HORMONE REPLACEMENT THERAPY - PRESENT AND FUTURE

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Hormone replacement therapy (HRT) in the United Kingdom is the term given to the administration of oestrogen-containing compounds that were initially developed to treat menopausal symptoms. In the USA this regimen is, perhaps more accurately, termed Estrogen Replacement Therapy (ERT). The role of HRT has continued to evolve since its launch in the 1970s. No longer simply a solution for climacteric troubles, oestrogen is now established in the prevention and treatment of osteoporosis, and its potential use in other areas is a field of intense current enquiry.

THE TOOLS

More than 40 preparations are now licensed as HRT products. In practice these vary both in oestrogen type, content and mode of delivery. European preparations are mostly oestradiol based while American drugs usually contain conjugated equine oestrogens. The selective oestrogen receptor modulators (SERMs) while not structurally oestrogens, will be discussed in this paper as they operate through the oestrogen receptor (ER). They provide an alternative to HRT in the older woman at risk of osteoporosis and may yet provide an alternative to oestrogen in other situations. Current preparations, their mode of delivery and bleeding pattern which may be associated with them are listed in Table 1 (refer to following page).

HRT PRESCRIPTION

HRT preparations should be prescribed in accordance with traditional medical practice and HRT should only be given when a sound indication is present. A history, physical examination and any required investigations must be performed to identify those women in whom HRT may be contraindicated, such as those with a history of oestrogen-dependent tumour or proven venous thromboembolism. The patient should be cautioned about the temporary start-up effects such as breast tenderness, calf cramps and weight gain. Initial follow-up should be at three months with an annual review thereafter. Physicians should be prepared for adjustment of dose or regimen with a view to individual patient satisfaction.

The choice of preparation may be made easier using the following information:

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- **Oestrogen alone should be prescribed for hysterectomised women.**
- **2 mg oral oestradiol (E_2)/50μg/hr Transdermal E_2/0.625mg Conjugated equine oestrogen/a 50 mg implant of E_2 are required for the prevention and treatment of bone loss. Lower doses may suffice for symptom control.**
- **Women more than one year from their last period may prefer a continuous combined oestrogen progestogen preparation, or Tibolone. These will achieve and maintain amenorrhoea in the great majority of women.**
- **Transdermal oestrogens raise triglycerides and HDL less than oral oestrogens but the clinical significance of these is uncertain. The lower mean oestradiol levels associated with this route of delivery may explain why side-effects such as headache and nausea are less.**
- **The younger the woman, the more oestrogen she is likely to need.**

SYMPTOMS OF MENOPAUSE

Menopause occurs at a median age of 51 in the UK and is classed as premature before the age of 45 years. It may be natural, or it may be caused by surgical oophorectomy or by the use of cytotoxic agents. Premature menopause may be spontaneous or may follow simple hysterectomy, when the time of ovarian failure may go unnoticed. Natural menopause may be accompanied, or preceded, by a range of physical or psychological symptoms.

The menopause affects most body systems. Vasomotor symptoms, psychological problems, alteration in cognitive function and sexual dysfunction may result in women seeking medical help. It is likely that many of these symptoms are not related purely to hypo-oestrogenism and a holistic approach must always be taken. In many cases the alleviation of the vasomotor symptoms, reversal of genital tract atrophy and improvement in cognitive function will materially improve quality of life.

OSTEOPOROSIS

Osteoporosis has been defined by the World Health Organisation (1993)[1] as:

> A systemic skeletal disorder characterised by low bone mass and micro-architectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture risk.

Bone mineral density (BMD) is usually determined by dual energy X-ray absorptiometry (DEXA). When this technique is used, osteoporosis is diagnosed when the BMD is more than 2.5 standard deviations (SD) below that of the

