CLIMACTERIC 2013;16:316–337

Updated 2013 International Menopause Society recommendations on menopausal hormone therapy and preventive strategies for midlife health

T. J. de Villiers, A. Pines, N. Panay†, M. Gambacciani‡, D. F. Archer**, R. J. Baber††, S. R. Davis‡‡, A. A. Gompel***, V. W. Henderson†††, R. Langer‡‡‡, R. A. Lobo****, G. Plu-Bureau††††*
and D. W. Sturdee‡‡‡‡, on behalf of the International Menopause Society

MediClinic Panorama and Department of Obstetrics and Gynecology, Stellenbosch University, Cape Town, South Africa; *Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel; †Queen Charlotte's & Chelsea Hospital, and Chelsea and Westminster Hospital, London, UK; ‡Department of Obstetrics and Gynecology, Pisa University Hospital, Pisa, Italy; **Jones Institute, Eastern Virginia Medical School, Norfolk, VA, USA; ††Sydney Medical School, The University of Sydney, NSW, Australia; ‡‡Department of Epidemiology and Preventive Medicine, School of Public Health and Preventive Medicine, Monash University, Melbourne, Victoria, Australia; ***UF de Gynécologie, Université Paris Descartes, AP-HP, Hôtel-Dieu, Paris, France; †††Departments of Health Research & Policy (Epidemiology) and of Neurology & Neurological Sciences, Stanford University, Stanford, CA, USA; ‡‡‡Associate Dean for Clinical and Translational Research and Professor of Family Medicine-Las Vegas, University of Nevada School of Medicine, Las Vegas, NV, USA; ****Department of Obstetrics and Gynecology, Columbia University, New York, NY, USA; ††††Unité de Gynécologie Médicale, Hôtel Dieu, Paris, France; ‡‡‡‡Heart of England NHS Foundation Trust, Solihull Hospital, Birmingham, UK

INTRODUCTION

Ten years after the first results from the Women's Health Initiative (WHI) trial were published, it seems that the atmosphere around the issue of menopausal hormone therapy (MHT) is increasingly evidence-based and more rational. The pendulum has swung back from its peak negative sentiment, primarily as a result of acknowledging the importance of the age at initiation and the good safety profile of MHT in women younger than 60 years. In November 2012, the International Menopause Society (IMS) organized a workshop with the participation of representatives from The American Society for Reproductive Medicine, The Asia Pacific Menopause Federation, The Endocrine Society, The European Menopause and Andropause Society, The International Osteoporosis Foundation, The North American Menopause Society and other related medical associations, with the aim of reaching a global consensus on the use of MHT and updating the 2011 IMS recommendations. The Global Consensus Statement emerging from this meeting was recently published simultaneously in *Climacteric* and *Maturitas* and was endorsed by the above societies in addition to the IMS.

The 2013 update of the IMS Recommendations is similar in structure and principle to the 2011 version but with additional clinical data where needed. Throughout the Recommendations, the term MHT has been used to cover therapies including estrogens, progestogens and combined therapies. The IMS is aware of the geographical variations related to different priorities of medical care, different prevalence of diseases, and country-specific attitudes of the public, the medical community and health authorities toward menopause management, different availability and licensing of products, all of which may impact on MHT. These Recommendations and the subsequent key messages therefore give a simple overview that serves as a common platform on issues related to the various aspects of hormone therapy, which could be easily adapted and modified according to local needs.

Key points derived from the 2013 Global Consensus (GC) Statement and the Asia Pacific Menopause Federation Consensus (APMF C) will be highlighted where appropriate.

GOVERNING PRINCIPLES

Consideration of MHT should be part of an overall strategy including lifestyle recommendations regarding diet, exercise, smoking cessation and safe levels of alcohol consumption for maintaining the health of peri- and postmenopausal women.

MHT must be individualized and tailored according to symptoms and the need for prevention, as well as personal and family history, results of relevant investigations, the woman's preferences and expectations.

Correspondence: Dr T. J. de Villiers, MediClinic Panorama, Parow 7500, Cape Town, South Africa

RECOMMENDATIONS

DOI: 10.3109/13697137.2013.795683

The risks and benefits of MHT differ for women during the menopause transition compared to those for older women.

MHT includes a wide range of hormonal products and routes of administration, with potentially different risks and benefits. Thus, the term 'class effect' is confusing and inappropriate. However, evidence regarding differences in risks and benefits between different products is limited.

Women experiencing a spontaneous or iatrogenic menopause before the age of 45 years and particularly before 40 years are at higher risk for cardiovascular disease and osteoporosis and may be at increased risk of affective disorders and dementia. MHT may reduce symptoms and preserve bone density and is advised at least until the average age of menopause.

In women with premature ovarian insufficiency, systemic MHT is recommended until the average age of the natural menopause. (GC)

Counselling should convey the benefits and risks of MHT in clear and comprehensible terms, e.g. as absolute numbers rather than, or in addition to, percentage changes from baseline expressed as a relative risk. This allows a woman and her physician to make a well-informed decision about MHT.

The option of MHT is an individual decision in terms of quality of life and health priorities as well as personal risk factors such as age, time since menopause and the risk of venous thromboembolism, stroke, ischemic heart disease and breast cancer. (GC)

Written information about risks and benefits as well as decision aids may be useful.

MHT should not be recommended without a clear indication for its use, i.e. significant symptoms or physical effects of estrogen deficiency.

Women taking MHT should have at least an annual consultation to include a physical examination, update of medical and family history, relevant laboratory and imaging investigations, a discussion on lifestyle, and strategies to prevent or reduce chronic disease. There is currently no indication for increased mammographic or cervical smear screening.

There are no reasons to place arbitrary limitations on the duration of MHT. Data from the WHI trial and other studies generally support safe use for at least 5 years in healthy women initiating treatment before age 60. Continued use beyond the 5-year window may be appropriate, based on a woman's individual risk profile.

Whether or not to continue therapy should be at the discretion of the well-informed woman and her health professional, dependent upon the specific goals and an objective estimation of ongoing individual benefits and risks.

Lower doses of MHT than previously used may reduce symptoms sufficiently and maintain quality of life for many women. However, long-term data on lower doses regarding fracture or cancer risks and cardiovascular implications are still lacking.

The dose and duration of MHT should be consistent with treatment goals, such as symptom relief, and should be individualized. (GC)

In general, progestogen should be added to systemic estrogen for all women with a uterus to prevent endometrial hyperplasia and cancer.

Estrogen as a single systemic agent is appropriate in women after hysterectomy otherwise addition of micronized progesterone/progestogen is required for endometrial protection. (GC)

Micronized progesterone and some progestogens have specific beneficial effects that could justify their use besides their expected actions on the endometrium, e.g. the well-documented blood pressure-lowering effect of drospirenone.

Progestogens are not alike with regard to potential adverse metabolic effects, cognitive effects or associated breast cancer risk when combined with systemic estrogen therapy.

Low-dose vaginal estradiol and estriol administered for the relief of urogenital atrophy are systemically absorbed, but not at levels that stimulate the endometrium, and so concurrent progestogen is not required.

Direct delivery of progestogen to the endometrial cavity from the vagina, or by an intrauterine system, does provide endometrial protection and may cause less systemic progestogenic effects than other routes of administration.

Androgen replacement should be reserved for women with clinical signs and symptoms of androgen insufficiency, primarily diminished sexual desire and arousal. Androgen replacement often has significant beneficial effects in women with bilateral oophorectomy, pituitary insufficiency or adrenal insufficiency, particularly on health-related quality of life and sexual function.

BENEFITS OF MHT

General

MHT remains the most effective therapy for vasomotor symptoms and urogenital atrophy.

MHT is the most effective treatment for moderate to severe menopausal symptoms and is most beneficial before the age of 60 years or within 10 years after menopause. (GC)

Other menopause-related complaints, including arthralgia and muscle pains, depression, sleep disturbances and vaginal atrophy, may improve during MHT. The administration of individualized MHT (including androgenic preparations when appropriate) may improve both sexuality and overall quality of life.

Postmenopausal osteoporosis

MHT is effective in preventing the acceleration of bone turnover and the bone loss associated with the menopause. MHT decreases the incidence of all osteoporosis-related fractures, including vertebral and hip fractures, even in women not at high risk of fracture. In postmenopausal women at risk of fracture and younger than 60 years, or within 10 years of menopause, MHT can be considered as one of the first-line therapies for the prevention and treatment of osteoporosis-related fractures.

> MHT is an effective treatment for the prevention of fracture in at-risk women before age 60 years or within 10 years after menopause. (GC)

The initiation of MHT for the sole purpose of the prevention of fractures after the age of 60 years is currently not recommended since the risk of long-term complications, e.g. breast cancer, outweighs the potential benefits. Therefore, the continuation of MHT after the age of 60 years for the sole purpose of the prevention of fractures should take into account the possible long-term benefits and risks of the specific dose and method of administration of MHT, compared to other proven non-hormonal therapies.

The protective effect of MHT on bone mineral density declines after cessation of therapy at an unpredictable rate, although some degree of fracture protection may remain after cessation of MHT. If the patient is still considered at risk for fracture after cessation of MHT, additional therapy with proven bone-sparing medication should be given.

Evidence of the fracture-protective effect of MHT is limited to standard dosages of conjugated equine estrogen (CEE) and medroxyprogesterone acetate (MPA), given by the oral route.

Evidence for protection against loss of bone mineral density is available for lower than standard doses in oral (CEE and 17β-estradiol) and transdermal (17β-estradiol) administration.

