

# STARLING REVIEW

## Postmenopausal hormone therapy: from monkey glands to transdermal patches

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### Abstract

The climacteric is not a condition of the modern age, although with increased life expectancy over the centuries, more women will experience this physiological transition. As women are living longer there is a greater expectation that good health will be maintained through to the late decade. Thus the potential long-term adverse health consequences of using hormonal therapies (HTs) to alleviate menopausal symptoms are of considerable concern for women and medical practitioners. This concern is often the basis for a decision whether or not to use HT.

We have reviewed the history of knowledge of the menopause and the development of HT for the treatment of climacteric complaints. We have also summarised the current evidence for specific benefits and risks of HT. Data indicate that postmenopausal HT is appropriate for

the management of vasomotor symptoms, but that HT should not be prescribed for the prevention of cardiovascular disease or dementia. HT does prevent bone loss and osteoporotic fracture; however, use for this purpose remains controversial. The risk of breast cancer with HT varies according to the preparation used, such that oestrogen without concurrent progestin appears to convey little, or possibly even no significant breast cancer risk. There is insufficient information regarding the long-term use of non-oral HT, low-dose HT or novel compounds such as tibolone or the selective oestrogen receptor modulators with respect to breast cancer and cardiovascular risk for specific recommendations to be made.

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### Introduction

Life expectancy has increased dramatically over the course of history, such that in contrast to earlier times, when the average life span was quite short, we are now in an era where we expect to grow old. In 1000 BC, the average life expectancy at birth was merely 18 years, with few women surviving to age 40 and beyond (Speroff *et al.* 1999). This increased to 25 years in the Greek and Roman times. By the Middle Ages, it had only crept up to 35 years, increasing to 36.5 years for a female at the beginning of the 19th century and extending to 45 years for an American woman by the end of the 1800s (Goldzieher 2000). By the early 1900s, life expectancy for an American female at birth had only reached age 49; however, this rapidly increased to more than 80 years by the year 2000 (Speroff *et al.* 1999).

Not only has life expectancy altered, with more women living past their menopause transition, but there have also

been significant societal changes in the developed world, with more women delaying pregnancy until their late reproductive years, and the expectancy of good health and vigour continuing well beyond midlife.

Historical explanations and approaches to healing menopausal symptoms altered most dramatically following several critical observations made during the 19th and early 20th centuries, which led to our contemporary understanding of the menopause. Through these landmark studies emerged the discovery of the female sex hormones, the oestrogens and progesterone. Their effectiveness in the treatment of climacteric symptoms was subsequently identified, ultimately leading to their commercial manufacture and extensive clinical use. By the 1990s observational research indicated that postmenopausal hormone therapy (HT) as oestrogen or oestrogen plus progestin (EP) would not only solve the problem of climacteric symptoms, but also prevent many of the adverse effects of ageing. Now, however, findings from randomised

controlled trials (RCTs) challenge the previously proposed benefits of postmenopausal HT and suggest that HT use is associated with risks that many women consider unacceptable.

### Historical understanding and management of the menopause

There is evidence indicating an awareness of the climacteric, experienced by women who lived beyond their menopause, in ancient times. The onset of menopause was documented with Aristotle (384–322 BC) observing that menstruation ceased in a woman at the age of 40 (Goldzieher 2000). The purpose of the menstrual cycle, particularly the bleeding, intrigued physicians. As a consequence of the pain, smell and occasionally putrefying appearance, it was believed that the menses were a form of detoxification of poisons from the woman's blood (Medvei 1993). Therefore, it was assumed that cessation of the menses resulted in the accumulation of these toxins within the now 'retained' menstrual blood. Such poisons were believed to stimulate disease and many otherwise unexplained physical and mental conditions were attributed to these toxins. Treatment was aimed at removing these disease-causing toxins by encouraging menstrual flow. If this failed, other purification methods were applied. Techniques used to encourage menstrual flow included: herbal emmenagogues; applying leeches to the genitalia or the cervix; and phlebotomy, whilst other methods of extraction of toxins included: purgation; cauteries; setons (one or more threads of horsehair or a strip of linen introduced beneath the skin by a knife or needle to provide drainage or formerly to produce or prolong inflammation); and induction of sweating (Wilbush 1988). Although these traditional therapies were not only unpleasant but also resulted in considerable morbidity, women were often greatly eager to undertake them in an attempt to avoid retention of such 'toxins' and alleviate their symptoms (Wilbush 1988).

Consequences of removal of the gonads have been known for centuries. The custom of employing eunuchs as servants is ancient, with evidence of castration displayed on the walls of ancient Egyptian tombs. Farmers and camel drivers knew that the removal of the ovaries resulted in cessation of the oestrous cycle (Medvei 1993). There are also reports of ancient Egyptians performing oophorectomy on women for the possible purpose of contraception (Himes 1936, Medvei 1993). In 1775, Percival Pott reported on the removal of human female ovaries (Pott 1775). He observed that bilateral oophorectomy of a young woman was followed by shrinkage of her breasts and cessation of her menses.

The climacteric syndrome was initially defined by the French physician C P L De Gardanne who, in 1816, coined the term 'La ménopause', which he subsequently shortened to *ménopause* in 1821 (De Gardanne 1821). It was the

first time that climacteric complaints were recognised as a syndrome with a common cause (van Keep 1990).

### Blood-borne secretions

Prior to the conceptualisation of endocrinology, the nervous system was considered the only means of communication between the organs of the body. The notion of internal secretion by cells was first suggested in 1775 by the Parisian physician Théophile de Bordeau who postulated that the organs release 'emanations' crucial to the rest of the body (De Bordeau 1775). Observing the characteristics of eunuchs and castrated animals, he conceived the idea of sexual secretions. He hypothesised that these secretions, released from the testes and ovaries into the blood stream, influenced secondary sexual characteristics.

De Bordeau's hypothesis was largely theoretical, and no controlled experimental work had been conducted on the subject. The first empirical evidence of the effect of an endocrine gland was demonstrated by the German physiologist Arnold Berthold in 1849. In a pioneering experiment in which he castrated young cockerels, Berthold noted that the capons did not exhibit any typical sexual behaviour. They did not crow or display aggression and failed to grow the wattle and comb, all male traits. However, reimplantation of the testes re-established normal development of the cockerels into roosters. Berthold concluded that there is a substance produced by the testes and released into the blood stream which is responsible for the development of the male secondary sex characteristics. As a consequence of the severed nerve supply, he further postulated that it must occur without direct neural innervation (Berthold 1849).