Hormone Replacement Therapy

Type	Brand	Oestrogen	Progestogen	Formulation	Bleed	RX* Charge	Cost/ 28 days
SYSTEMIC							
Sequential combined therapy	Climagest	Oestradiol (1mg, 2mg)	Norethisterone (1mg)	Tabs	M	2	£4.38
	Cyclo-progynova	Oestradiol (1mg, 2mg)	Levo/norgestrel(0.25mg/0.5mg)	Tabs	M	2	£3.50
	Elleste Duet	Oestradial (1mg, 2mg)	Noreethisterone (1mg)	Tabs	M	2	£3.24
	Estracombi	Oestradiol (50mcg)	Norethisterone (0.25mg)	Patches	M	2	£11.14
	Estrapak	Oestradiol (50mcg)	Norethisterone (1mg)	Patches +Tabs	M	2	£9.48
	Evorel-pak	Oestradiol (50mcg)	Norethisterone (1mg)	Patches +Tabs	M	2	£8.45
	Evorel Sequi	Oestradiol (50mcg)	Norethisterone (170mcg)	Patches	M	2	£11.00
	Femapak	Oestradiol (40mcg, 80mcg)	Dydrogesterone (10mg)	Patches +Tabs	M	2	£8.45 £8.95
	Femoston	Oestradiol (1mg, 2mg)	Dyrogesterone (10mg)	Tabs	M	2	£4.99
	Femoston 2/20	Oestradiol (2mg)	Dyrogesterone (20mg)	Tabs	M	2	£7.48
	Nuvelle	Oestradiol (2mg)	Levonorgestrel (75mcg)	Tabs	M	2	£4.59
	Nuvelle TS	Oestradiol (50mcg,80mcg)	Levonorgestrel (20mcg)	Patches	M	2	£11.00
	Premique Cycle	Conjoestrogens (0.625mg)	Medroxyprogesterone (10mg)	Tabs	M	2	£7.54
	Prempak-C	Conjoestrogens (0.625, 1.25mg)	Norgestrel (150mcg)	Tabs	M	2	£4.46
	Tridestra	Oestradiol (2mg)	Medroxyprogesterone (20mg)	Tabs	Q	2	£8.30
	Trisequens	Oestradiol (2mg, 2mg, 1mg; 4mg, 4mg, 1mg)	Norethisterone (1mg)	Tabs	M	2	£6.85
Continuous combined therapy	Climesse	Oestradiol (2mg)	Norethisterone (0.7mg)	Tabs	X	1	£7.90
	Elleste Duet Conti	Oestradiol (2mg)	Norethisterone (1mg)	Tabs	X	1	£6.03
	Evorel Conti	Oestradiol (50mcg)	Norethisterone (170mcg)	Patches	X	1	£12.90
	Kliofem	Oestradiol (2mg)	Norethisterone (1mg)	Tabs	X	1	£8.65
	Kilovance	Oestradiol (1mg)	Norethisterone (0.5mg)	Tabs	X	1	£8.65
	Premique	Conjoestrogens (0.625mg)	Medroxyprogesterone (5mg)	Tabs	X	1	£7.54
Gonadom-imetic	Lival	Tribone (2.5mg)		Tabs	X	1	£13.66
Unoppossed oestrogen	Climaval	Oestradiol (1mg, 2mg)		Tabs		1	£2.34
	Dermestril	Oestradiol (25, 50, 100mcg)		Patches		1	£5.75, £6.35, £6.99
	Elleste Solo	Oestradiol (1mg, 2mg)		Tabs		1	£1.78
	Elleste Solo MX	Oestradiol (40, 80mcg)		Patches		1	£5.96 £6.75
	Estraderm TTS/ Estraderm MX	Oestradiol (25, 50, 100mcg)		Patches		1	£6.75, £7.45, £8.20
	Evorel	Oestradiol (25, 50, 75,100mcg)		Patches		1	£6.75, £7.45, £7.90 £8.20
	Fematrix	Oestradiol (40mcg, 80mcg)		Patches		1	£6.45, £6.95
	FemSeven	Oestradiol (50, 75, 100mcg)		Patches		1	£6.44, £7.49, £8.19
	Harmogen	Oestrone (0.93mg)		Tabs		1	£3.14
	Hormonin	Oestriol/ oestradiol/ oestrone 1 strength		Tabs		1	£2.00
	Menorest	Oestradiol (37.5, 50, 75mcg)		Patches		1	£6.34, £6.44, £7.50
	Oestrogel	Oestradiol (1.5mg)		Gel		1	£7.95
	Premarin	Conjoestrogens (0.625, 1.25mg, 2.5mg)		Tabs		1	£2.45, £3.33, £3.55
	Progynova	Oestradiol (1mg, 2mg)		Tabs		1	£2.34
	Progynova TS	Oestradiol (50, 100mcg)		Patches		1	£6.44, £8.33
	Sandrea	Oestradiol (0.5mg, 1mg)		Gel		1	£5.95, £6.85
	Zumenon	Oestradiol (1mg, 2mg)		Tabs		1	£2.55
Adjunctive progestogen	Crinone		Progesterone (4%)	Vaginal Gel		1	£11.60
	Duphaston HRT		Dydrogesterone (10mg)	Tabs		1	£2.77
	Micronor	HRT	Norethisterone (1mg)	Tabs		1	£1.25
LOCAL							
Oestrogen only	Estring	Oestradiol (7.5mcg)		Vaginal ring		1	
	Ortho Dienoestrol	Dienoestrol (0.01%)		Vaginal cream		1	
	Ortho-Gynest Pressy	Oestriol (0.5mg)		Pressary		1 1	
	Ortho-Gynest Cream	Oestriol (0.01%)		Vaginal cream			
	Oveestin	Oestriol (0.1%)		Vaginal cream		1	
	Premarin	Conjoestrogens (0.625%)		Vaginal cream		1	
	Tampovagen	Stilboestrol (0.5mg)		Pessary		1	
	Vagifem	Oestradiol (25mcg)		Vaginal tabs		1	