Tibolone, a synthetic preparation metabolized to molecules that have affinity for the estrogen, progesterone and androgen receptors, has proven efficacy against vertebral and non-vertebral fractures.

The selective estrogen receptor modulators (SERMs), raloxifene and bazedoxifene, reduce the risk of vertebral fracture in postmenopausal women with or without prevalent vertebral fractures. Bazedoxifene in addition prevents hip fracture in at-risk patients. The combination of bazedoxifene and CEE has been shown to alleviate vasomotor symptoms, reduce bone turnover rate and prevent bone loss.

Raloxifene is also indicated for reduction in risk of invasive breast cancer in postmenopausal women with osteoporosis, but is associated with an increased risk of venous thromboembolism (VTE) similar to MHT.

Cardiovascular disease

Cardiovascular disease is the principal cause of morbidity and mortality in postmenopausal women. Major primary prevention measures are smoking cessation, weight loss, blood pressure reduction, regular aerobic exercise and diabetes and lipid control. MHT has the potential for improving the cardiovascular risk profile through its beneficial effects on vascular function, cholesterol levels and glucose metabolism.

There is evidence that estrogen therapy may be cardioprotective if started around the time of menopause (often referred to as the 'window of opportunity' concept).

MHT also reduces the risk of diabetes and, through improving insulin action in women with insulin resistance, it has positive effects on other related risk factors for cardiovascular disease such as the lipid profile and metabolic syndrome.

In the WHI, younger women, 50–59 years, or <10 years from the onset of menopause, had a trend to benefit for coronary artery disease. In the estrogen trial, a composite coronary score was significantly reduced; at 10-year follow-up, there was a significant reduction in coronary events, myocardial infarction and a reduction in mortality. In the estrogen–progestogen trial, the point estimate suggested a reduction in risk, though not statistically significant.

Meta-analyses of randomized, controlled trials (RCTs), including data from the WHI, have shown a significant reduction in coronary artery disease (CAD) as well as mortality in women under the age of 60. A 10-year follow-up study of younger women receiving CEE alone in the WHI confirmed earlier findings of decreased coronary disease and mortality in this group.

The recent Danish Osteoporosis Prevention Study (DOPS) RCT studied younger women at the onset of menopause who received standard doses of estradiol and norethisterone in an open-label fashion for 10 years and had 16 years of follow-up. There were significant reductions in mortality and in hospitalizations for myocardial infarction and congestive heart failure.

Two further RCTs evaluated the effects of MHT measuring intermediate end-points of carotid intima-media thickness and coronary calcium. The Kronos Early Estrogen Prevention Study (KEEPS) recently completed and did not show a difference between CEE 0.45 mg, transdermal estradiol 0.05 mg and placebo. These young healthy women had virtually no CAD and it is possible that there was insufficient progression over 4 years to detect differences between the groups. Data from the Early versus Late Intervention Trial with Estradiol (ELITE), which studied the effects of oral estradiol 1 mg and placebo in two groups of women, one <6 years from

menopause and the other > 10 years from menopause, will be analyzed in 2014.

Given this information, in women less than 60 years old, who are recently menopausal and with no evidence of cardiovascular disease, the initiation of estrogen-alone therapy appears to reduce morbidity and mortality from coronary heart disease. The combined estrogen–progestogen data are less robust but there is possibly a cardioprotective benefit in this younger age group. Continuation of MHT beyond the age of 60 years should be decided as a part of the overall risk–benefit analysis, though few long-term RCT data exist for women using MHT in this context.

RCT and observational data provide strong evidence that standard-dose estrogen-alone MHT decreases coronary disease and all-cause mortality in women younger than 60 years of age and within 10 years of menopause. (GC)

Data on estrogen–progestogen therapy in this population show a similar trend but with less precision. (GC)

MHT does not increase coronary events in healthy women less than 60 years of age or within 10 years of menopause. (GC)

Initiation of MHT in elderly women or those who are more than 10 years postmenopause may be associated with increased risk for coronary events, mainly in the first 2 years of use. Some data suggest that concomitant use of statins may mitigate the risk of coronary events following initiation of MHT in women over age 60. It is therefore not recommended to initiate MHT beyond the age of 60 years solely for the purpose of primary prevention of CAD. The implications for those who initiated MHT prior to the age of 60 are unclear.

Other benefits

Systemic MHT and especially local estrogen can correct estrogen deficiency changes in the urogenital tract and maintain vaginal health.

Local low-dose estrogen therapy is preferred for women whose symptoms are limited to vaginal dryness or associated discomfort with intercourse. (GC)

In additional to relief of vaginal symptoms, low-dose vaginal estrogen has also been shown to alleviate sensory urgency and reduce the frequency of urinary tract infections.

MHT also has benefits for connective tissue, skin, joints and intervertebral disks. Combined estrogen and progestogen therapy and tibolone have been shown to be associated with a reduced risk of colon cancer. MHT initiated around the time of menopause or in younger postmenopausal women is associated with a reduced risk of Alzheimer's disease.

POTENTIAL SERIOUS ADVERSE EFFECTS OF MHT

Studies on the risks of MHT have mainly focused on breast and endometrial cancer, venous thromboembolic events (pulmonary embolism or deep vein thrombosis), stroke and coronary artery events.

Breast cancer

The incidence of breast cancer varies in different countries. Therefore, currently available data may not be applicable everywhere.

The degree of association between breast cancer and postmenopausal MHT remains controversial. The possible increased risk of breast cancer associated with MHT is small (less than 0.1% per annum, or an incidence of < 1.0 per 1000 women per year of use), and lower than the increased risks associated with common lifestyle factors such as reduced physical activity, obesity and alcohol consumption.

Randomized controlled data from the WHI study demonstrated no increased risk in first-time users of MHT during the 5–7 years since initiation of treatment. The WHI study also demonstrated that 7.1 years of treatment with unopposed CEE decreased the risk of breast cancer diagnosis and mortality in hysterectomized women. However, the majority of subjects in the WHI study were overweight or obese, which may have affected their basal breast cancer risk. This cannot reliably be extrapolated to younger and less obese women.

Several observational studies suggest that long-term administration of unopposed estrogens alone can be associated with a small increase in the relative risk of breast cancer in leaner, younger women, but lower than that associated with combined treatment. For instance, the UK Million Women Study (MWS), a large observational survey, raised concerns over the long-term safety of MHT from the perspective of breast cancer. However, a recent critique applied causal criteria, such as biases and biological plausibility, to assess the MWS findings. The analysis highlighted several design flaws that would potentially have skewed the findings.

A large European observational study suggested that micronized progesterone or dydrogesterone used in association with oral or percutaneous estradiol may be associated with a better risk profile for breast cancer than synthetic progestogens. A registry study from Finland also reported no increase in risk with dydrogesterone after at least 5 years of use compared to synthetic progestogens which were associated with a small increase in risk.

In addition, no difference seems to exist in risk among oral and transdermal routes of estrogen administration. However, there are not enough data from adequately powered clinical studies to fully evaluate possible differences in the incidence of breast cancer using different types, doses and routes of estrogen, micronized progesterone, progestogens and androgen administration.

Baseline mammographic density is an independent risk factor for breast cancer risk.

Some MHT preparations increase mammographic density, predominantly in women with high baseline breast density.

It is unclear whether the MHT-induced increase in mammographic density correlates with increased breast cancer risk.

The combined estrogen–progestogen therapy-related increase in mammographic density may impede the diagnostic interpretation of mammograms.

The possible greater risk of breast cancer observed with MHT may be partially decreased by selecting women with a lower individual baseline risk (e.g. no baseline or treatment-induced increase in breast density) and by providing education about preventive lifestyle measures (reducing body weight, alcohol intake and increasing physical activity).

One caveat, however, is that MHT does not appear to increase the risk of breast cancer diagnosis in overweight or obese women whereas it does in women who are not overweight.

Tibolone does not appear to be associated with an adverse effect on mammographic density. Tibolone may convey a lower breast cancer risk than estrogen–progestogen therapy but increases the rate of recurrence in breast cancer survivors.

The risk of breast cancer in women over 50 years associated with MHT is a complex issue. (GC)

The increased risk of breast cancer is primarily associated with the addition of a progestogen to estrogen therapy and related to the duration of use. (GC)

The risk of breast cancer attributable to MHT is small and the risk decreases after treatment is stopped. (GC)

There is a lack of safety data supporting the use of MHT (estrogen therapy or estrogen–progestogen therapy) in breast cancer survivors. (GC)

Endometrial cancer

Unopposed estrogen administration induces a dose-related stimulation of the endometrium. Women with a uterus should have progestogen supplementation to counteract this effect. Continuous combined estrogen–progestogen regimens are associated with a lower incidence of endometrial hyperplasia and cancer than occurs in the normal population. Direct intrauterine delivery systems may have advantages. Regimens containing low-/ultra-low-dose estrogen and progestogen cause less endometrial stimulation and less bleeding. Long-cycle regimens and long-term use of monthly sequential regimens do not provide optimal endometrial protection.

SERMs other than tamoxifen do not stimulate the endometrium and do not increase the incidence of endometrial spotting or bleeding compared to women not using any hormonal therapy.

Thromboembolism and cerebrovascular events

The MHT-related risk for serious venous thromboembolic events increases with age (although rare in low-risk women until age 60) and is also positively associated with obesity, smoking and thrombophilia.

Transdermal estrogen may avert some risk associated with oral MHT by avoiding first-pass hepatic metabolism. Accordingly, transdermal therapy should be considered in higher-risk women.