In 1855, the concept of internal secretions, suggested earlier by De Bordeau, was revisited by a French professor named Claude Bernard. Whilst researching the disease diabetes, he coined the term 'internal secretions', incorrectly designating sugar an internal secretion of the liver (Bernard 1855). In 1889, at the age of 72, Charles Edouard Brown-Séquard rediscovered the fundamental observations of Berthold. He reported in *The Lancet* the rejuvenating effects of self-administering canine testicular extracts (Brown-Séquard 1889). Upon finding that no harmful effects eventuated in the test animals, Brown-Séquard gave himself a series of eight s.c. injections of filtered, ground dog testes in water, claiming the restoration of his strength, vigour and mental acuity. Dramatic effects of the liquid extracts from rabbit and guinea pig testes were also observed in three other men aged 54, 56 and 68 years, whereas two men treated with water as a placebo noted no clinical benefit (Brown-Séquard 1889). From these observations, Brown-Séquard suggested that the ovaries must produce a similar substance to the testes, resulting in physiological effects. Subsequently, in 1890 he reported that a midwife he knew had self-administered liquid obtained from pig ovaries, claiming she also

experienced a beneficial effect (Medvei 1993). Not surprisingly, the work of Brown-Séquard was viewed with considerable scepticism by many of his contemporary physicians. Most criticism was directed at the auto-suggestive basis of his therapy. However, his reports also stimulated interest by other physicians into the application of replacement therapy using organ extracts, a treatment that became known as 'organotherapy'. With George Redmayne Murray in 1891 successfully using thyroid tissue to treat hypothyroidism, the popularity of organotherapy increased (Murray 1891).

In 1896, a 29-year-old Austrian gynaecologist, named Emil Knauer, experimented with auto-transplantations of ovarian tissue into oophorectomised rabbits. He observed that if the grafts survived, female secondary sex characteristics developed normally, compared with otherwise castrated, non-grafted rabbits. Furthermore, by transplanting ovarian tissue from older animals into younger ones, Knauer was able to successfully accelerate the onset of sexual maturity (Knauer 1900). This work complemented the testicular transplant experiments of Berthold in 1849. Knauer's findings were the basis of the administration of desiccated ovarian tissue to women with the hope of alleviating menopausal symptoms (Sneader 1989). A series of three separate trials, conducted almost simultaneously by different groups in 1896, all reported the successful alleviation of climacteric symptoms by means of such therapy. It is, however, most unlikely that these very crude ovarian extracts had any true hormonal effect.

In 1902, William Bayliss and Ernest Starling commenced their experiments which provided the first scientific evidence to prove the existence of internal secretions (Bayliss & Starling 1901, Berman 2003). During discussions with Sir William B Hardy of Cambridge, it was suggested that these be given the name 'hormone' from the Greek word *ὁρμωω*, meaning '*I excite*'. The new term was adopted and first used by Starling in 1905 in his Croonian Lectures, stating 'These chemical messengers . . . or 'hormones' as we may call them, have to be carried from the organ where they are produced to the organ which they affect, by means of the blood stream' (cited in Medvei (1993), p 189).

## The oestrogens

With the acceptance of the hormone theory, there was increased effort put into isolating and purifying these novel chemical substances. Ovarian extracts came into popular clinical use in the pre-World War I period, with the most potent of these prepared by Henri Iscovesco, a Parisian gynaecologist. In 1912, Iscovesco reported the extraction of a potent substance from sows' ovaries using lipid solvents (Iscovesco 1912). The extract induced premature sexual maturation when injected into young rabbits. When administered to humans, it was said to be a

successful therapy for dysmenorrhoea and amenorrhoea. In 1913 Otfried Fellner of Vienna independently produced lipid extracts from sows' ovaries and reported similar results to Iscovesco in young female rabbits and guinea pigs (Fellner 1913).

Lack of a reliable and inexpensive assay to detect and quantify the activity of ovarian extracts provided a major obstacle to early commercialisation (Sneader 1989). However, in 1917 Charles Stockard and George Papanicolaou observed histological changes in the vaginal mucosa cells that closely paralleled the phases of the menstrual cycle. Following oophorectomy, the changes were abolished (Stockard & Papanicolaou 1917). Consequently, the first biological assay for the efficacy of ovarian extracts was established.

In 1923, Edgar Allen and Edward Doisy isolated follicular fluid from hog ovaries for injection into oophorectomised mice and rats (Allen & Doisy 1923). Treatment with this *liquor folliculi* restored the castrated rodents' oestrous cycles. This was determined by the cytological changes in the vaginal epithelial cells as described by Stockard and Papanicolaou's method. Through their investigations, Allen and Doisy concluded that the oestrous hormone was produced in the ovarian follicle, excluding the corpus luteum and interstitial tissue as a possible source (Allen & Doisy 1923). Further research was limited by lack of availability of follicular raw material (Medvei 1993). In 1926, the chemists S Loewe and F Lange detected oestrogenic hormones in human urine (Loewe & Lange 1926), and 12 months later Selmar Aschheim reported even greater quantities in the urine of pregnant women (Aschheim 1927). These findings led to the isolation of oestrone in crystalline form from the urine of pregnant women by Doisy and his students Veler and Thayer in 1929 (Doisy *et al.* 1930). Only a few months later, Adolf Butenandt of Göttingen isolated the same compound (Butenandt & von Ziegner 1930), followed by Ernst Laqueur in Amsterdam, who isolated a similarly active material (Parkes 1966). Allen and Doisy called their new hormone 'theelin', a name that was protected by a university-held patent, preventing its general use. A S Parkes and C W Bellerby coined the basic word 'oestrin' (now known as oestrone) to describe the hormone(s) responsible for oestrus in animals. This provided a useful stem for extension to the subsequently discovered hormone oestriol, isolated from human pregnancy urine in 1930 by Guy Marriam (Marriam 1930) and the more potent oestradiol, isolated from sows' ovaries by Doisy in 1936 (Medvei 1993).

## Commercialisation of postmenopausal HT

Pharmaceutical interest in the production of the oestrogens for the treatment of climacteric symptoms soon developed, with injectable products in early use (Goldzieher 2000).

In 1928, Schering developed the first commercially available oestrogen 'Progynon', at first produced from animal placentas, and then later from the urine of pregnant women (Schmidt-Gollwitzer 2001). In 1930, James Collip of McGill University, Canada, whilst researching placental hormones for Ayerst Laboratories, discovered an orally active hormone which, when extracted and purified, resembled oestrin (Government of Canada 2004). This substance, called 'Emmenin', was soon manufactured by Ayerst Laboratories who isolated the hormone from the urine of pregnant women using Collip's technique. Ayerst Laboratories launched Emmenin for clinical use in the United States in 1933 (Jaffe 2004). The market potential of Emmenin was large; however, raw material for production was limited, as only minute quantities could be isolated from human urine, threatening Emmenin's long-term viability. This problem of high cost, low yield was partly resolved in the 1930s with Bernhard Zondek's critical discovery that the urine of pregnant mares was replete with oestrogens (Medvei 1993). Further to this, in 1932, Girard reported at the inaugural meeting of the International Conference on the Standardisation of Sex Hormones, that he had developed a new method of isolating large quantities of oestrone from pregnant mares' urine (Speroff *et al.* 1999, Lorentzen 2001). Following two years of research, lead by Gordon Grant of Ayerst Laboratories, 'Premarin' (conjugated oestrogens extracted from PREgnant MAREs urINe) was created and launched in Canada in 1941 and in the United States in 1942 as the first orally active oestrogen (Speroff *et al.* 1999).