Bleed - M = Monthly; Q = Quarterly; X = No Bleed **Combination packs incur multiple prescription charges**

FIGURE 1
Hormone Replacement Therapy Table.
This table was reproduced courtesy of *MIMS* June 1999 p344.

Hormone Replacement Therapy

Type	Brand	Oestrogen	Progestogen	Formulation	Bleed	RX* Charge	Cost/ 28 days
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	Estrapak	Oestradiol (50mcg)	Norethisterone (1mg)	Patches +Tabs	M	2	£9.48
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	Evorel Sequi	Oestradiol (50mcg)	Norethisterone (170mcg)	Patches	M	2	£11.00
	Femapak	Oestradiol (40mcg, 80mcg)	Dydrogesterone (10mg)	Patches +Tabs	M	2	£8.45 £8.95
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	Ortho-Gynest Pressy	Oestriol (0.5mg)		Pressary		1	
	Ortho-Gynest Cream	Oestriol (0.01%)		Vaginal cream		1	
	Oveestin	Oestriol (0.1%)		Vaginal cream		1	
	Premarin	Conjoestrogens (0.625%)		Vaginal cream		1	
	Tampovagen	Stilboestrol (0.5mg)		Pessary		1	
	Vagifem	Oestradiol (25mcg)		Vaginal tabs		1	

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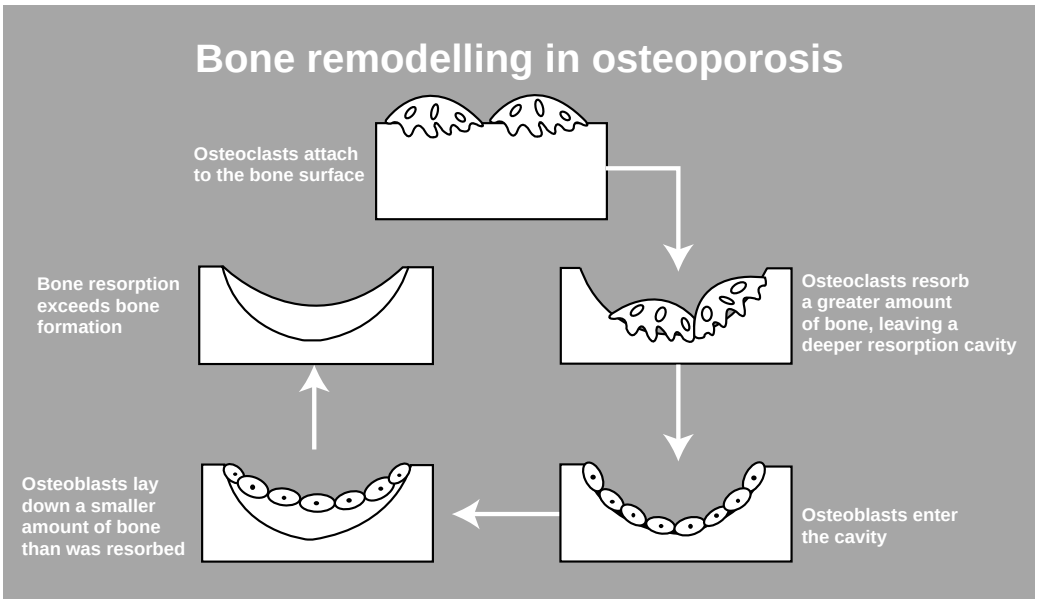

FIGURE 1
Bone remodelling in osteoporosis.

young normal mean. Osteopenia is characterised by a BMD of between 1-2.5 Standard Deviations (SD).