The impact on the risk of a thromboembolic event may also be affected by the type and duration of progestogen. MPA may be associated with greater risk when used in oral therapy, as is the use of continuous combined regimens compared with sequential regimens. In younger women, the absolute risk of VTE is small. In the WHI, in the 50–59-year-old group, the excess risk was 11 additional cases per 10 000 women-years for estrogen–progestogen therapy, and four additional cases with estrogen alone; both far less than the risk of VTE in normal pregnancy.

RCTs do not demonstrate an increase in the risk of VTE with tibolone but there does appear to be an increased risk of stroke in women in their sixties.

The risk of stroke is correlated with age, but stroke is a rare event before age 60. MHT further increases that risk, becoming significant after the age of 60. The risk in younger women is of borderline significance; the 30% increased risk translates into a very small absolute risk. In the WHI study, the excess risk was approximately one to two more cases per 10 000 women-years.

Observational findings from the large Nurses' Health Study showed significant findings of this magnitude even in younger women, but the risk was not observed with lower oral doses (CEE 0.3 mg).

In a large observational study from the UK, transdermal estradiol at a dosage ≤ 50 μg did not increase the risk of ischemic stroke, whereas risk was increased with higher doses of transdermal estradiol and with oral estrogens. Low-dose transdermal preparations therefore do not appear to be associated with increased risk for stroke, although absolute safety can be difficult to judge when the event rate is low. Safety data from studies of low-dose and ultra-low-dose regimens of estrogen and progestogen are encouraging, with fewer adverse events, but data from large prospective trials are awaited.

The risk of venous thromboembolic events and ischemic stroke increases with oral MHT but the absolute risk is rare below age 60 years. (GC)

Observational studies point to a lower risk with low-dose transdermal therapy. (GC)

The incidence of venous thromboembolism with MHT is very low among Asian women. (APMF C)

ALTERNATIVE TREATMENTS

The efficacy and safety of complementary alternative medicines for the alleviation of significant menopausal symptoms have not been demonstrated and further studies are required.

Selective serotonin reuptake inhibitors (SSRI), selective noradrenaline reuptake inhibitors (SNRI) and gabapentin are effective in reducing vasomotor symptoms in short-term studies. Their long-term safety needs further evaluation.

An oral SERM (ospemifene) has recently received FDA regulatory approval for the treatment of moderate to severe dyspareunia.

'Customized bioidentical hormonal preparations' have not been adequately evaluated for dosage or efficacy in studies, and their purity and risks are unknown.

> The use of custom compounded bioidentical hormone therapy is not recommended. (GC)

The measurement of hormone levels in the saliva has not been proven to be useful.

RESEARCH

There is urgent need for further research especially into the risks and benefits of lower doses, regimens and routes of administration of MHT and into late-life cognitive effects of midlife MHT use.

CONCLUSION

MHT is not a standard regimen given to a standard woman. The benefits and risks vary greatly in individual circumstances, but research over the last decade has helped to show that risks can be minimized and benefits maximized with selection of the optimal regimen at the optimal time.

The safety of MHT largely depends on age. Healthy women younger than 60 years should not be unduly concerned about the safety profile of MHT where there are indications for its use. New data and re-analyses of older studies by women's age show that, for most women, there is potential benefit for MHT given for a clear indication and there are few risks when initiated and used within a few years of menopause.

The WHI and other studies strongly suggest that it is the progestogen component of MHT that is more significant in any increase in breast cancer risk rather than the estrogen. Thus, it seems prudent to minimize progestogen use where safely possible. Future research may clarify whether risks:

- are lower for one progestogen compared to another,
- vary according to cycle duration, and
- are reduced by SERMs that do not adversely affect the breast but inhibit endometrial proliferation.

There is increasing evidence that non-oral routes of estrogen have little or no increased risk of VTE and would be the regimens of choice in women with thromboembolic risk factors, if MHT were considered appropriate.

There is mounting evidence from laboratory, animal, observational studies and RCTs that there is a probable therapeutic window of benefit for long-term cardioprotection and possibly for aspects of long-term neuroprotection if MHT is prescribed in midlife for vasomotor symptoms.

Women can have the option of MHT for as long as they derive symptomatic benefit and are aware of the risks for their regimen and personal circumstances. They can try without MHT every few years, but menopausal symptoms in some women can last for many years and should be treated with the lowest effective dose.

It is very unlikely that large, long-term RCTs, like the WHI which finished prematurely, will ever be funded or be practically possible in the future. Therefore, clinicians in any field must treat or not treat on the balance of the available data. Such data for the foreseeable future have and will come from smaller randomized trials such as DOPS or studies using surrogate end-points for long-term morbidities such as KEEPS and ELITE. Data from large, long-term cohort studies (e.g. Nurses' Health Study) or from systematic reviews of the quality literature are also very useful.

The excessive conservatism engendered by the presentation to the media of the first results of the WHI in 2002 has disadvantaged many women over more than a decade who have unnecessarily suffered severe menopausal symptoms and who may have missed the potential therapeutic window to reduce their future cardiovascular, fracture and dementia risk. These IMS evidence-based recommendations are intended to encourage better care of all women in mid-life.

KEY MESSAGES

EXERCISE IN THE MENOPAUSE

- Regular exercise reduces cardiovascular and total mortality.
- Better metabolic profile, balance, muscle strength, cognition and quality of life are observed in physically active persons. Heart events, stroke, fractures and breast and colon cancers are significantly less frequent.
- The benefits of exercise far overweigh possible adverse consequences: the more, the better, but too much may cause harm.
- Optimal exercise prescription is at least 150 minutes of moderate-intensity exercise per week. Two additional weekly sessions of resistance exercise may provide further benefit. However, the recommended intensity of

aerobic activity should take into account the older adult's aerobic fitness.

HEALTHY LIFESTYLE

- Obesity (body mass index >30 kg/m^2) affects over 20% of the population in many parts of the world and is becoming an increasing problem in the lower socioeconomic sectors and also among children. It can be associated with insulin resistance and thus increases not only a woman's risk of cardiovascular disease and diabetes, but also increases the risk for breast, colon and endometrial cancers and is associated with higher rates of depression and sexual dysfunction.
- Weight loss of only 5–10% is sufficient to improve many of the abnormalities associated with the insulin resistance syndrome.
- The basic components of a healthy diet are: several servings/day of fruits and vegetables, whole grain fibers, fish twice per week, and low total fat (but the use of olive oil is recommended). Consumption of salt should be limited and the daily amount of alcohol should not exceed 30 g for men and 20 g for women.
- Smoking should be prohibited.
- Lifestyle modifications include socializing and being physically/mentally active.
- The public health approach to lifestyle promotion requires a multidisciplinary approach, starting from schools through to work places, involving the food and advertising industry, as well as medical insurers and health authorities. A new paradigm in doctor–patient relations is required, where the doctor becomes more of an advisor and the patient has to take the responsibility for his/her own health.

UROGYNECOLOGY

- Symptoms such as vaginal dryness, soreness, dyspareunia, urinary frequency, nocturia and urgency are extremely common in postmenopausal women. Incontinence in women increases in prevalence with age. Overall, 25% of women report urinary incontinence of which 7% consider it to be significant; 50% of women complain of stress incontinence, 11% urge incontinence and 36% mixed incontinence.
- However, there is a wide variation in symptoms and signs of urogenital aging.
- The loss of lubrication and hormonal changes may lead to sexual dysfunction. Treatment of this condition improves quality of life, not only for the woman but also for her partner.
- Urogenital symptoms respond well to estrogens. Long-term treatment is often required as symptoms can recur on cessation of therapy. Systemic risks have not been identified with local low-potency/low-dose estrogens.
- Use of systemic MHT does not seem to prevent urinary incontinence and is not preferable to low-dose local estrogens in the management of urogenital atrophy or recurrent lower urinary tract infections.
- After lifestyle changes and bladder retraining, antimuscarinic drugs combined with local estrogens constitute first-line treatment in postmenopausal women with symptoms suggestive of an overactive bladder.
- All women complaining of stress urinary incontinence will benefit from pelvic floor muscle training in the first instance. Duloxetine may work synergistically with conservative therapy. However, some women will ultimately undergo surgery, and retropubic and trans-obturator tapes are the most popular procedures.
- There is currently no role for systemic estrogen therapy in women with pure stress urinary incontinence.

OSTEOPOROSIS

General guidelines

The disease

- Osteoporosis is a systemic skeletal disease of diminished bone strength that results in fractures when falling from one's own body height. Bone strength is determined by a combination of bone density and microarchitectural integrity.
- Postmenopausal osteoporosis can be caused by the failure to attain peak bone density or accelerated bone loss after menopause.
- Although skeletal health is a function of genetic predisposition, it can be modified by lifestyle factors such as diet, weight-bearing exercise and the avoidance of bone-toxic substances.
- Hip fracture is responsible for a large proportion of the financial burden of osteoporosis to health-care systems but other osteoporosis-related fractures, particularly vertebral fractures, cause considerable morbidity which can be long-standing.

Diagnosis and assessment

- The diagnosis of osteoporosis is based on assessment of bone mineral density by dual X-ray absorptiometry (DXA), expressed as the *T*-score, or the presence of fragility fractures.
- Bone mineral density assessment is not a cost-effective population screening tool but is best applied on a selective basis, based on age and other risk factors including a family history of fractures, history of amenorrhea, corticosteroids, etc.
- The 10-year probability of fracture in an individual can be estimated using a model that integrates various risk factors for fracture, such as the FRAX model developed through

the World Health Organization, which is available online at www.sheffield.ac.uk/FRAX/.
- An appropriate assessment of prevalent fractures and secondary causes of osteoporosis should precede any therapeutic decisions.