Ayerst Laboratories undertook a massive marketing campaign during the 1950s, highlighting the efficacy of Premarin in alleviating the symptoms of menopause (Lorentzen 2001). Premarin sales were further boosted in 1966 with the publication of the book '*Feminine Forever*' by New York gynaecologist Robert Wilson, which extolled the value of oestrogen therapy as a means of sustaining youth and sexuality (Wilson 1966). Wilson described menopause as a deficiency disease, resulting in not only climacteric complaints but a whole range of degenerative processes, which could be treated with oestrogen therapy. Financial support for Wilson's book was provided by Ayerst Laboratories (van Keep 1990). Over 100 000 copies of *Feminine Forever* were sold within seven months, and by 1975 Premarin had become the number one dispensed drug in the United States, reportedly taken by approximately 6 million women (Jaffe 2004).

### Differing oestrogen preparations

By the early 1980s several oral oestrogen preparations were in common usage, including conjugated equine oestrogens (CEE), piperazine oestrone sulphate, micronised oestradiol and ethinyl oestradiol (Mashchak *et al.* 1982). One of the earliest reports of the novel transdermal patch

delivery system for oestradiol was published in 1983 (Laufer *et al.* 1983).

In postmenopausal women the most abundant oestrogen in the circulation is oestrone sulphate, levels of which have been measured at 10–25 times greater than levels of oestrone and oestradiol (Lobo 1987). Oestrone sulphate 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 (Slater *et al.* 2001). In their unsulphated forms, oestradiol and oestrone as well as testosterone are partly bound to sex hormone-binding globulin (SHBG). Variations in the plasma level of SHBG impact significantly on the amount of free, or bioavailable, oestradiol and bioavailable testosterone and to a lesser extent bioavailable oestrone (Dunn *et al.* 1981). Today oral oestrogen preparations include CEE, synthetically derived piperazine oestrone sulphate, oestriol, micronised oestradiol and oestradiol valerate. Oestradiol may also be given transdermally as a patch or gel, as a slow-release percutaneous implant, and more recently as an intranasal spray. Intra-vaginal oestrogens include topical oestradiol in the form of a ring or pessary, oestriol in pessary or cream form, dienoestrol and conjugated oestrogens in the form of creams.

Oral micronised oestradiol and other oral oestrogen preparations may result in up to 10-fold higher levels of circulating oestrone sulphate than transdermally administered oestradiol at comparable or even higher doses (Nachtigall *et al.* 2000, Slater *et al.* 2001). Oestrogen-sensitive target tissues such as breast and endometrium have a high capacity to metabolise oestrone sulphate through to oestradiol (Pasqualini *et al.* 1996). Orally administered oestrogen therapy also increases SHBG to a greater extent than non-orally administered oestrogens (Slowinska-Szednicka *et al.* 1992) and this may result in a clinically significant reduction in the bioavailability of sex steroids.

### Progesterone

The gynaecologist Ludwig Fraenkel's experimentation with hundreds of pregnant rabbits led to the landmark discovery in 1903 of the hormonal function of the corpus luteum (Medvei 1993, Notelovitz 1999). Fraenkel demonstrated that implantation of the fertilised ova into the uterus was most likely the function of the corpus luteum. However, the literature on the function of ovarian secretions, at this time, was in a very confused state, with many researchers erroneously concluding that experimental outcomes were a manifestation of the effects of a single ovarian hormone. This concept was modified with Allen and Doisy's fundamental discovery of oestrus producing extracts in their *liquor folliculi*, exogenous to the corpora lutea (Parkes 1966). George Corner and Willard Allen demonstrated that injections of corpora luteal extracts



into rabbits, oophorectomised shortly after mating, prevented abortion, which provided further proof for a second hormone (Allen & Corner 1930). Attempts to isolate the active principle from these extracts were successful in 1934, when four laboratories independently announced the isolation of crystalline progesterone (Allen & Wintersteiner 1934, Butenandt & Westphal 1934, Hartmann & Wettstein 1934, Slotta *et al.* 1934). At the Second International Conference on Standardisation of Sex Hormones, the corpus luteum hormone was named 'progesterone', due to its ability to maintain gestation.

Progesterone was prohibitively expensive to produce, requiring the corpora lutea of 50 000 sows to yield only 20 mg and thus rendered it commercially unfeasible. But in 1943 Russell Marker successfully synthesised 2 kg of progesterone from the precursor diosgenin that he had isolated from the Mexican yam *cabeza de negro* (Goldzieher 2000). Diosgenin, a saponin, could be efficiently converted into synthetic progestin with a few chemical steps. As the pharmaceutical giant Parke Davis & Co. declined Marker's new methodology, Marker approached the small firm of Laboratorios Hormona, which he had located in a Mexico City phone book. The company's founding partners, Emeric Somlo and Frederick Lehmann, recognised the financial potential of Marker's process and, in 1944, established the new company Syntex, with the intent of manufacturing pure crystalline progestin, a synthetic form of progesterone.

The therapeutic use of Marker's synthetic progesterone was limited by its oral inactivity. But Carl Djerassi, working for Syntex in Mexico, created and patented the potent norethindrone in 1951, and Frank Colton, at G D Searle and Company in Chicago, synthesised the closely related compound norethynodrel, both enabling oral administration.

With so many women by the mid 1970s using oestrogen therapy, its adverse effects on the endometrium, when used unopposed, soon became evident (Goldzieher 2000). An increased risk from oestrogen therapy was shown for invasive as well as non-invasive endometrial cancer, and a dose-response effect was demonstrated (Smith *et al.* 1975, Ziel & Finkle 1975, Mack *et al.* 1976). Consequently, oestrogen usage dropped dramatically, soon followed by a decline in the incidence of endometrial cancer, providing compelling evidence of an association between oestrogen exposure and this disease (Hertig 1983). Introduction of cyclical progestin therapy was based on earlier reports that progestins counteract the proliferative effects of oestrogens and are thus protective (Kistner 1959, Whitehead *et al.* 1981).