Albright first described the intimate relationship between osteoporosis and oestrogen in 1941.[2] The menopause is associated with rapid bone loss that tends to occur in the ten years following the last period, and can be tracked by a declining BMD. The basis of this bone loss is the disruption of the bone remodelling process. In hypo-oestrogenic postmenopausal women there is osteoclast overactivity, the resorptive effects of which are compounded by incomplete osteoblast refilling of the cavity of the bone-remodelling unit (Figure 1).

An average individual will have c. 0.5 million such units active at any one time. Thus, the imbalance or uncoupling of bone resorption and formation is of serious importance. Osteoclastic action is thought to be responsible for the structural damage seen in the trabecular bone of the spinal column and hip in postmenopausal women. Recoupling can be brought about by oestrogen therapy[3] through a restraint both on the recruitment of new remodelling units and on the activity of individual osteoclasts.

The use of oestrogens to prevent bone loss is not restricted to the peri-menopause. One important study[4] showed that oestrogen, in this case mestranol, can increase metacarpal bone density in women who had significant bone loss monitored following the cessation of ovarian function, even when treatment was delayed for up to 6 years. Studies[5,6] have shown improved BMD at the vertebral column and femoral neck during treatment.

The acid test, however, for any treatment of osteoporosis is its ability to reduce the rate of hip fracture, 60,000 of which occur annually in the UK. The question of hip fracture has been evaluated by analysis of epidemiological and observational data. These studies suggest that current use of HRT reduce the risk of hip fracture by up to 50%.[7] However, there are as yet no prospective controlled interventional studies to attest to the effect of oestrogen upon hip fracture rate. There is also some evidence that oestrogen therapy reduces the incidence of spinal fracture. A one-year double-blind randomised placebo-controlled trial[8] which involved 75 women found that the relative risk of treated women sustaining a vertebral fracture compared to controls was 0.39 (CI 0.16 to 0.95).

The dose of oestrogen required to inhibit post-menopausal bone loss has been found to equate with serum oestradiol levels of 60-90 pg/ml (220-330 pmol/l), levels similar to those found in pre-menopausal women in the follicular phase of the cycle. These levels have been shown to inhibit bone resorption as determined by chemical markers.[9] Similarly, the histomorphometric analysis of iliac crest biopsies taken from women receiving oestrogen exhibits this reduction in bone turnover.[10] Women receiving oestrogen in the form of 75 mg oestradiol implants had significant reductions in the osteoid volume, osteoid surface, eroded surface and activation frequency. There is evidence that long-term oestrogen implantation is truly anabolic, and not just anti-catabolic.[11] The addition of a progestogen to oestrogen in order to protect the endometrium is mandatory in non-hysterectomised women. The use of an androgenic progestogen of the 19-nor testosterone group, such as Norethisterone Acetate (NETA), may enhance the bone sparing properties of oestrogen.

CORTICOSTEROID-INDUCED OSTEOPOROSIS

Approximately 1.7% of UK women over the age of 55 take continuous oral steroids.[12] Women who receive oral prednisolone in doses of 7.5mg per day, or more for six months are at increased risk of developing osteoporosis. This group also appears to have greater propensity to fracture. In untreated postmenopausal women a decrease in BMD of 1SD is associated with a doubling of fracture risk.[13] In contrast, women with rheumatoid arthritis who take glucocorticoids resulting in a similar bone mass show a 6.2 fold increase in the risk of sustaining a vertebral fracture.[14] HRT has been shown to improve BMD at the lumbar spine in women taking steroids for asthma and rheumatoid arthritis. No primary prevention data are available. The UK consensus group[15] has recently published its

recommendations in which HRT is suggested as possible treatment in women on continuous steroids with a BMD T-score <-1.5, previous fracture or where one or more risk factors (Table 2) for osteoporosis are present.

TABLE 2
Risk factors for osteoporosis.

Premature Ovarian Failure	Loss of height
Thyrotoxicosis	Prolonged Secondary Amenorrhoea
Radiological Suspicion	Osteoperosis in a 1st degree relative
Inability to weight bear	Low-impact fracture

Markers of bone resorption (N and C telopeptides of Type I collagen, deoxypyridinoline) and formation (Alkaline Phosphatase, osteocalcin) may be used to monitor treatment.