Treatment

- The goal of management in osteoporosis is the prevention of fracture. Choice of therapy should be based on a balance of effectiveness, risk and cost.
- Intervention thresholds for therapy can be based on 10-year fracture probability and will be country-specific.
- Alternatively, treatment can be given to all patients with a fragility fracture or a *T*-score of ≤ -2.5 (osteoporosis), or a *T*-score of $< -1.0 > -2.5$ (osteopenia) and additional risk factors, as a large proportion of fractures occur in individuals with osteopenia.
- Monitoring of therapy by serial DXA should be interpreted with caution and take into account the site monitored, time interval, drug-specific expectations and the value of least significant change as calculated for the specific device and operator.
- The monitoring of treatment by biochemical markers of bone turnover is presently not recommended in routine clinical practice.
- The cost-effectiveness of treatments to prevent osteoporotic fracture will be highest where they are used in women who have increased fracture risk. The relevant fracture risk threshold will be specific to the individual health-care system.

Menopausal hormone therapy

- MHT decreases bone turnover and the incidence of all osteoporosis-related fractures, including vertebral and hip fractures.
- MHT can be considered as one of the first-line therapies for the prevention and treatment of osteoporosis-related fractures in women below 60 years.
- The initiation of MHT for the sole purpose of the prevention of fractures after the age of 60 years is not recommended.
- The protective effect of MHT on bone mineral density declines after cessation of therapy at an unpredictable rate.
- Data for protection against loss of bone density is available for low doses of oral (CEE and 17β-estradiol) and transdermal (17β-estradiol) administration.

Other therapies

Tibolone

- Standard-dose tibolone (2.5 mg/day) has proven efficacy against postmenopausal osteoporosis.
- Low-dose tibolone (1.25 mg/day) is effective in reducing vertebral and non-vertebral fractures.

Calcium and vitamin D

- Postmenopausal women need a dietary reference intake (DRI) of 1000–1500 mg of elemental calcium.
- Calcium supplementation should be restricted to bridge the shortfall between dietary intake and the DRI and to patients being treated for high fracture risk. Routine dietary calcium supplementation cannot be justified in terms of efficacy and health economics.
- Excessive calcium supplementation in addition to adequate or high dietary calcium may be associated with increased cardiovascular risk.
- The DRI for vitamin D is 800–1000 IU in the postmenopausal period.
- As the major source of vitamin D is dependent on sunlight exposure, the need for supplementation will vary. Measuring the blood 25-hydroxyvitamin D level may be helpful in selected individuals.
- Vitamin D supplementation has been shown independently to lower the risk of fracture and of falling in elderly patients.

Bisphosphonates

- The bisphosphonates are potent inhibitors of bone resorption and decrease the rate of bone turnover, with proven efficacy in the prevention of vertebral and hip fractures.
- A drug-free holiday may be considered after 3–5 years of bisphosphonate therapy in patients with a good response of bone mineral density to treatment, without prevalent fractures.
- Bisphosphonates have benefits in some cancers and may prevent bone metastases from breast cancer.
- Bisphosphonate-related osteonecrosis of the jaw is a rare complication when dosages as recommended for fracture prevention are used.
- An association has been suggested between atypical femur shaft fractures and over-suppression of bone turnover in patients exposed to bisphosphonates for longer than 3–5 years.

SERMs

- The SERMs, raloxifene and bazedoxifene, reduce vertebral fractures in postmenopausal women with or without prevalent vertebral fractures.
- Bazedoxifene prevents hip fracture in at-risk patients.
- Bazedoxifene and CEE have been shown to reduce bone turnover rate and prevent bone loss whilst also alleviating vasomotor symptoms.

Parathyroid hormone

- Parathyroid hormone (PTH) produces a significant reduction in the risk of vertebral and non-vertebral fractures by stimulation of bone formation. There is no indication that combining PTH with a bone resorption inhibitor has any additional benefit to giving either drug alone. Prior treatment with a bisphosphonate blunts the effect of subsequent PTH.
- PTH is given as a daily subcutaneous injection for a maximum of 18 months. Use is limited by high cost.

Strontium ranelate

- Given in a daily oral dose, strontium ranelate significantly reduces the risk of vertebral and non-vertebral fractures in osteoporotic and osteopenic patients, irrespective of the presence of a fracture or age. The mode of action of strontium ranelate involves stimulation of bone formation as well as inhibition of resorption.

Denosumab

- A human monoclonal antibody to the receptor activator of nuclear factor-kappa B ligand (RANKL), at a dose of 60 mg subcutaneously 6-monthly, significantly reduces the risk of vertebral, non-vertebral and hip fractures. As with other biological therapies, denosumab may have adverse immunological effects.

SKIN, CARTILAGE AND OTHER CONNECTIVE TISSUES

Skin, the carotid artery and intervertebral discs

- Estrogen protects connective tissue metabolism in the whole body.
- After the menopause, there is loss of connective tissue in the dermis of the skin which in some cases is reversed with estrogen therapy.
- Similar changes in connective tissue are observed at the arterial media layer.
- Intervertebral discs become thinner after the menopause and this may be prevented by estrogen therapy.

Articulated joints and the menopause

- The marked predominance of polyarticular osteoarthritis in women and, in particular, the marked increase of osteoarthritis in women after the menopause suggest that female sex steroids are important for cartilage homeostasis.
- Timely initiation of estrogen/SERM treatment can effectively prevent both bone and cartilage loss accompanying the menopause, involving both direct and indirect mechanisms.

CARDIOVASCULAR SYSTEM

Gender-specific characteristics of atherosclerosis in menopausal women

- The clinical course of cardiovascular disease has gender-specific characteristics.
- Risk factors for CAD increase at the time of menopause due to the potential effects of ovarian failure on cardiovascular function, blood pressure and various metabolic parameters (glucose tolerance, lipid profile).
- Arterial hypertension, high triglyceride level and especially diabetes negate the gender advantage of women compared to men in cardiovascular event rates.
- Preventative strategies should be focused in women on reducing blood pressure and controlling weight and insulin resistance
- Women may have angina with non-obstructed coronary arteries but, when they develop an infarct, their prognosis is significantly worse than that of men.
- Accordingly, it is imperative to evaluate symptoms despite the lower positive predictive value of angina in women.

MHT and coronary artery disease

- Estrogen induces beneficial effects on various CAD metabolic risk factors.
- MHT is associated with a lower risk of new-onset type 2 diabetes.
- The majority of preclinical data and observational studies support the potential benefits of MHT in reducing risk of CAD.
- Previous observational data on the protective effects of MHT were based on studies in younger women.
- Age of initiation, near to the time of menopause, is a critical factor in determining whether MHT reduces or increases CAD risk.
- RCTs in women with established CAD have shown that there is no coronary benefit of MHT in these women.
- Certain hormonal regimens and progestogen types may be important in determining the potential CAD benefit in younger women, as has been shown with estrogen alone; however, there are no comparative trials.
- Overall, data strongly suggest a coronary benefit with estrogen alone, and possibly with estrogen and progestogen in young women at onset of menopause.

MHT and stroke

- Although both CAD and stroke are arterial vascular diseases, the effects of postmenopausal hormones on these common conditions are not necessarily similar.
- Hypertension and body mass index significantly increase the risk of ischemic stroke.

- Oral estrogen therapy and estrogen–progestogen therapy increase the risk of ischemic stroke by about one-third in relatively healthy postmenopausal women.
- Low-dose tibolone (1.25 mg) increases the risk of stroke in women over 60 years.
- The excess absolute risk of MHT is expected to be lower among women below the age of 60 years, because stroke incidence is lower in this younger age group.
- In the Nurses' Health Study, the risk of stroke was not increased with lower oral doses of MHT (CEE 0.3 mg.)
- Low-dose transdermal estradiol (below 50 μg) does not increase the risk of stroke.
- Evidence from basic science studies reaffirms the neuronal protective effects of estrogen in the setting of experimental infarction.
- Based on findings from a single, well-designed clinical trial of postmenopausal women with a history of ischemic stroke or transient ischemic attack, estrogen therapy should not be prescribed for the secondary prevention of stroke.
- Data on progestogen use versus unopposed estrogen use have not been consistent.

COAGULATION

VTE safety

- VTE is one of the major adverse events during use of oral MHT and SERMs.
- The risk increases with estrogen dose, age and body mass index and is greater during the first years of therapy.
- Consistent observational data suggest that the risk of VTE is not increased with transdermal therapy using 17β-estradiol, unless high doses are used.
- Some progestogens, e.g. MPA, nor-pregnane derivatives and continuous combined regimens, may be associated with greater risk of VTE in oral MHT users.
- In younger women, the absolute risk of VTE is small.
- The incidence of VTE is less frequent among Asian women.
- Population screening for thrombophilia is not indicated prior to MHT use.
- Selective screening may be indicated on the basis of personal and familial history.
- Smoking should be strongly discouraged in women using any estrogen-containing products

Arterial disease safety

- Oral MHT induces both pro-inflammatory (liver biomarkers) and anti-inflammatory (vascular biomarkers) effects. Modification of inflammation in either direction can be good or bad for arterial disease depending upon the individual status of inflammation in the vascular wall, potentially related to age and time after menopause.
- The liver-derived pro-inflammatory effects of estrogen may be avoided by non-oral administration of 17β-estradiol.
- There is limited evidence that different progestogens modulate liver and vascular inflammatory effects.