## Current concepts

### *Insights into oestrogen action*

There are at least two oestrogen receptors (ERs), ER $\alpha$  and ER $\beta$ , expressed in varying amounts throughout the body

(Green *et al.* 1986, Kuiper *et al.* 1996). The ligand-binding domains of both ERs are capacious and promiscuous such that a variety of compounds can bind to these receptors and act as agonists, antagonists or elicit mixed agonist/antagonist responses. This has been attributed to the unique three-dimensional conformation induced by the binding of the ligand to the ER, which in turn determines how the ligand-bound receptor will behave (Pike *et al.* 1999). This complex molecular biology explains why plant chemicals (phytoestrogens), environmental chemicals (xenoestrogens) and the new class of therapeutic compounds known as selective ER modulators (SERMs) can activate the ERs. Growth factors and other such compounds can activate the ER $\alpha$  in the N-terminal region of the receptor (known as the AF1 region) and elicit oestrogen-like actions without acting as traditional ligands, and therefore not actually being oestrogens in the classic sense.

Although endogenous oestrogens are classic ER agonists, exogenous compounds that can bind to the ER may result in agonistic, antagonistic, or mixed agonist/antagonist responses. Furthermore, activation of the ERs can lead to both immediate non-genomic effects or more delayed genomic effects. Thus from a therapeutic perspective, defining a compound as an oestrogen is no longer straightforward and generalisations cannot be made about the pharmacological effects of this now very broad group of compounds.

### *The therapeutic use of HT today*

In the 1980s and 1990s it appeared that HT indeed offered women better health after midlife with the prospect of not only symptom relief, but also prevention of cardiovascular disease (CVD) (Colditz *et al.* 1987) and mortality due to CVD (Stampfer *et al.* 1991), no adverse effect on stroke (Stampfer *et al.* 1991), prevention of dementia (Paganni Hill & Henderson 1996, Tang *et al.* 1996), reduction in colon cancer risk (Chute *et al.* 1991), and decreased overall mortality (Henderson *et al.* 1991).

The use of HT has recently generated much debate following publication of the results of the oestrogen-only and EP arms of the Women's Health Initiative (WHI) (Writing Group for Women's Health Initiative Investigators 2002, Anderson *et al.* 2004), and the Million Women's Study (Million Women Study Collaborators 2003).

Although these studies provide important research outcomes, they each have specific limitations. The primary limitation of the Million Women's Study is that as an observational study it is subject to clear bias, primarily due to participant selection. Being such a large study, the size amplifies any small error in outcome due to bias, making the effect appear real, when it may indeed have been an error. In contrast WHI was an RCT, but evidence to answer the most pressing questions is lacking. That is, it

did not evaluate the benefits and risks of HT use in symptomatic women in their 50s.

### The WHI oestrogen and EP studies

The WHI is a major 15-year research initiative undertaken in the USA funded by the National Institutes of Health to address the most common causes of death, disability and poor quality of life (QOL) in postmenopausal women. Two arms of this study were dedicated to the evaluation of postmenopausal HT. Commencing in 1997 the HT studies were designed to determine whether the long-term use of oral HT in women aged 50–79 years at baseline would prevent heart disease, osteoporosis and colon cancer. They were not designed to address the benefits of HT for the relief of menopausal symptoms. Only 10% of women in these studies were under 55 years, i.e. the population of interest in terms of HT benefit and risk, and the study was not powered to evaluate this subgroup.

The combined oral CEE plus medroxyprogesterone acetate (MPA) therapy arm of the study was stopped in 2002 after an average of 5.2 years of participation. This was because the slightly greater rate of invasive breast cancer in the combined hormone-treated women reached the safety level determined by the study monitoring committee. The CEE-only arm of the WHI study, intended to run until 2005, was stopped prematurely in 2004, after seven years, because the rate of strokes in women randomised to CEE exceeded the rate in women randomised to placebo therapy. After complete data collection and analysis, neither of the stopping points for each of these studies achieved statistical significance.

The study has attracted widespread debate as to whether it was a primary intervention study and concern regarding the discrepancy in unblinding between the two groups (approximately 6% in the placebo group and 43% in the HT group) (Creasman *et al.* 2003). Nonetheless, WHI provides a wealth of valuable information regarding the benefits and risks of continuous combined oral HT and oral oestrogen in postmenopausal women aged over 50 years.

### Potential benefits of HT

HT is predominantly used by women for the relief of menopausal vasomotor symptoms (Schneider 2002). In many women, relief of these symptoms is imperative to an improved QOL and wellbeing. Other symptoms which are commonly reported by perimenopausal and postmenopausal women include depression, anxiety, palpitations, headaches, insomnia, lack of energy, fluid retention, back ache, difficulty in concentrating and dizzy spells. These are usually not highly correlated with menopausal status, although they are strongly correlated with each other and

are more common among women who experience severe flushing (Greene & Cooke 1980, Avis & McKinley 1991).

At least 50% of postmenopausal women suffer symptoms of urogenital atrophy, including vaginal dryness, dyspareunia, recurrent urinary tract infections and stress incontinence (Bachmann 1997). ERs have been demonstrated in the lower genitourinary tract and pelvic floor. There is still some controversy as to whether systemic oestrogen therapy alleviates symptoms of urogenital atrophy. A previous meta-analysis supports the use of systemic oestrogen for this purpose (Cardozo *et al.* 1998); on the other hand, the Nurses' Health Study, an observational study, suggested that HT may worsen urinary incontinence (Grodstein *et al.* 2004). However, most clinicians still believe that vaginal administration of oestrogen is effective in alleviating vaginal dryness and atrophy, and is safe and acceptable to women.

### HT and QOL

The WHI findings of the effects of CEE plus MPA on health-related QOL have been reported (Hays *et al.* 2003). There was a statistically significant but not clinically relevant improvement in sleep disturbance at one year follow-up. Physical functioning and bodily pain, two components of the SF36 wellbeing questionnaire, were also reported to have improved at 12 months. However, the statistical methodology used in the analysis of the SF36 assumed normal distribution of data, whereas it is well known that the SF36 analysis requires non-parametric statistical procedures. Furthermore, the SF36 does not measure QOL parameters that would be expected to vary with HT; the Modified Mini Mental State Examination used is a gross measure of intellectual decline and not a tool sensitive for the measure of change within health; lack of sexual change was based on a single question; and finally there was no assessment of the QOL symptoms previously shown in RCTs to improve such as vaginal and urinary tract symptoms. The majority of women in the WHI were 15 years postmenopausal, of which only 12% had moderate or severe vasomotor symptoms and the effect on urogenital symptoms was not assessed. Women with vasomotor symptoms were actively discouraged from entering the study. If they were symptomatic, their symptoms were unlikely to be disabling, as women were willing to be randomly assigned to placebo. Among the women with vasomotor symptoms at one year follow-up in this QOL analysis, 76.7% of HT users experienced an improvement in their symptoms compared with 51.7% in the placebo group ( $P < 0.001$ ). At three year follow-up, 71% of HT users had improvement compared with 52.8% in the placebo group ( $P < 0.001$ ), thereby improving QOL.