HRT AND THE CARDIOVASCULAR SYSTEM

Until recently cardiovascular benefit has been quoted as a certain benefit of HRT. The Nurses Health Study,[16] a large prospective case control study, provided powerful evidence to support this view. This study found that the current HRT user had a lower all-cause mortality (RR 0.63; 95% CI 0.56-0.7) than the never-user. The greatest apparent decrease was in cardiovascular disease and this was then examined further. It was found that those women who had at least one cardiovascular risk factor (smoking, high cholesterol, diabetes, Body Mass Index (BMI) >29, parental history of premature myocardial infarction, hypertension) were found to have a greater reduction in their risk of death (RR0.51; 95% CI 0.45-0.57) than those who did not possess a risk factor (RR0.89; 95%CI 0.62-1.28). This benefit appeared to disappear within five years of stopping treatment. Previous data reviews had come to similar conclusions.[17]

Reduction in cardiovascular mortality would seem logical given that it has been shown that HRT alters blood lipid profiles favourably. The lipid and heamostatic effects of oestrogen have been the subjects of many studies.

The Post Menopausal Estrogen/Progestin Interventions (PEPI) Trial[18] analysed the effect of unopposed conjugated equine oestrogen (CEE), and of CEE combined with medroxyprogesteone acetate cyclical (10 mg for 12 days) and continuous combined (2.5 mg daily). This randomised double-blind placebo-controlled trial involved 875 women. All active treatments were associated with a reduction in LDL-C and an increase in triglycerides. HDL-C increased in all oestrogen treatment groups but the increase was greatest in the unopposed group. Lipoprotein (a) appears to act independently of other lipids and when raised acts as an independent risk factor for cardiovascular disease and its long-term role merits investigation. When studied as part of PEPI[19] Lipoprotein (a) levels were consistently reduced in all treatment groups. Lip[20] in his study of 27 women following hysterectomy and removal of both ovaries, found that following hysterectomy, levels of Lipoprotein (a) were significantly increased and that six weeks of HRT did not alter the level. He also investigated haemostatic factors and endothelial function markers and found significant reductions in Von Willebrand factor, soluble thrombomodulin and tissue plasminogen activator, all suggesting beneficial effects on endothelial function and atherogenesis.

The Heart and Estrogen /Progestin Replacement Study[21]

This study was instigated to establish the efficacy of postmenopausal HRT for preventing coronary heart disease in at risk women. This double-blind randomised placebo-controlled trial recruited 2,763 women with established heart disease. The treatment group received 0.625 mg CEE and 2.5 mg MPA daily. They were followed up for an average of 4.1 years. The expected rise in HDL-C and fall in LDL-C occurred. The treatment and placebo groups did not however differ significantly in respect of death due to coronary heart disease and non-fatal myocardial infarctions (primary events), or secondary events (including cardiac failure, unstable angina and cardiac surgery). When looked at from a temporal viewpoint the data appeared to suggest that HRT was associated with an increase risk of a primary cardiovascular event in the first year and with a decrease in subsequent years. It is hoped that further trials, like the Women's Health Initiative randomised intervention trial which aims to recruit 27,000 women and report in 2005, will shed light on this difficult problem. In the meantime, blanket prescription of HRT for cardiovascular benefit cannot be supported.

HRT AND THE CENTRAL NERVOUS SYSTEM

Alzheimer's disease is complex. Its development has been linked to amyloid formation, disruption of cholinergic pathways and abnormalities in circulating apolipoprotein E associated with increased frequency of the ε–4 allele. This complexity has resulted in the investigation of different therapeutic avenues. Cholinesterase-inhibitors such as tacrine and donepezil are licensed for the treatment of Alzheimer's disease.[22] Oestrogen receptors are known to be associated with cholinergic neurons in the basal forebrain[23] and oestradiol has been shown in animal studies to enhance the potassium stimulated acetylcholine release.[24] In addition oestrogen appears to stimulate the secretase metabolism of the amyloid precursor protein[25] and may interact with apolipoprotein E.[26]

Even allowing for the fact that women live longer than their male counterparts, Alzheimer's disease is more prevalent in women. Thus it is encouraging that prospective case-control studies have reported reductions in the relative risk of developing Alzheimer's disease among women who reported oestrogen use. One New York group[27] followed 1,227 women for up to five years and found that oestrogen use reduced the risk of developing the disease RR 0.4[95%CI 0.22-0.85]. This reduction in risk was greatest in women who had taken HRT for more than one year. The numbers involved were however small. This study demonstrated that the reduction in risk of developing Alzheimer's disease was present in those women who were APO ε–4 heterozygous.

The Baltimore Longitudinal Study of Ageing[28] followed 472 post- or peri-menopausal women for up to 16 years. In this group the relative risk for developing Alzheimer's disease in the oestrogen group was 0.46(95% CI 0.209-0.997). Women who had received either oral or transdermal oestrogen were included.

Further research development of in this field may provide women with a further reason to consider the use

of HRT.