BRAIN

General

- During development and adulthood, the human brain is a target for estrogens and other gonadal steroid hormones. Estrogens influence neural function and neurological disease directly, through effects on neurons and glia, and indirectly, through effects on oxidative stress, inflammation, the cerebral vasculature and the immune system.
- With menopause, the cessation of ovarian production of estrogens and progesterone has the potential to influence processes in the central nervous system relevant to neurological and psychiatric disorders. Within the brain, however, some neurons remain capable of synthesizing small amounts of estradiol.
- Many women note cognitive and emotional symptoms at times that are associated with changes in circulating levels of gonadal steroids. It has been more difficult, however, to demonstrate consistent cognitive and affective effects of MHT.

Cognition and cognitive aging

- For midlife women, observational evidence indicates no persisting effects of the natural menopause on memory or other cognitive functions. During the menopausal transition, however, some women experience transient problems, the magnitude of which is usually small.
- Limited evidence from short-term clinical trials in midlife women suggests that MHT has no substantial cognitive effect after natural menopause. This needs clarification from further research.
- For older women without cognitive impairment, there is convincing clinical trial evidence that MHT started in the late postmenopause has no substantial impact on cognitive abilities.
- For surgically menopausal women, limited evidence from small clinical trials suggests that estrogen therapy could be of short-term cognitive benefit when initiated at the time of oophorectomy.
- The long-term cognitive consequences of MHT initiated during the menopausal transition or early postmenopause are unknown. There remains an urgent need for further research in this area.
- For healthy postmenopausal women, there is clinical trial evidence that isoflavone supplements in a daily dose comparable to that consumed in traditional Asian diets have no overall effect on cognition.

Alzheimer's disease

- For women with dementia due to Alzheimer's disease, limited clinical trial evidence indicates that MHT does not improve dementia symptoms or slow disease progression.
- Limited clinical trial evidence indicates that MHT increases all-cause dementia risk when initiated in the late postmenopause. For women aged 65–79 years, the excess risk of dementia attributed to hormone use is about 1.2 per 1000 women-years for estrogen therapy and 2.3 per 1000 women-years for estrogen–progestogen therapy. In this age group, MHT risk may be higher for women with lower cognitive function at baseline.
- Observational evidence implies that MHT used by younger women around the time of menopause is associated with lower risk of Alzheimer's disease. Findings from several observational studies support the concept of a therapeutic window, suggesting that MHT initiation and use in midlife may be beneficial, with respect to Alzheimer's risk, whereas starting MHT in later life is harmful.
- The long-term cognitive consequences of MHT initiated during the menopausal transition or early postmenopause are largely unknown.
- There remains a need for further research in this area.

Depression

- The prevalences of depressive symptoms are similar before and after the menopause. However, depression risk may be increased during the menopausal transition and the early postmenopause.
- Limited clinical trial evidence suggests no effect of estrogen therapy on depression in the late postmenopause.
- Accumulating clinical trial evidence suggests that short-term estrogen therapy significantly benefits depression during the menopausal transition.
- Large studies should be conducted to further evaluate the potential benefits of estrogen both as monotherapy and as adjunctive treatment for the management of depression in the menopause transition.

Other neurological disorders

- Potential effects of MHT on the incidence or symptoms of Parkinson's disease are largely unknown.
- Based on evidence from a single, small clinical trial, combined MHT may increase seizure frequency in postmenopausal women with epilepsy.
- Progesterone therapy before the menopause has no substantial effect on seizure frequency. It is not known whether this finding generalizes to postmenopausal women with epilepsy.
- Headache prevalence is lower after menopause than before. Limited observational evidence suggests that current MHT is positively associated with increased headache frequency.
- Multiple sclerosis symptoms may be influenced by hormonal status. It is not known whether MHT affects multiple sclerosis symptoms or progression.

ONCOLOGY

MHT and breast cancer

- The incidence of breast cancer varies in different countries.
- The possible increased risk of breast cancer associated with MHT is small.
- The WHI study demonstrated no increased risk in first-time users of MHT and decreased risk of breast cancer diagnosis and mortality in hysterectomized women using unopposed CEE.
- Unopposed estrogens can be associated with a small increase in relative risk of breast cancer in leaner, younger women.
- Micronized progesterone or dydrogesterone used with estradiol may be associated with a better risk profile for breast cancer than synthetic progestogens.
- More data are required to evaluate the incidence of breast cancer using different types, doses, routes of estrogen, progesterone, progestogens and androgens.
- Baseline mammographic density correlates with breast cancer risk, but this is independent of breast cancer association with MHT.
- The combined MHT-related increase in mammographic density may impede interpretation of mammograms.

Endometrial safety, bleeding, MHT and endometrium

- Unopposed estrogen therapy is associated with a duration and dose-related increase in risk of endometrial hyperplasia and cancer.
- This increased risk persists for many years after cessation of therapy.
- Progestogen prevents the endometrial proliferation of estrogen.
- Endometrial protection requires an adequate dose and duration of progestogen.
- Long-term use of sequential combined MHT regimens may increase the risk of endometrial hyperplasia and cancer, particularly the long-cycle regimens.
- Continuous combined regimens are associated with a lower risk of endometrial cancer than in the untreated population.
- In the WHI and Million Women Study, there was no difference in risk of endometrial cancer with continuous combined regimens.
- New lower-dose regimens cause less endometrial stimulation and less bleeding.
- Intrauterine delivery of progestogen is a logical route of administration and provides effective endometrial

suppression, but outpatient insertion may be problematic in postmenopausal women.
- Data from RCTs on the effect of tibolone on the endometrium suggest a similar effect to continuous combined regimens.
- Tamoxifen has an estrogenic effect on the endometrium whereas raloxifene and other modern SERMs have no apparent effect.
- Following treatment for endometrial cancer, the use of MHT is not generally recommended, although there are few data.
- Obesity increases the risk of developing endometrial pathology.

MHT and cancers other than breast

Ovarian cancer

- Premenopausal use of the combined oral contraceptive pill is associated with a reduced risk of developing ovarian cancer.
- The WHI study is the only RCT to examine MHT and ovarian cancer risk. In women receiving combined MHT, there was no significant increase in risk.
- Several case–control and population studies suggest a significant increase in risk, but the effect of duration or type of therapy varied among the studies. In one large-scale trial, the increased risk rapidly returned to normal within 2 years of cessation, consistent with a promoter rather than inducer effect.
- In summary, long-term, estrogen-only therapy may be associated with a small attributable risk of ovarian cancer of 0.7 per 1000 women per 5 years of use, whilst either a significantly smaller, or no, increased risk is seen with combined estrogen plus progestogen therapy.

Lung cancer

- Lung cancer incidence in women continues to increase, mainly due to smoking, and lung cancer is the largest contributor to cancer mortality in women.
- Large observational studies have reported a protective effect of hormonal contraception and MHT on lung cancer risk.
- In the WHI RCT of estrogen-only therapy, there was no increase in the risk of non-small cell lung cancer in users of MHT compared to placebo.
- In the WHI RCT of combined estrogen–progestogen therapy, there was an overall non-significant trend towards an increase in risk of non-small cell lung cancer.
- The increased risk became significant only in women aged 60–69 years where the absolute attributable risk was 1.8 extra cases of lung cancer per 1000 women taking MHT for 5 years.
- The risk of death from lung cancer was also higher for MHT users and this increase was greatest amongst those who were smokers.
- In women aged 50–59 years, no increased risk of lung cancer was observed.

Colorectal cancer

- The majority of observational studies show a reduced risk of colorectal cancer amongst users of oral MHT.
- Three meta-analyses have reported a reduced risk of colorectal cancer with MHT use with benefit persisting for 4 years after cessation of therapy. A typical effect was relative risk (RR) 0.80 (95% confidence interval (CI) 0.74–0.86) for ever-users and 0.66 (95% CI 0.59–0.74) for current users.
- The LIFT study demonstrated that tibolone was associated with a reduced risk of colon cancer in women aged 60–79 years.
- Results from the WHI randomized trial of estrogen-only therapy showed no effect of estrogen-only therapy on risk of colorectal cancer.
- In the WHI RCT of estrogen–progestogen therapy, colorectal cancer risk was reduced (RR 0.56; 95% CI 0.38–0.81). This effect was predominantly for local disease and, where spread had occurred, there was more node involvement and a more advanced stage at diagnosis amongst users of MHT.
- MHT should not be used solely for the prevention of colorectal cancer.
- There are no data for an effect of non-oral MHT on risk of colorectal cancer.

Cervical cancer

- Long-term cohort studies have shown no increased risk of cervical cancer with MHT use.
- In the WHI RCT, there was no increase in risk of cervical cancer with MHT use.

Upper gastrointestinal tract cancer

- Gastric and esophageal cancers are predominantly a disease of men. The reason for this is unclear and no hormonal mechanism has been found.
- A nested case–control study showed a reduction in stomach cancer for users of MHT (RR 0.48; 95% CI 0.29–0.79) but no effect on esophageal cancer.
- Oral MHT is known to affect gall bladder function and observational studies have reported an increased incidence of cholecystectomy amongst users of MHT.
- The only report of gall bladder cancer and MHT comes from a small case–control study which found an increased risk associated with MHT use and with duration of use (RR 3.2; 95% CI 1.1–9.3).