### HT and bone health

Osteoporosis is a significant cause of morbidity and mortality in postmenopausal women. At age 50, a woman has

a 60% lifetime risk of sustaining an osteoporotic fracture, and a 16% risk of hip fracture (Cummings *et al.* 1989). These risks are partly attributable to accelerated bone loss, which occurs after the menopause as a result of oestrogen deficiency.

HT reduces bone turnover, increases bone mineral density (BMD) and decreases vertebral and hip fracture rates by up to 35% (Seeman 1997). Importantly, the beneficial skeletal effects of oestrogen therapy are not attenuated by increased age. Progestin does not appear to enhance the effects of oestrogen on BMD. If HT is stopped, bone loss resumes (Henry *et al.* 1998). As the median age of hip fracture is 79 years (Cummings *et al.* 1989), women who use HT short-term for symptom relief may gain little or no protection against fracture beyond the age of 70 (Felson *et al.* 1993).

With regard to the effects of oestrogen on fracture rates, in the WHI study comparing the effects of continuous CEE 0.625 mg plus MPA 2.5 mg vs placebo, the absolute risk of all fractures was reduced by 44 per 10 000 HT users per year and that of hip fractures by 5 per 10 000 HT users per year (Writing Group for Women's Health initiative Investigators 2002). For the oestrogen-only arm there was a 39% reduction in hip fracture risk with active therapy, hazard ratio 0.61, 95% confidence interval (CI) 0.41–0.91. Of note, these study populations were not selected on the basis of osteoporosis risk.

For the most effective protection against fracture, HT should either be started at the menopause and continued long-term, which many now consider unacceptable, or be started later in life when the risk of fracture is greater (Ettinger & Grady 1993). Alternatively, HT may be initiated to manage menopausal symptoms with progression to other agents as women age. Women for whom HT should still be considered, with respect to bone health, would include: those who have on-going menopausal symptoms and osteopenia or osteoporosis without a fracture; women with premature menopause and are still less than 45 years; women who have primary amenorrhoea (such as Turner Syndrome) or prolonged secondary amenorrhoea; hysterectomised women who thus require oestrogen-only therapy which has a lesser risk profile (see below); women with osteoporosis who are at low CVD risk and who are intolerant of or do not have access to other therapies.

#### *Colorectal cancer and HT*

There are data to suggest that postmenopausal hormone use may decrease the risk of colorectal cancer (Calle *et al.* 1995, Grodstein *et al.* 1999). However, the WHI study outcomes do not support a benefit of HT for prevention of colon cancer (Writing Group for Women's Health Initiative Investigators 2002, Anderson *et al.* 2004).

## **Potential risks with HT**

### *Endometrial cancer*

The increased risk of endometrial cancer with unopposed oestrogens in women who have not had a hysterectomy is generally considered unacceptable such that a progestin is routinely co-prescribed in this situation (Writing Group for the PEPI Trial 1995).

The duration of progestin use required to prevent endometrial hyperplasia remains an ongoing source of controversy. Epidemiological data suggest high rates of endometrial hyperplasia and cancer amongst women supposedly on adequate cyclical regimens (Beresford *et al.* 1997), indicating that in reality, either compliance is poor, endometrial protection is inadequate, or both. There is up to a 10-fold variation in the bioavailability of the various progestins following oral administration (Pasqualini 1996). The vaginal route results in therapeutic levels in the endometrium. Vaginal gels and tablets of micronised progesterone are commonly used in *in vitro* fertilisation protocols. Used in an alternate-day regimen for 12 days, transvaginal progesterone has been shown to be effective as part of a cyclic HT regimen. However, long-term this route of administration is inconvenient and unsatisfactory for most women. A vaginal levonorgestrel-impregnated intra-uterine device is available in some countries and in appropriate circumstances is an excellent option for progestin effects to be achieved in the endometrium with minimisation of systemic side effects. Progestins can also be administered transdermally as a cream, patch or gel. Currently in combination with 17 $\beta$ -oestradiol, norethisterone is available in a patch using either a sequential or cyclical regimen and oestradiol combined with norethisterone administered intranasally has been developed but is not at present available.

Following a *Lancet* publication by Lee (1998), compounded progesterone creams became widely available, with the belief that this treatment would: preserve bone; alleviate climacteric symptoms; be substituted for synthetic progestins in HT regimes; and alleviate menstrual and premenstrual symptoms. Lee claimed improvement in bone density in postmenopausal women over three years with transdermal progesterone cream (Lee 1998). Cooper *et al.* (1998) performed a randomised, double-blind, placebo-controlled cross-over study to evaluate the absorption, metabolism and urinary excretion of progesterone administered transdermally. Serum levels achieved were inadequate for endometrial protection. In contrast, Burry *et al.* (1999) reported mean serum concentrations of progesterone of 1.6–3.3 ng/ml with the administration of 60 mg progesterone cream transdermally each day. Furthermore, Anasti *et al.* (2001) demonstrated that topical 1.4 and 4% progesterone cream had antiproliferative effects on the endometrium when given for 14 days with continuous CEE 0.626 mg/day. Another placebo-controlled study investigating topical progesterone cream

reported that 20 mg daily showed reduction in vasomotor symptoms but no protective effect on bone density after one year (Leonetti *et al.* 1999). Thus recent studies indicate that if a sufficient amount can be administered, transdermal progesterone may alleviate vasomotor symptoms and afford endometrial protection short-term, but long-term benefits and safety need to be established. There is no evidence that transdermal progesterone prevents bone loss.

### *Breast cancer risk with HT use*

Breast cancer is a disease that mostly affects women in their postmenopausal years when they are in a state of relative oestrogen deficiency. In a large meta-analysis evaluating over 52 000 women with breast cancer and 108 000 controls, no significant increase in breast cancer risk was observed for women using HT for less than five years (Collaborative Group on Hormonal Factors on Breast Cancer 1997). For women who used oestrogen with or without a progestin beyond five years, a relative risk of 1.35 was reported. In the combined HT arm of WHI, women treated with CEE-MPA had a 1.26-fold greater risk of invasive breast cancer than women treated with placebo. This translates to an absolute risk of 8 extra cases per 10 000 women per year. However, 12 305 women in the study had not used HT prior to commencing the study, and for these women the risk of breast cancer was not increased (relative risk 1.05). Thus the findings from WHI are consistent with the epidemiological findings cited above. Counter-intuitively, a family history of breast cancer does not appear to increase the risk of developing breast cancer with HT use. Furthermore, mortality due to breast cancer is not increased with HT use (Willis *et al.* 1996) and observational studies have found no evidence that HT use after breast cancer increases recurrence or breast cancer mortality (Eden *et al.* 2001).