COLORECTAL CANCER

In a case control study performed in Northern Italy[29] which involved 1,701 women it was found that HRT usage was more common in the controls, 7.6% as opposed to 3.2% in the cases. A reduced risk of developing colorectal cancer was observed in women who had ever taken HRT; the odds ratio being 0.58 [95% CI 0.36-0.92]. The relative risk was inversely related to duration being 0.46 for <2 years of use and 0.25 when use was >2 years. These findings are similar to those in other observational studies.

HRT AND BREAST CANCER

Breast cancer is more common in women less than 65 years than cardiovascular disease, and many women have personal experience of a friend or relative with breast cancer. A woman's decision to take HRT is greatly affected by her personal experience and it is not therefore surprising that women are more concerned about the risk of breast cancer associated with HRT than either the risk of thromboembolic or gallbladder disease.

It is perhaps surprising that until recently breast cancer was not thought to be associated with HRT. In 1972 analysis of the Connecticut Cancer Registry[30] revealed that the younger a woman was at the time of surgical menopause the lower her risk of breast cancer (Table 3).

TABLE 3
Breast cancer risk and surgical menopause.

Age at Surgical Menopause	Relative Risk of Breast Cancer
<35	0.36
35-39	0.68
40-44	0.65
45-49	0.73
>50	0.98

It would therefore seem logical that prolonging oestrogen exposure would increase the risk of breast cancer. The Nurses Health Study[31] analysis suggested that HRT was associated with an increased risk of breast cancer. This appeared to increase with the duration of use and the age of the women. It appeared that the risk was limited to use beyond five years. In the all-cause mortality analysis in the same study,[16] the survival benefit accorded to HRT was attenuated among long-term users (10 + current years) which was attributed to increase in the number of breast cancer deaths. The most recently published longitudinal study[32] examined 7,944 Finnish women and showed that current HRT use was not associated with an increase in breast cancer morbidity or incidence when compared to a control population. However, as in the previous studies, the HRT group was self-selected and was healthier and of higher social class. Separate analysis of the cardiovascular outcomes in the lower socio-economic group alone was undertaken. In this, the benefits of HRT treatment were confirmed.

In 1997 an important reanalysis of the data involving HRT and breast cancer was published.[33] This reviewed 51 studies which included 52,705 women with breast cancer and was performed by a team from the ICRF in Oxford led by Beral. It concluded that in women who had used HRT for less than five years the risk of having breast cancer diagnosed increased by a factor of 1.023 per year. This degree of risk is comparable to the annual effect of delayed menopause on breast cancer risk. In practical terms use of HRT for four years results in one extra cancer per 1,000 women while continued use up to 13 years results in one extra cancer per 100.

In this reanalysis information was available on tumour spread in 54% of cases. The excess risk of breast cancer seen was confined to localised disease. As in previous papers, the effect of HRT on breast cancer risk has disappeared within five years of ceasing therapy.

HRT AND VENOUS THROMBOEMBOLISM

While women raise their concerns about breast cancer, it is important that their physicians are aware of the problem of venous thromboembolism(VTE).

It was originally felt that HRT was free from the problems of venous thromboembolism and the combined oral contraceptive pill. However in1996 *The Lancet* published an American case control study[34] in which the relative risk of VTE in women who had taken HRT was 3.6. A similar UK study[35] derived an adjusted odds ratio of 3.5 for VTE in the women treated with HRT. A dose-effect was seen in the US study, 1.25 mg of CEE was associated with a relative risk of developing VTE of 6.9. In the HERS study the relative risk of developing a VTE on treatment was calculated as 2.89. In this study two women on treatment died following a pulmonary embolus.

The absolute risk of VTE is however small, 9-11 per 100,000 women per year in non-users and 27-32 per 100,000 women per year in users. The treatment of menopausal symptoms should begin with a low dose (1mg) oestrogen, advancing to a higher dose at three months if symptoms are incompletely resolved.

The mechanism by which this apparent alteration in the haemostatic system occurs is unclear. Before the prescription of any potentially thrombotic agent, clues to the presence of an underlying thrombophilia must be sought. Particular attention should be paid to family history, previous pregnancies and oral contraceptive usage as historical episodes may herald the presence of Factor V Leiden which until recently was not detectable. Evidence is lacking as to whether HRT should be prescribed in incidental mild thrombophilias; therefore careful discussion with the women is important. In cases of thrombophilia and previous VTE or ongoing risk factor HRT is best avoided.[36] Specialists in the field may consider concomitant antithrombotic drugs warfarin, low dose aspirin in special cases where risk is significant but oestrogen replacement is absolutely necessary.

