report significant reductions in vaginal dryness and dyspareunia.
- Randomised studies indicate that tibolone has positive effects on mood compared with placebo and that it alleviates several adverse mood parameters to a similar extent as does conventional hormone replacement therapy.[38] Improved mood is associated with increased plasma β-endorphin.[39]
- Tibolone and its Δ4-isomer transactivate the androgen receptor, exerting androgenic effects,[34] and significantly lower sex hormone binding globulin, thus increasing the availability of endogenously produced testosterone.[18] Tibolone is associated with improvements in sexual function that appear greater than those seen with standard hormone therapy.[40]
- In bone, tibolone is oestrogenic.
- In the breast, tibolone inhibits the enzyme sulfatase, and the sulfated 3α and 3β metabolites are not activated.[30] This tissue-specific sulfate inhibition may also reduce desulfation of oestrone sulfate in the breast. Tibolone inhibits proliferation of human breast cells and stimulates apoptosis.[41] The incidence of breast tenderness is low,[42] and mammographic density does not increase with tibolone, in contrast to oral oestrogen–progestin therapy.[43]
- With respect to thrombotic risk, tibolone increases fibrinolysis parameters without significantly altering coagulation parameters.[44] No increase in thromboembolic events has been reported in clinical trials (unpublished review of database of clinical trials, Dr Esme Nijland, Organon, Oss, Netherlands).

Despite all its attributes, tibolone is not the perfect therapy for all women at the climacteric. Some will have insufficient alleviation of vasomotor symptoms with this therapy, others may have inadequate restoration of mood and libido, and some complain of side effects similar to those reported with progestins. Whether these variations reflect individual differences in tissue metabolism of tibolone is not known. Studies are needed to establish whether the theoretical breast-protective effects of tibolone are of clinical significance, and whether tibolone can be safely used in women who have had breast cancer or have established cardiovascular disease.

Selective oestrogen receptor modulators

Selective oestrogen receptor modulators (SERMs) are a class of compounds that mimic oestrogen in some tissues and act as anti-oestrogens in others. Tamoxifen, the first SERM, is extensively used as adjuvant treatment for oestrogen-receptor-positive breast cancer, but in primary prevention is associated with significantly increased risk of venous thromboembolic events and endometrial cancer.[45]

Raloxifene is a SERM available for managing postmenopausal osteoporosis. Analysis of both 3- and 4-year trial data[46,47] shows that postmenopausal women with osteoporosis who were receiving raloxifene had a 72% risk reduction for invasive breast cancer compared with those receiving placebo (relative risk [RR], 0.28; 95% CI, 0.17–0.46). This equates to 1.3 versus 4.7 breast cancers per 1000 women-years. Among women at high risk of coronary heart disease, those taking raloxifene had statistically significant reductions in the risk of any cardiovascular event (28 events in 359 women treated with raloxifene [60 mg daily] versus 41 events in 317 women treated with placebo) and of stroke (six events in 359 women treated with raloxifene

[60 mg daily] versus 14 events in 317 women treated with placebo).[48] These findings must be confirmed by an adequately powered, randomised trial, with breast cancer and cardiovascular events as predefined outcomes. Nonetheless, the large number of women participating in the study, its randomised placebo-controlled design and long duration add to the significance of the findings in this group of postmenopausal women. Neither tamoxifen nor raloxifene alleviates vasomotor symptoms. In fact, exacerbation of vasomotor episodes can be a problem with both.

The search for the "ideal" SERM is underway, but a novel approach is to combine a SERM with oestradiol. Recent insight into the differential action of SERMs justifies this approach. We now know that when a hormone (or chemically similar compound, such as a SERM) binds to a receptor, the hormone–receptor complex binds a portion of DNA and initiates the recruitment of protein cofactors. These may act as either co-activators or co-repressors of the response, and the balance between the two types of cofactor ultimately determines whether the target gene is turned on or off. After oestradiol binds to its receptor, the receptor may either bind to a target gene directly at the promoter region or act indirectly through another mechanism. In both instances, co-activators are recruited. In breast tissue, where tamoxifen and raloxifene act as oestrogen antagonists, the SERM–oestrogen receptor complexes bind directly to oestrogen response elements and recruit co-repressor proteins. In contrast, in the endometrium, SERMs influence genes through an indirect mechanism and show differential actions: tamoxifen recruits co-activators (and thus mimics oestrogen), whereas raloxifene does not,[49] and consequently has no effect at this site. Preliminary research indicates that raloxifene might be combined with low-dose oestradiol, so that raloxifene's anti-oestrogenic effects dominate in the breast, while oestradiol alleviates vasomotor symptoms; both are protective of bone, and the combination is endometrial-neutral.[50] However, a SERM with a specific anti-oestrogenic effect on the endometrium may be required for this type of long-term combined therapy. Nonetheless, the concept of combining oestradiol with a SERM rather than a progestin, resulting in both breast and endometrial protection, is therapeutically attractive.

Selective androgen receptor modulators are in development, but no studies of their use in humans have yet been reported.

Specific needs of perimenopausal women

Around menopause, erratic and elevated oestradiol levels due to increased levels of follicle stimulating hormone may lead to mastalgia and menorrhagia,[51] while intermittent oestrogen deficiency may produce vasomotor symptoms. With irregular and often anovulatory cycles, this period is also characterised by relative progestin insufficiency, and, in the setting of relative oestrogen excess, this time has been described as a "window of risk" for future endometrial cancer.[51] Although it has become commonplace to prescribe sequential oestrogen–progestin therapy during this phase, the side effects of treatment may be worse than the presenting problem. For women with symptoms of oestrogen excess, cyclical or continuous progestin therapy may result in considerable relief.[51] Alternatively, the use of low-dose oral contraceptive therapy in women with oestrogen deficiency symptoms who have low risk of venous thromboembolic disease may be extremely efficacious. Neither tibolone nor SERMs are appropriate for the management of a perimenopausal woman with an intact uterus.

Conclusion

Menopause is not life-threatening but, for most women, significantly interferes with quality of life. The dilemma of balancing the benefits and risks of available therapies is probably greater for physicians than for patients, as those with severe symptoms generally expect treatment, including those who may be considered to have traditional contraindications to therapy. We now have a greater understanding of sex steroid metabolism and action, and new hormonal analogues and modes of delivery are available. In the next decade, we will see new SERMs with different properties, combination therapy with oestrogen antagonists and oestrogen, and selective androgen receptor modulators. In addition, androgen supplementation (not discussed here) is likely to become standard practice in postmenopausal women,[52] and acceptable clinical practice in those who are premenopausal.[53]

Competing interests

The author has received honoraria for lectures and consulting from Organon, Novartis and Servier, and has been an investigator for research studies supported by Organon, Servier, Eli Lilly and Proctor & Gamble.

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(Received 22 Oct 2002, accepted 24 Mar 2003) ❑