In WHI, for CEE-alone vs placebo, the hazard ratio for invasive breast cancer was 0.77 (95% CI 0.59–1.01) after a mean follow-up of 6.8 years (Anderson *et al.* 2004). Consistent with this finding, several studies have indicated that the concurrent use of a progestin may confer a significantly greater risk of breast cancer than the use of oestrogen alone (Ross *et al.* 2000, Schairer *et al.* 2000). The extrapolation of these findings has been that progestins increase breast cancer risk when given with oestrogen. However, it may instead be the case that the reason women do not require progestin therapy is protective. That is, women who have undergone bilateral oophorectomy (around 40% in the oestrogen-only study vs 0.3% in the oestrogen-progestin WHI study) may have such increased protection from breast cancer due to loss of their ovaries that adding HT makes no difference.

In the Million Women Study, current users of HT at recruitment were more likely than never users to develop breast cancer (Million Women Study Collaborators 2003).

This was a Level 2 observational study of over a million women aged 50–64 years having mammography, that retrospectively looked at their HT use and subsequent breast cancer. Such studies do not replace the data from Level 1 RCTs. The merits of this study were its size and its ability to look at trends across several hormonal types, regimens and routes. However, these positives were outweighed by bias from non-randomisation; short follow-up; non-blinding of histologists; non-centralisation of histology; extrapolation of the data to 10 years; and comparison of the HT data to data from a historical control population, many of whom did not have mammography and thus had less chance of breast cancer detection. Misclassification of type and length of HT use was possible as no clinical data were collected after trial entry. The study did support the trend for progestins use to be associated with an increase in breast cancer risk. In contrast to the literature, this paper reported an increase in breast cancer mortality. The relative risk was 2.00 for combined HT users and 1.30 for users of oestrogen-only preparations. The risk of breast cancer increased with increasing duration of HT use; however, past users of HT were not at increased risk. The estimates of increase in risk were based on self-reported duration of use at baseline, not duration of use by the time of diagnosis. Thus a woman who reported a duration of use of oestrogen plus progestin of less than one year at baseline, who had her cancer diagnosed two or three years later was really an HT user for more than two years, not less than one year as this statement incorrectly implies. To further complicate matters: 22% of women who said they were current users at baseline were no longer users 2.2 years later; 81% of past users were no longer past users (thus 19% must have become current users); and 89% of never users were no longer never users (thus 11% must have turned into current users). However, every woman was assessed according to her reported usage at baseline. The ability of this study to tell us reliably about duration of exposure and breast cancer risk is questionable.

In summary, long-term use of oral oestrogen-progestin therapy appears to be associated with a small, but statistically significant increase in the risk of invasive breast cancer. Furthermore combined EP use is associated with increased mammographic density and possibly delayed diagnosis (Chlebowski *et al.* 2003). The extent to which breast cancer risk may vary with dose, formulation, or mode of EP administration is not known. Use of oral oestrogen alone for up to about seven years has not been shown in RCTs to be associated with an increase in breast cancer risk, an outcome that may reflect protection from reasons why certain women do not require progestin, rather than the ill effects of progestin.

### *Ovarian cancer*

The American Cancer Society's Cancer Prevention Study II, a prospective US cohort study with mortality follow-up



in 211 581 postmenopausal women, noted a small increase in ovarian cancer mortality with 10 or more years of oestrogen therapy (Rodriguez *et al.* 2002). Ovarian cancer death rates were: 6.4 and 3.8 per 10 000 women for baseline and former users of oestrogen therapy for 10 or more years respectively; and 2.6 per 10 000 women for never users. This study relied upon recall of prior HT use. Data were not available on type of HT use and only a small proportion of women had used HT for more than 10 years. Another cohort study, of 44 241 postmenopausal women, reported a slight increase in absolute risk of ovarian cancer in women using oestrogen therapy for 10 or more years compared with non-users, of 2 more cases per 10 000 woman years of HT use (Lacey *et al.* 2002). The increased risk was confined to women with a prior hysterectomy as these women were more likely to be prescribed long-term unopposed oestrogen therapy. However, the role of hysterectomy in the development of ovarian cancer in itself is unclear. In this study, results were presented as a cumulative of total person years of oestrogen use and were not stratified into the number of women in each group of long-term, short-term and non-users of oestrogen therapy. It also relied upon recall of prior HT use. Neither the oestrogen-only nor EP arms of the WHI study reported an increase in ovarian cancer risk vs placebo (Writing Group for Women's Health initiative Investigators 2002, Anderson *et al.* 2004).

#### Coronary heart disease (CHD)

The risk of acute coronary events for women increases exponentially with age and following the menopause. Women who have undergone a premature surgical menopause have double the risk of coronary artery disease compared with those who have undergone natural menopause (Colditz *et al.* 1987). However, the extent to which oestrogen insufficiency contributes to this increased risk is uncertain. The role of HT for the primary prevention of CHD is controversial; however, most would agree that HT has no role in secondary CHD prevention.

**Primary prevention** There is strong epidemiological evidence that unopposed oestrogen may reduce CVD risk in menopausal women without established disease (Colditz *et al.* 1987). This appears to be attributable directly to plasma lipid changes, reduced low-density lipoprotein (LDL) and lipoprotein (a) and increased high-density lipoprotein (Darling *et al.* 1997) as well as favourable effects of oestrogen on endothelial function (Mendelsohn & Karas 1999). Conversely, oral oestrogen increases serum levels of inflammatory markers that have been associated with CHD risk, an effect in part attenuated by oral progestin therapy (Davison & Davis 2003). In epidemiological research, concurrent progestin use does not appear to attenuate the beneficial effects of oestrogen on the cardiovascular system (Grodstein *et al.* 1996).

**Secondary prevention** Once adverse CHD conditions have developed beyond menopause, the benefits of oral oestrogen therapy are greatly diminished, such that the potential procoagulant effects appear to outweigh favourable lipid effects. In a study of hypercholesterolaemic postmenopausal women with poor endothelial function, presumably secondary to their hyperlipidaemia, treatment with oral oestrogen did not result in normalisation of endothelial function (Davis *et al.* 2002). This contrasts normalisation of impaired endothelial function with oestrogen therapy in otherwise healthy postmenopausal women (Koh *et al.* 1999). Two large RCTs of CEE-MPA have shown a small initial increase in CHD risk within the first year of therapy, but with no overall risk difference from placebo following several years of therapy (Hulley *et al.* 1998, Writing Group for Women's Health Initiative Investigators 2002). The oEStrogen in the Prevention of ReInfARCTion Trial (ESPRIT) has shown neither increased risk nor protection against CHD events for two years after a primary event with oestradiol valerate (2 mg) compared with placebo (ESPRIT Team 2002). In this study, treatment was initiated within weeks of a first myocardial infarction. The oestrogen-only WHI study showed no increase in risk with CEE 0.625 mg for non-fatal infarction or CHD death (Anderson *et al.* 2004). One RCT has evaluated the effects of transdermal oestrogen therapy in women with established CHD. During the first two years of follow-up, the HT group had a higher, but not statistically significant, event rate than the placebo group (Clarke *et al.* 2002).