COMPLIANCE (CONTINUATION (UK) AND ADHERENCE (US)

Clearly HRT has its problems. While continuation of HRT does not tend to be a problem in women troubled by menopausal symptoms, long-term treatment of osteoporosis in women who require the endometrial protection of progesterone leads to poor continuation. In a large study[37] performed in Hull, to look at the feasibility of population densitometry using DXA and directed HRT intervention. 1127/1425 (69%) of those offered HRT, on the basis of

their BMD result, started therapy. In the following two years, 335 of these women stopped treatment. Thus only 48% of women were receiving appropriate therapy after 23 months. Problems with cyclical bleeding was given as the reason for stopping by 87/335 (26%). It is important to remember that cyclical HRT is only necessary around the menopause and that the newer continuous combined preparations (oral and transdermal) and tibolone are available to the women who have been amenorrhoeic for more than one year.

The imperfect nature of HRT has prompted researchers to look for a drug that will have the beneficial effects of oestrogen on bone, brain and the cardiovascular system without its breast, thrombotic and endometrial effects. Raloxifene, the first of the SERMs, is an encouraging beginning in this quest.

SELECTIVE OESTROGEN RECEPTOR MODULATORS (SERMS)

Tamoxifen, a non steroidal triphenylethylene widely used as adjuvant therapy in breast cancer provided the first indication it may be possible to develop a drug behaving as an oestrogen at some sites but not others. Jordan,[38] a pioneer in this field, found that bone mineral density in ovariectomized rats was preserved when given Tamoxifen and Raloxifene. This led to intense interest in both the triphenylethylenes and benzothiophenes. Subsequent study of BMD in postmenopausal women with breast cancer treated with Tamoxifen confirmed these findings.[39]

Raloxifene has become the first commercially available SERM while Idoxifene and continues to undergo Phase III trials. Raloxifene was initially developed as a treatment for metastatic breast cancer as in vitro it appeared more potent than tamoxifen against MCF-7 breast cancer cells.[40] In Phase II breast cancer treatment clinical trials, it demonstrated no objective response.[41] Further development of raloxifene was based on its potential to prevent bone loss. In this instance Phase II studies were promising,[42] raloxifene (200mg) reduced bone turnover, as determined by serum and urinary markers. Importantly, given the association between tamoxifen and endometrial carcinoma,[43] this was achieved without endometrial stimulation. Delmas,[44] in a larger longer study involving 601 postmenopausal women, revealed that the alteration in bone resorption was translated into an increase in BMD 2.4%(+/-0.4) at both the lumbar spine and the hip in the raloxifene (60mg) group. In this study the endometrium was evaluated by ultrasound and even two years after commencing treatment there was no difference between the controls and the treatment groups. Interestingly in this study serum triglyceride levels did not change.

The lipid and haemostatic effects of raloxifene were compared directly with HRT (0.625mg CEE and 2.5 mg MPA) in a double blind RCT.[45] Raloxifene reduced the levels of LDL-C, fibrinogen and Lp (a), raised HDL2-C and once again did not affect triglyceride levels. In contrast to HRT, raloxifene did not alter the levels of HDL-C and plasminogen activator type 1 (PAI-1). These changes bear similarities to those seen in women taking tamoxifen. This may prove to be cardioprotective. The Scottish study[46] of the use of tamoxifen in breast cancer found that the incidence of fatal myocardial infarction in the treatment group was significantly lower than in the observation arm ($\chi 2 = 6.88, p = 0.0087$). The cardiovascular effects of raloxifene are currently being examined by the RUTH (Raloxifene Use for The Heart) trial.

Raloxifene has been licensed for the prevention of osteoporosis in postmenopausal women. In the UK this followed the release of the two-year data from the MORE (Multiple Outcomes of Raloxifene Evaluation) trial. These showed that two years of raloxifene therapy reduced the risk of radiographically and clinically diagnosed vertebral fractures by 38-52% compared to controls receiving only calcium and vitamin D.[47]

The MORE trial has generated great interest because of the breast cancer analysis after 33 months of follow-up.[48] The raloxifene women had a 70% lower risk of developing invasive breast cancer than controls (95%CI, 0.16-0.52). This was due to an 87% reduction in the risk of developing an oestrogen receptor positive cancer. Recently a study of tamoxifen and raloxifene (STAR) study has been initiated in women at risk of breast cancer.