ATTITUDES TO SEXUALITY AND QUALITY OF LIFE IN THE MENOPAUSE

Clinical evaluation/diagnosis

- Healthy status represents a major determinant of quality of life, particularly in elderly people, but sexuality is an important factor at all ages as well.
- A complex interplay of biological, psychological and socio-relational factors determines women's sexual health. This may negatively affect the entire sexual response cycle, inducing significant changes in desire, arousal, orgasm and satisfaction at menopause and beyond.
- Both age and declining sex hormones have detrimental effects on sexual functioning, with a significant increase in vaginal dryness/dyspareunia and a significant decrease in desire and sexual responsiveness.
- The partner's general and sexual health and the relationship itself may significantly contribute to the relevance of sexual symptoms in postmenopausal women.
- Reduced libido is the most common sexual complaint experienced by women and the proportion increases with age. However, there are age-related changes in sexually related personal distress, which are especially evident in surgically menopausal women. These women are at increased risk for hypoactive sexual desire disorder.
- Women may not be willing to initiate a conversation on sexual interest, behavior and activity themselves, but they usually appreciate being questioned by doctors.
- Validated tools (self-administered questionnaires/daily diaries and event logs/semi-structured interviews) may be used properly to diagnose sexual symptoms and to gain information on sexual constructs and relationships; sex steroid assays are not generally helpful.
- An accurate sexual history and a focused clinical evaluation may help clinicians in the management of sexual symptoms that are causing significant distress.
- Vaginal atrophy should be always diagnosed and appropriately treated.
- Hormonal and non-hormonal treatments and/or psychosexual strategies should be individualized and tailored according to a woman's history and current needs.

Androgen therapy in the postmenopause

- Androgen levels decline with age prior to the menopause such that by menopause most women have half the level of circulating testosterone and pre-androgens, androstenedione and dehydroepiandrosterone (DHEA) that they had in their twenties.
- The consequences of the decline in androgens in women with age need to be better understood.
- The primary indication for testosterone is for the treatment of desire, arousal and orgasmic disorder.
- Several large, placebo-controlled RCTs have consistently show benefits of *continuous* testosterone for sexual satisfaction, desire, arousal, pleasure and orgasm in surgically postmenopausal women on estrogen, naturally postmenopausal women on estrogen–progestogen therapy, postmenopausal women on no hormone therapy and premenopausal women in their late reproductive years.
- Before considering androgen therapy, factors such as dyspareunia, depression, medication side-effects, relationship issues and other health problems need to be identified and managed.
- Androgenic side-effects are dose-related and avoidable with the use of appropriate formulations and dose.
- There is no evidence from large, placebo-controlled RCTs that transdermal testosterone in appropriate doses results in adverse metabolic effects or effects on the endometrium.
- Available data do not indicate an increase in risk of breast cancer with transdermal testosterone; no large study with this outcome has yet been published.
- Oral DHEA does not improve sexual function, well-being or metabolic health in postmenopausal women.
- Oral DHEA may improve health-related quality of life and depression in women with adrenal insufficiency.
- The role of vaginal DHEA administration for improving sexual function in postmenopausal women requires confirmation.
- Preliminary data support the need for research to clarify the role of testosterone for prevention of bone and muscle loss, maintenance of cognitive performance and cardiovascular effects.

Non-hormonal approaches to the management of menopausal symptoms

Non-pharmacological and lifestyle interventions

- High-quality data from studies of non-pharmacological and lifestyle interventions for vasomotor symptoms have been limited.
- Meditation, relaxation, controlled breathing and cognitive behavior therapy show promise in managing hot flushes, but adequately powered randomized trials are still needed.
- There is little evidence that dietary modifications or exercise improve hot flushes but they may improve mood and quality of life.
- Regular exercise, weight reduction, and avoiding triggers to hot flushes (such as caffeine or direct heat) may help to minimize hot flushes or their impact.
- Randomized trials of acupuncture have not consistently shown a beneficial effect in reducing vasomotor symptoms

Complementary therapies for vasomotor symptoms

- High-quality studies to date have not consistently supported the efficacy of complementary or over-the-counter

therapies in reducing severity or frequency of hot flushes or night sweats.
- Black cohosh and soy products are not superior to placebo in the treatment of hot flushes.

So-called 'bioidentical' or 'natural' hormones

- Such labelling and advertising has no sound scientific basis to delineate them from many current forms of registered MHT.
- Estradiol, estrone or estriol, whether pharmaceutically produced or compounded as a 'bioidentical' product, are synthesized usually from the vegetable yam and are identical to ovarian estrogens.
- Other so-called 'natural' but synthesized human hormones that can be mixed into untested 'bioidentical' concoctions can be progesterone, testosterone, DHEA, thyroxine, growth hormone and melatonin.
- These hormones are usually administered in troches (buccal lozenges) or transdermal creams, compounded by local chemists on the prescription of medical practitioners, in combinations and doses that have never been tested in published quality clinical trials.
- There are inadequate quality data to show the long-term safety or efficacy of any of these products.
- Endometrial cancer has been associated with estrogen-containing bioidentical hormones. If used in the bioidentical mixture at all, the progesterone used may not inhibit estrogen-induced endometrial hyperplasia.
- Hormonal assay of saliva is sometimes claimed as a way of assessing hormonal need and of titrating the compounded 'natural' hormones. There are no data to show that salivary hormonal assay can reliably achieve these aims.
- Bioidentical hormones are extensively marketed direct to the public on the internet and in other media, often with unproven and unlikely claims such as they have no side-effects, are safe, will help you lose weight and are anti-aging.
- Locally compounded 'bioidentical' hormones are not subject to the scrutiny of pharmaceutical regulatory bodies in many countries and the manufacturers can avoid having to test their products for quality control, safety and efficacy.
- These unproven products and the associated inaccurate saliva tests are usually promoted for commercial gain and are much more expensive than proven registered pharmaceutical hormone therapies.
- All main-stream scientific, clinical and regulatory bodies in women's health advise against the prescription and use of these hormones.
- The prescriber is at risk of future medico-legal claims.

Pharmacological agents for vasomotor symptoms

- The mechanisms underlying vasomotor symptoms are still not well understood.
- There have been very few head-to-head studies of non-hormonal agents.
- Currently, the only preparation which has demonstrated equivalent efficacy to estrogen is gabapentin. Gabapentin (300 mg three times per day) was equivalent to low-dose estrogen (0.5 mg CEE or a 25 μg estradiol patch) for vasomotor symptoms.
- No other agents have been directly compared with estrogen for the reduction of vasomotor symptoms.
- Venlafaxine, desvenlafaxine, fluoxetine, paroxetine and citalopram have all been shown in RCTs to reduce vasomotor symptoms. A recent head-to-head study found that venlafaxine (37.5 mg per day increasing to 75 mg controlled release) was equally effective but better tolerated than gabapentin (300 mg once per day increasing to 300 mg three times per day) in breast cancer patients. Both products reduced the frequency and severity of hot flushes (by 66%) but side-effects were greater with gabapentin.
- In breast cancer patients, the SNRI venlafaxine was equally as effective as clonidine in reducing vasomotor symptoms but clonidine was better tolerated. Efficacy up to 12 weeks has been demonstrated for these agents.
- In general, these non-hormonal agents reduce hot flushes by 50–60%. This level of reduction appears to be acceptable to many women who wish to avoid hormones.
- For those with mild/moderate hot flushes, it is reasonable to start with clonidine treatment. For moderate to severe hot flushes, or, when clonidine fails or is not available, consider venlafaxine or gabapentin. These agents may act by different mechanisms, so, if one fails or is not well tolerated, the other can be tried. If these are not effective, consider paroxetine, but avoid in those on tamoxifen. Citalopram can be considered in tamoxifen users.
- A key consideration in breast cancer patients using non-hormonal agents is concomitant tamoxifen use. Agents which inhibit the enzyme CY2D6 can affect tamoxifen metabolism and may reduce the efficacy of tamoxifen in preventing new breast cancers or their recurrence. Agents which interact with the cytochrome P450 system include paroxetine, fluoxetine and buproprion and these should not be used in conjunction with tamoxifen for the treatment of depression or vasomotor symptoms. If antidepressants are to be used with tamoxifen, venlafaxine, desvenlafaxine, citalopram and escitalopram appear to be safe.
- Sudden cessation of a SNRI or SSRI may cause withdrawal symptoms and they should be discontinued gradually by reducing the dose over 2 weeks.

POSTMENOPAUSAL VAGINAL ATROPHY

- Vaginal atrophy becomes clinically apparent 4–5 years after the menopause and objective changes as well as subjective complaints are present in 25–50% of all postmenopausal women.

- Postmenopausal women have a poor understanding of vaginal atrophy and it is often considered a taboo subject.
- It is essential that health-care attendants routinely engage in open and sensitive discussion with postmenopausal women about their urogenital health to ensure that symptomatic atrophy is detected early and managed appropriately.
- Treatment should be started early and before irrevocable atrophic changes have occurred.
- Treatment needs to be continued to maintain the benefits.
- All local estrogen preparations are effective and patient preference will usually determine the treatment used.
- All currently available topical estrogens are absorbed, the extent depending on dose and formulation.
- Additional progestogen is not indicated when appropriate low-dose, local estrogen is used although long-term data (more than 1 year) are lacking.
- If estrogen is ineffective or undesired, vaginal lubricants and moisturizers can relieve symptoms due to dryness.
- There are few data on the use of vaginal estrogens in women with gynecological hormone-responsive cancers so they should be used with discretion.
- Use of local estrogen in women on tamoxifen or aromatase inhibitors needs careful counselling and discussion with the patient and the oncology team.
- Estriol and testosterone preparations may be an option for such patients but more studies are needed.

NEW HORMONAL THERAPIES AND REGIMENS

Newly approved medications

- Low- and ultra-low-dose oral and transdermal preparations appear to maintain benefits for symptom relief and osteoporosis while minimizing side-effects and risks.
- A number of new SERMs have been approved by regulatory agencies for indications related to osteoporosis.
- Ospemifene, an oral SERM, has received FDA approval for the treatment of moderate to severe dyspareunia.
- The IMS recommendations on management of vaginal atrophy have highlighted the excellent benefit/risk ratio of estrogenic and non-hormonal vaginal preparations.
- An ultra-low-dose 10 μg estradiol vaginal tablet has received regulatory approval and is now available globally.
- A new injectable monoclonal antibody, targeting RANK ligand (denosumab) is available for the prevention of fractures in postmenopausal women with osteoporosis and high fracture risk.