In summary, when all RCTs are taken together, resulting in the participation of over 20 000 women for more than 4.9 years on average, there is no overall significant excess in CHD, with a relative risk of 1.1 (95% CI 0.96–1.3) (Beral *et al.* 2002).

Thus the use of HT for primary and secondary prevention of CHD should be strongly discouraged. The risk of CHD events in typical HT users who are younger peri/postmenopausal woman being treated for menopausal symptoms is not known. However, CHD is uncommon in otherwise healthy women before the seventh decade and any small increase in risk in this otherwise low-risk population is unlikely to translate into any clinically significant absolute increase in events.

#### Venous thromboembolism

The most concerning outcome from various RCTs of HT has been the clear 2- to 3-fold increase in risk of venous thromboembolic disease (VTE) (Hulley *et al.* 1998, Writing Group for Women's Health initiative Investigators 2002, Anderson *et al.* 2004). This appears to be greatest following major surgery or hospitalisation (Grady *et al.* 2000), with a decrease in risk with aspirin or statin use, suggestive of a protective effect of both therapies against VTE for HT users. Clearly women should cease

oral HT before major surgery or during an immobilising illness. Of significance is the decreased risk of VTE noted. Potentially, the increased risk of VTE may be focused in those with predisposing genetic susceptibility for thrombosis. Women in the WHI study who tested positive for Factor V Leiden mutation had a 6.7-fold increase in risk of thrombosis. The prothrombin 20210A variant was not sufficiently common to enable any conclusions to be drawn. In contrast, observational data suggest that transdermal oestrogen therapy is not associated with an increase in VTE vs non-treatment (Scarabin *et al.* 2003); however, this requires confirmation in appropriately powered RCTs. The routine screening of women for haemostatic abnormalities prior to commencing HT is not recommended, but a thorough history of family or personal experience of VTE or recurrent abortion is essential to screen specific women for known mutations.

### Stroke

Several studies have now raised concerns regarding an increased risk of stroke with HT use. In the Womens' oEstrogen and Stroke Trial (WEST) 664 postmenopausal women were randomised to either 1 mg 17 $\beta$ -oestradiol or placebo within weeks of a stroke (Viscoli *et al.* 2001). There was an increased risk of stroke during the first 6 months of the study with oestrogen use, with the strokes reported as more severe in the oestradiol group. In the Heart and Estrogen/Progestin Replacement Study (HERS) of women with known CVD, combined continuous HT had no effect on stroke risk in postmenopausal women (Hulley *et al.* 1998). However, both the oestrogen and EP studies of the WHI were associated with a significantly increased hazard ratio for stroke, notably for ischaemic stroke. For the EP study this was equivalent to an absolute increase by 8 cases per 10 000 women years (Writing Group for Women's Health Initiative Investigators 2002) and for the oestrogen-only study, an additional 12 cases per 10 000 women years (Anderson *et al.* 2004). The WHI-EP study reported an increased hazard ratio for EP in the 50- to 59-year-old age group, but an increased risk in this age group was not seen with oestrogen alone.

Clearly the risk of stroke is increased in older women, and this must be taken into consideration in discussing the use of HT for symptom relief. HT should not be commenced for primary or secondary prevention.

### Gall bladder disease

Several observational studies as well as the HERS study suggest a 2- to 3-fold increase in gall bladder disease in oral HT users (Hulley *et al.* 1998).

### HT effects on cognition and dementia

Identification of the gender difference in incidence of dementia combined with early epidemiological data

(Paganni Hill & Henderson 1996, Tang *et al.* 1996) and *in vitro* work (Jaffe *et al.* 1994, Sohrabji *et al.* 1995, Wickelgren 1997) laid the foundations for the belief that oestrogen therapy might favourably influence cognition and prevent dementia in women.

In a meta-analysis of the role of HT in cognitive function, women with menopausal symptoms had improvements in verbal memory, vigilance, reasoning, and motor speed (Le Blanc *et al.* 2001). No effects were observed in asymptomatic women. The meta-analysis was limited by inadequate numbers of RCTs, the predominant use of oral CEE, and small study sizes. The results of the Womens' Health Initiative Memory Study (WHIMS), an RCT, found that CEE (0.625 mg) plus MPA (2.5 mg) did not significantly worsen or improve cognitive function compared with placebo (Rapp *et al.* 2003). This study had fundamental methodological limitations and the findings are not surprising given that the women were aged over 65 years, women in whom HT is not routinely commenced.

In the Cache County Study (Zandi *et al.* 2002), a prospective observational study of 1889 elderly women (mean age 74.5 years), prior HT use and current HT use exceeding 10 years was associated with reduced risk of Alzheimer's disease (AD). However, the WHIMS reported no benefit for HT in the prevention of dementia (Shumaker *et al.* 2003). In this study of 4532 women, average age 71 years, the absolute risk of dementia with oral CEE-MPA therapy was 45 cases per 10 000 HT users per year vs 22 cases per 10 000 women per year in the placebo group. Two RCTs of oestrogen therapy in women with established AD have each reported no benefit of HT. A 1.25 mg/day dose of CEE administered for 12 consecutive weeks did not produce a meaningful effect on cognitive performance, dementia severity, behaviour, mood, or cerebral perfusion in female AD patients (Wang *et al.* 2000). In 120 women with mild to moderate AD, oestrogen therapy for one year did not slow disease progression, nor did it improve global, cognitive or functional outcomes (Mulnard *et al.* 2000).

Taken together these studies do not support a role of HT for prevention of dementia or for the treatment of this disease. The findings from WHI are inconclusive and at this time there are insufficient data to provide any recommendations regarding sex steroid therapy and cognitive functioning.