It is thought that raloxifene and the other SERMs act by interacting with the oestrogen receptor. There are at least two oestrogen receptors α and β with a varied tissue specific distribution. Using electron crystallography[49] raloxifene has been shown to occupy, and distort the receptor. This is thought to alter downstream gene transcription. Knowledge gained about receptor function may enable synthesis of drugs to manipulate receptor function more precisely.

Clinically raloxifene is well tolerated. The side effects are mild and include hot flushes, mild leg cramps and occasionally a vaginal discharge. Like conventional oestrogen replacement therapy raloxifene is associated with an increased risk of venous thromboembolism.

TIBOLONE

The advent of the SERM as a clinical reality has rekindled interest in tibolone. Tibolone is important because, unlike raloxifene, it is as effective as CEE (0.625mg) and MPA (5mg for 12 days) in the treatment of menopausal symptoms.[50]

Tibolone, a gonadomimetic, acts through its three metabolites: Δ-4-isomer, 3α-hydroxy metabolite and 3β-hydroxy metabolite. This conversion may occur at target tissues, therefore there is an element of tissue specificity. The α and β metabolites act as weak oestrogens. The $\Delta 4$ isomer is crucial in the unique action of tibolone. This has a high affinity for both progesterone and androgen receptors.

The $\Delta 4$ isomer is formed locally at the level of the endometrium, as tibolone is metabolised by 3β hydroxy steroid dehydrogenase. The progestogenic action of the isomer inhibits endometrial proliferation. The evidence suggests that women are less likely to bleed on tibolone than on continuous combined oestrogen therapy.[51] Ensuring that women are at least one year since their last menstrual period does appear to improve the bleeding profile.[52] The androgenic action of tibolone is thought to be responsible for its positive effect on libido.

1980 saw the publication of the first evidence that tibolone was bone active.[53] Consequent double blind osteoporosis randomised control trials have shown gains in BMD at the spine and forearm.[54] In this study tibolone (2.5 mg) was well tolerated in women with a mean age of 65.5 years. 70/91 women completed the study, seven women in each group dropped out. Tibolone is licensed for the

treatment of osteoporosis. Efficacy at the femoral neck[55] has also been shown.

It is felt that while the overall lipid profile of tibolone (Table 4) is probably neutral; benefit may derive from the tendency towards fibrinolysis and unchanged coagulation.[56] Knowledge of the effect of tibolone on breast tissue is based mainly on preclinical data, which is encouraging. *In vitro* studies involving the MCF-7 cell line showed tibolone to have a weak proliferative effect approximately 1% that of oestradiol. Using Dimethylbenzanthracene (DMBA) to induce mammary tumours in rats, *in vivo* studies demonstrated reduction in tumour load with the addition of tibolone.[57]

TABLE 4
Tibolone: effects on lipids and coagulation.

Unchanged	Lowered
LDL-C	HDL-C
Apiloprotein B	Triglycerides
Lipoprotein (a)	Total Cholesterol
Antithrombin III	Apolipoprotein A-1
	Tissue Plasminogen Activator
	Plasminogen Activator Activity
	Fibrinogen

It is possible that the increase in breast density seen in the mammograms of women taking conventional oestrogen[58] is ameliorated in women taking tibolone.[59]

SUMMARY

The use of hormone replacement therapy is challenging. Women are often formidably well-informed on treatment options thereby obligating their physicians to be abreast of recent advances. Frank discussion about the risks and benefits of HRT has been shown to be the principal influence in a woman's choice regarding HRT.[60] Specifically, a rehearsal of the small absolute excess risk of breast cancer should encourage acceptance.

Conventional cyclical HRT will continue to have an important role in the treatment of menopausal symptoms. In those women several years beyond their last natural bleed a decision regarding treatment can only be made after careful consideration of the indications for treatment and at this time amenorrhoeic regimens should be considered.

Currently, only natural human oestrogen or conjugated equine oestrogens are the only preparations that have been shown to influence the neurological symptoms and therefore where this is the primary concern, conventional therapy is appropriate. Tibolone and continuous combined therapy can be used for the treatment of osteoporosis, menopausal symptoms and have positive lipid effects. The absence of cyclic bleeding within these regimens may be a positive advantage. Raloxifene currently has a role in the older women who are asymptomatic, are at risk of osteoporotic fracture, and where she or her physician has concerns about the safety of oestrogen.

Oestrogens have a central reproductive role and numerous other functions. The development of agents to maintain these extra-reproductive roles after menopause, while bypassing the reproductive tissues of breast and endometrium, will be a worthy challenge to pharmacology and clinical medicine into the next millennium.

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