Late-stage products

- Clinical studies are ongoing into the possible use of vaginal DHEA for atrophy and low libido.
- Studies of SSRI and SNRIs are ongoing for treatment of vasomotor symptoms.
- A SERM/estrogen combination (CEE/bazedoxifene), developed to treat menopausal symptoms and osteoporosis, has completed phase III trials and is seeking regulatory approval.
- Approval of a dose-appropriate androgenic formulation for women for desire/arousal/orgasmic disorder is needed to abrogate the need for physicians prescribing compounded testosterone or modifying doses of testosterone formulated for men.

Route of administration

- Non-oral estradiol and progestogens avoid the first-pass metabolism and therefore have the potential for less stimulation of the liver proteins and a neutral metabolic profile.
- The risk of VTE and stroke is less with transdermal than with oral estradiol.
- First uterine pass of vaginal delivery of progestogens leads to adequate local concentrations and good endometrial protection, but with very low systemic progestogen levels.
- The combination of non-oral administration of estradiol and direct intrauterine delivery of progestogen or vaginal ring delivery of progesterone may improve compliance. Long-term, good-quality studies are still needed.

INFLUENCE OF METHODOLOGY AND EPIDEMIOLOGY ON PERCEPTION OF MHT

- There is a hierarchy of scientific evidence which should be taken into account when drawing conclusions from any scientific investigation. In general (from the highest standard or level of evidence to the lowest), the standards of evidence are replicated findings from high-quality RCTs, RCTs, cohort studies, case–control studies, case series and case reports, and, lastly, expert opinion. However, RCTs and observational studies must be interpreted with caution, particularly with reference to MHT.
- Observational studies (e.g. Nurses' Health Study) are primarily used for hypothesis development and do not provide strong evidence of causality. Inherent biases in many observational studies of MHT typically include: selection bias – healthier women prescribed MHT; recall bias – less healthy women may not accurately recall prior hormone usage; prevention bias – monitoring and treating more intensively in women prescribed MHT; compliance bias – patients with greater adherence (even to placebo) have better outcomes; survivor bias – MHT may be stopped due to illness; prevalence-incidence bias – early adverse effects of MHT may not be observed if the user dies before becoming part of cohort.
- RCTs (e.g. the WHI) are primarily used for hypothesis testing, to prove or disprove cause and effect. They can be downgraded in their level of evidence due to factors such as: poor compliance and large dropout rate, loss of blinding, and non-generalizability (lack of adequate representation of the applicable group of women). It has

been argued that the WHI should be downgraded to a level of evidence equivalent to that of a well-conducted observational cohort study, primarily due to loss of blinding.

- The World Health Organization Council for International Organizations of Medical Sciences (CIOMS) classifies the frequency of drug reactions, which would include the impact of MHT or estrogen therapy, as:

Very common	>1/10 (>10%)
Common (frequent)	>1/100 and < 1/10 (> 1% and <10%)
Uncommon (infrequent)	>1/1000 and < 1/100 (> 0.1% and <1%)
Rare	>1/10 000 and <1/1000 (>0.01% and <0.1%)
Very rare	<1/10 000 (<0.01%)

  However, these frequencies do *not* necessarily correspond to statistical significance. Rare findings in large RCTs and observational studies may be statistically significant because of the large sample size, but may be of minor clinical importance in their application to a particular patient in the clinical setting. Failure to provide a clinical context is often a problem in understanding and interpreting study outcomes.

- Future guidelines from the IMS will include the levels of evidence and grade of recommendations based on the available data.

INFLUENCE OF THE MEDIA AND PERCEPTION OF MHT

- The mass media has a tremendous influence over what the public 'knows' about MHT. Media-driven perceptions also influence clinical decision-making, particularly by those less familiar with the primary data being reported by the media. Each new news report is often treated as if it were the most important and of the highest quality, often to the exclusion of other scientific evidence. For example, the initial results of the WHI estrogen–progestogen arm received enormous media coverage – more than 400 newspaper stories and 2500 television-radio stories in the US alone, yet subsequent WHI reports have received much less press coverage, leading to the impression that surgically menopausal women on estrogen without progestogen have similar risks as noted in the initial reports.
- The press more often focuses on negative outcomes (i.e. breast cancer) than on positive findings such as fracture reduction or cardiovascular disease reductions in younger women. Media coverage sometimes includes superficial and uncritical evaluations.
- However, most journalists write well-balanced accurate articles given the correct information. It is important that health professionals present the facts to the media in a professional, clear, unbiased way so that accurate reporting can take place.
- Media coverage has done a good job of telling women what to be concerned about if they are using MHT, but a poor job of providing the information women need to determine whether the latest findings apply to them. It is important that health professionals provide this information for women to individualize the benefits and risks of MHT.
- There is a general distrust of large organizations and particularly of research done by the pharmaceutical industry despite conformance to regulatory agencies, both in North America (the Food and Drug Administration; Health Canada) and in other countries of the world (e.g. European Medicines Agency).

ACTION POINTS

How should we optimize the impact of the Global Consensus Statement and the Updated 2013 Recommendations? These six action points are suggested:

- Health Departments and Regulators: Immediate discussions to encourage a change of policy to a more lenient stance on MHT given new favorable data in younger menopausal women, e.g. removal of the 'black box' warning for women <60 years.
- Prescribers: Expansion of clinical education and training in menopause, particularly in primary care, to increase confidence in management of the menopause and health promotion.
- Media: Positive engagement of the media to increase awareness of menopause issues and to highlight new data on MHT.
- Pharma industry: Effective communication with pharma industry to help reverse negative commercial decisions on MHT products and encourage research and development of new regimens.
- Menopausal women: Improve access to information for women about menopause, treatment of menopausal symptoms, health promotion, and disease prevention, thus empowering women to optimize their quality of life and future health.
- MHT: Planning of future research programs to seek clarification of the differences in action and risk profiles of various MHT regimens – the term 'class effect' is outdated and misleading where MHT is concerned.

Conflict of interest The authors report no associations or financial relationships with any pharmaceutical company, other than consultative agreements, honoraria for lecturing at scientific meetings, and research support. Details of all disclosures have been updated and are on file in the IMS Secretariat.

Source of funding The IMS Workshop in November 2012 was supported by unrestricted grants from Abbott GmbH, Bayer Pharma AG, Besins Healthcare, Novo Nordisk, Pfizer Inc., Shionogi Inc. and Teva.

2011 Updated IMS Recommendations Authors: D. W. Sturdee and A. Pines on behalf of the International Menopause Society Writing Group. Writing Group: D. F. Archer, R. J. Baber, D. Barlow, M. H. Birkhäuser, M. Brincat, L. Cardozo, T. J. de Villiers, M. Gambacciani, A. A. Gompel, V. W. Henderson, C. Kluft, R. A. Lobo, A. H. MacLennan, J. Marsden, R. E. Nappi, N. Panay, J. H. Pickar, D. Robinson, J. Simon, R. L. Sitruk-Ware and J. C. Stevenson.

Suggested Reading

General

Evenson KR, Wilcox S, Pettinger M, *et al*. Vigorous leisure activity through women's adult life: the Women's Health Initiative observational cohort study. *Am J Epidemiol* 2002;156:945–53

Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progesterone in healthy postmenopausal women. *JAMA* 2002;288:321–33

Anderson GL, Judd HL, Kaunitz AM, *et al.* for the Women's Health Initiative Investigators. Effects of estrogen plus progestin on gynecologic cancers and associated diagnostic procedures. *JAMA* 2003;290:1739–48

Million Women Study Collaborators. Breast cancer and hormone replacement therapy in the Million Women Study. *Lancet* 2003; 362:419–27

Asikainen TM, Kukkonen-Harjula K, Miilunpalo S. Exercise for health for early postmenopausal women. A systematic review of randomised controlled trials. *Sports Med* 2004;34:753–78

Harman SM, Brinton EA, Cedars M, Lobo R, *et al*. The Kronos Early Estrogen Prevention Study. An ongoing trial of the effects of early initiation of HRT on coronary artery disease. *Climacteric* 2005;8:3–12

Center for Media and Public Affairs; commissioned by the Hormone Foundation. Analysis of media coverage of hormone therapy for menopause management: 2002 through 2007. http://www.hormone.org/Menopause/upload/media-analysis-081309.pdf

Dubnov-Raz G, Pines A, Berry EM. Diet and lifestyle in managing postmenopausal obesity. *Climacteric* 2007;10(Suppl 2):38–41

Haskell WI, Lee IM, Pate RR, *et al*. Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. *Circulation* 2007;116:1081–93

Vickers MR, MacLennan AH, Lawton B, *et al*. Main morbidities recorded in the Women's International Study of long Duration Oestrogen after Menopause (WISDOM): a randomised controlled trial of hormone replacement therapy in postmenopausal women. BMJ 2007; doi:10.1136/bmj.39266.425069.AD http://www.bmj.com/cgi/content/full/bmj.39266.425069.AD. Abridged print version *BMJ* 2007;335:239–44

Assessment and Management of Cardiovascular Risks in Women; a Short Guide for Menopause Physicians. Worthing, UK: Cambridge Medical Publications, 2008. Available for free download on the IMS website (www.imsociety.org)