## Newer alternatives to postmenopausal HT

### Tibolone and tissue specific steroid activation

Tibolone is a synthetic steroid that exhibits a hormonal profile that is dependent upon its initial metabolism and activation in peripheral tissues. The parent compound has been described as a pro-drug as, following ingestion, it is quickly metabolised in the gastro-intestinal tract to

two oestrogenic metabolites,  $3\alpha$  and  $\beta$ , which then circulate predominantly in their sulphated inactive forms (Kloosterboer 2000). These metabolites become oestrogenically active when desulphated in target tissues. The global effect of tibolone would thus be expected to be oestrogenic. However, tibolone itself and its  $3\beta$  metabolite may be converted to a  $\Delta 4$ -isomer by the enzyme  $3\beta$ -hydroxysteroid dehydrogenase-isomerase (Kloosterboer 2001). The  $\Delta 4$ -isomer can bind and transactivate the progesterone receptor and the androgen receptor (AR), such that in the endometrium, tibolone exerts a predominantly progestogenic effect (Kloosterboer 2000). Tibolone alleviates postmenopausal vasomotor symptoms (Kicovic *et al.* 1982, Siseles *et al.* 1995, Moore 2001) without stimulating the endometrium (Tax *et al.* 1987). Hence, a progestin is not required and cyclical bleeding is not induced. Tibolone normalises the vaginal karyopyknotic and maturation indices and alleviates symptomatic atrophic vaginitis (Botsis *et al.* 1997, Morris *et al.* 1999) and women treated with tibolone report significant reductions in vaginal dryness and dyspareunia, effects which may be secondary to both oestrogenic and androgenic actions. Randomised studies indicate tibolone has positive effects on mood compared with placebo and alleviates several adverse mood parameters to a similar extent as conventional HT (Egarter *et al.* 1996). Tibolone and its  $\Delta 4$ -isomer transactivate the AR and exert androgenic effects (Moore 2001), which significantly lowers SHBG, further adding to its androgenicity (Doren *et al.* 2001). Unblinded studies suggest tibolone is associated with improvements in sexual function that appear to be greater than those achieved with standard HT (Castlo-Branco *et al.* 1995).

In contrast to its actions in other tissues such as bone, in the breast, tibolone is believed to inhibit the sulphatase enzyme such that activation of the sulphated metabolites in breast tissue is thought not to occur (Kloosterboer 2000). Human breast cell proliferation is inhibited by tibolone while apoptosis is stimulated (Gompel *et al.* 1997). The incidence of breast tenderness is low (Hammar *et al.* 1998) and mammographic density does not increase with tibolone, unlike with classic EP therapy (Valdivia & Ortega 2000). One large observational study indicates an increase in breast cancer risk with tibolone (Million Women Study); however, this finding needs to be verified by a formal RCT. With respect to thrombotic risk, tibolone increases fibrinolysis parameters without significantly altering coagulation parameters (Winkler *et al.* 2000) and no increase in thromboembolic events have been reported from clinical trials.

Tibolone is not the perfect therapy for all climacteric women. Some women will have insufficient alleviation of vasomotor symptoms with this therapy and others may have inadequate restoration of mood and libido. Whether these variations reflect inter-individual tissue metabolism of tibolone is not known.

## SERMs

SERMs exhibit selective oestrogenic and anti-oestrogenic activities in differing tissues as a result of their binding to the ERs. Understanding of the consequences of the interactions between various ligands (such as SERMs) with ER $\alpha$  and  $\beta$  has been enhanced by the crystal structures of the ER $\alpha$  and  $\beta$  ligand-binding domains (LBDs) 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 a ligand may act as an agonist or antagonist. The binding of oestradiol to the LBD places helix 12 in an agonist position such that coactivators can bind the complex and transcription is activated. Compounds such as tamoxifen and raloxifene *in vitro* distinctly place helix 12 in an antagonist position (Pike *et al.* 1999). As yet, it is not clear which factors determine when SERMs act as agonists or antagonists. Raloxifene exhibits oestrogen agonist activity on bone and lipids, and antagonist activity on breast and the endometrium. Earlier studies confirmed the positive effects of raloxifene vs placebo on increasing BMD and lowering of total and LDL cholesterol in postmenopausal women (Delmas *et al.* 1997). The 'Multiple Outcomes of Raloxifene Evaluation' study has translated this benefit on BMD into data on fractures in postmenopausal, osteoporotic women (Ettinger *et al.* 1999). Results from this randomised clinical trial demonstrated a significantly reduced risk of vertebral fractures in women receiving two doses of raloxifene, as compared with placebo. Risk of non-vertebral fractures did not differ significantly, and those women receiving raloxifene had an increased relative risk of venous thromboembolism of 3.1 (95% CI 1.5–6.2). In the analysis of three and four year data (Lippman *et al.* 2001, Yaffe *et al.* 2001), women receiving the two doses of raloxifene had a 72% reduction in the risk of invasive breast cancer, as compared with placebo (relative risk 0.28, 95% CI 0.17–0.46). In particular, those women with oestradiol levels in the highest third had over a 2-fold increase in the risk of invasive breast cancer. The main limitations with interpreting these data are that details of previous HRT use were patchy, and most women participating in the study were white. Nonetheless, the large number of women participating in the study, its randomised placebo-controlled design, and its long duration, all add to the significance of the findings in this group of postmenopausal women. With regard to cognition, there was no difference between cognitive scores in women treated with raloxifene vs placebo after three years, although a trend towards less decline was noted in tests of verbal memory and attention in the group of women receiving two doses of raloxifene.

Unfortunately both tamoxifen and raloxifene have the tendency to cause rather than alleviate hot flushes and

vaginal dryness, which limits their acceptability in postmenopausal women. Several new SERMs are currently undergoing clinical trials.

### Future therapeutic HT options

A future alternative HT regimen being studied is the use of both an oestrogen and a SERM concurrently (Davis *et al.* 2004). The hypothesis underlying this approach is that the SERM will protect the breast and endometrium and the oestrogen will exert the desired effects in other tissues. New non-hormonal compounds to treat hot flushes are also undergoing clinical trial. Combinations of oestrogen-androgen therapy look favourable in terms of less adverse breast effects, but further RCTs are required to establish the long-term safety of such regimens (Somboonporn & Davis 2004). Some enthusiasm for dehydroepiandrosterone therapy in the wake of WHI has been rekindled, but again, large well-designed RCTs are needed to determine the efficacy and safety of this therapy.

It is generally recommended that the prescription of systemic oestrogen therapy should be at the lowest available dose that alleviates symptoms. However, there is no evidence that this approach confers greater safety. Lower-dose combinations of micronised oestradiol and norethisterone acetate are associated with equivalent symptom relief as higher-dose combinations but lower rates of mastalgia and vaginal bleeding (Stadberg *et al.* 1996).

### Conclusions

Research has left us in a situation in this field with more questions than answers. Following several years of great enthusiasm that most women should consider using HT, there is now widespread suspicion of prescribed HTs and increasing use of treatments considered 'natural'. However, when put into appropriate perspective, the reported risks of HT use are very small. It is often said that the interpretation of any risk should be in line with the symptomatology and risk profile of each woman. Although doctors are advised to assess each woman's risk profile, there is actually no evidence, with the exception of high thrombotic risk or fracture risk, that a given profile indicates greater risk or benefit with HT.

Large clinical trials involving different HT combinations, different delivery modes and exploration of new therapies, such as SERMs, alone or in combination with oestrogen are required.

Oestrogen therapy, with or without concomitant progestin as indicated, remains a valuable therapy for the treatment of perimenopausal and postmenopausal symptoms such that for most early menopausal symptomatic women the benefits are likely to outweigh the risks.

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