Kenfield SA, Stampfer MJ, Rosner BA, Colditz GA. Smoking and smoking cessation in relation to mortality in women. *JAMA* 2008;299:2037–44

Moayyeri A. The association between physical activity and osteoporotic fractures: a review of the evidence and implications for future research. *Ann Epidemiol* 2008;18:827–35

Welton AJ, Vickers MR, Kim J, *et al*. Health related quality of life after combined hormone replacement therapy: randomised controlled trial. *BMJ* 2008;337:a1190.doi:10.1136/bmj.a1190

Aging, menopause, cardiovascular disease and HRT. Proceedings of the 8th IMS workshop. *Climacteric* 2009;12(Suppl 1)

Eliassen AH, Hankinson SE, Rosner B, *et al*. Physical activity and risk of breast cancer among postmenopausal women. *Arch Intern Med* 2010;170:1758–64

Friedenreich CM, Neilson HK, Lynch BM. State of the epidemiological evidence on physical activity and cancer prevention. *Eur J Cancer* 2010;46:2593–604

Baer HJ, Glynn RJ, Hu FB, *et al*. Risk factors for mortality in the Nurses' Health Study: a competing risks analysis. *Am J Epidemiol* 2011;173:319–29

Burger HG, MacLennan AH, Huang KE, Castelo-Branco C. Evidence-based assessment of the impact of the WHI on women's health. *Climacteric* 2012;15:281–7

Langer RD, Manson JE, Allison MA. Have we come full circle – or moved forward? The Women's Health Initiative 10 years on. *Climacteric* 2012;15:206–12

Pines A, Sturdee DW, Maclennan AH. Quality of life and the role of menopausal hormone therapy. *Climacteric* 2012;15:213–16

Purbrick B, Stranks K, Sum C, MacLennan AH. Future long-term trials of postmenopausal hormone replacement therapy – what is possible and what is the optimal protocol and regimen? *Climacteric* 2012;15:288–93

de Villiers TJ, Gass ML, Haines CJ, *et al*. Global Consensus Statement on Menopausal Hormone Therapy. *Climacteric* 2013;16:203–4

Panay N, Fenton A. A global consensus statement on menopause hormone therapy – aims, aspirations and action points. *Climacteric* 2013;16:201–2

Hormones and breast cancer

Million Women Study Collaborators. Breast cancer and HRT in the Million Women Study. *Lancet* 2003;362:419–27

Chen WY, Manson JE, Hankinson SE, *et al*. Unopposed estrogen therapy and the risk of invasive breast cancer. *Arch Intern Med* 2006;166:1027–32

Stefanick ML, Anderson GL, Margolis KL, *et al*. Effects of conjugated equine estrogens on breast cancer and mammography screening in postmenopausal women with hysterectomy. *JAMA* 2006;295: 1647–57

Fournier A, Fabre A, Mesrine S, *et al*. Use of different postmenopausal hormone therapies and risk of histology- and hormone receptor-defined invasive breast cancer. *Int J Cancer* 2008;26:1260–8

Fournier A, Mesrine S, Boutron-Ruault MC, Clavel-Chapelon F. Estrogen-progestagen menopausal hormone therapy and breast cancer: does delay from menopause onset to treatment initiation influence risks? *J Clin Oncol* 2009;27:5138–3

Lyytinen H, Pukkala E, Ylikorkala O. Breast cancer risk in postmenopausal women using estradiol–progestogen therapy. *Obstet Gynecol* 2009;113:65–73

Chlebowski RT, Anderson GL, Gass M, *et al*. Estrogen plus progestin and breast cancer incidence and mortality in postmenopausal women. *JAMA* 2010;304:1684–92

Gompel A, Plu-Bureau G. Is the decrease in breast cancer incidence related to a decrease in postmenopausal hormone therapy? *Ann NY Acad Sci* 2010;1205:268–76

Kerlikowske K, Cook AJ, Buist DS, *et al*. Breast cancer risk by breast density, menopause, and postmenopausal hormone therapy use. *J Clin Oncol* 2010;28:3830–7

Bakken K, Fournier A, Lund E, *et al*. Menopausal hormone therapy and breast cancer risk: impact of different treatments. The European Prospective Investigation into Cancer and Nutrition. *Int J Cancer* 2011;128:144–56

Anderson GL, Chlebowski RT, Aragaki AK, *et al*. Conjugated equine oestrogen and breast cancer incidence and mortality in postmenopausal women with hysterectomy: extended follow-up of the Women's Health Initiative randomised placebo-controlled trial. *Lancet Oncol* 2012;13:476–86

Crandall CJ, Aragaki AK, Cauley JA, *et al*. Breast tenderness and breast cancer risk in the estrogen plus progestin and estrogen-alone Women's Health Initiative clinical trials. *Breast Cancer Res Treat* 2012;132:275–85

Gompel A, Santen RJ. Hormone therapy and breast cancer risk 10 years after the WHI. *Climacteric* 2012;15:241–9

Nichols HB, Trentham-Dietz A, Newcomb PA, *et al*. Postoophorectomy estrogen use and breast cancer risk. *Obstet Gynecol* 2012;120:27–36

Ritte R, Lukanova A, Berrino F, *et al*. Adiposity, hormone replacement therapy use and breast cancer risk by age and hormone receptor status: a large prospective cohort study. *Breast Cancer Res* 2012;14:R76

Shapiro S, Farmer RD, Stevenson JC, Burger H, Mueck AO. Does hormone replacement therapy cause breast cancer? An application of causal principles to three studies. 4: The Million Women Study. *J Fam Plann Reprod Health Care* 2012;38:102–9

Ovarian, lung and other cancers

Grodstein F, Newcomb P, Stampfer M. Postmenopausal hormone therapy and the risk of colorectal cancer: a review and meta-analysis. *Am J Med* 1999;106:574–82

Ritenbaugh C, Stanford J, Wu L, *et al*. Conjugated equine estrogens and colorectal cancer incidence and survival: the Women's Health Initiative randomized clinical trial. *Cancer Epidemiol Biomarkers Prev* 2008;17:2609–18

Marsden J, Sturdee D. Cancer issues. *Best Pract Res Clin Obstet Gynaecol* 2009;23:87–107

Morch L, Lokkegaard E, Andreasen A, *et al*. Hormone therapy and ovarian cancer. *JAMA* 2009;302:298–305

Chlebowski R, Anderson G, Manson J, *et al*. Lung cancer among postmenopausal women treated with estrogen alone in the Women's Health Initiative randomized trial. *J Natl Cancer Inst* 2010; 102:1413–21

Delellis Henderson K, Duan L, Sullivan-Halley J, *et al*. Menopausal hormone therapy use and risk of invasive colon cancer: the California Teachers Study. *Am J Epidemiol* 2010;171:415–25

Freedman ND, Lacey JV Jr, Hollenbeck AR, *et al*. The association of menstrual and reproductive factors with upper gastrointestinal tract cancers in the NIH-AARP cohort. *Cancer* 2010;116:1572–81

Barnes EL, Long MD.Colorectal cancer in women: hormone replacement therapy and chemoprevention. *Climacteric* 2012;15:250–5

Gender-specific characteristics of cardiovascular disease in women

Stramba-Badiale M, Fox KM, Priori SG, *et al*. Cardiovascular diseases in women: a statement from the policy conference of the European Society of Cardiology. *Eur Heart J* 2006;27:994–1005

Collins P, Rosano G, Casey C, *et al*. Management of cardiovascular risk in the perimenopausal women: a consensus statement of European cardiologists and gynecologists. *Climacteric* 2007;10: 508–26

Executive Writing Committee, Mosca L, Benjamin EJ, Berra K, *et al*. Effectiveness-based guidelines for the prevention of cardiovascular disease in women – 2011 Update: A guideline from the American Heart Association. *Circulation* 2011;123:1243–62

Postmenopausal hormones and coronary artery disease

Hulley S, Grady D, Bush T, *et al*. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. *JAMA* 1998;280:605–13

Hsia J, Langer RD, Manson JE, *et al*. Conjugated equine estrogens and coronary heart disease: the Women's Health Initiative. *Arch Intern Med* 2006;166:357–65

Grodstein F, Manson JE, Stampfer MJ. Hormone therapy and coronary heart disease: the role of time since menopause and age at hormone initiation. *J Women's Health* 2006;15:35–44

Prentice RL, Langer RD, Stefanick ML, *et al*. Combined analysis of Women's Health Initiative observational and clinical trial data on postmenopausal hormone treatment and cardiovascular disease. *Am J Epidemiol* 2006;163:589–99

Salpeter SR, Walsh JM, Greyber E, Salpeter EE. Coronary heart disease events associated with hormone therapy in younger and older women. A meta-analysis. *J Gen Intern Med* 2006;21:363–6

Rossouw JE, Prentice RL, Manson JE, *et al*. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. *JAMA* 2007;297:1465–77

Salpeter SR, Cheng J, Thabane L, Buckley NS, Salpeter EE. Bayesian meta-analysis of hormone therapy and mortality in younger women. *Ann Intern Med* 2009;122:1016–22

Stevenson JC, Hodis HN, Pickar JH, Lobo RA. Coronary heart disease and menopause management: the swinging pendulum of HRT. *Atherosclerosis* 2009;207:336–40

Toh S, Hernández-Días S, Logan R, Rossouw JE, Hernán MA. Coronary heart disease in postmenopausal recipients of estrogen plus progestin therapy: does the increased risk ever disappear? A randomized trial. *Ann Intern Med* 2010;152:211–17

Hodis HN, Collins P, Mack WJ, Schierbeck LL. The timing hypothesis for coronary heart disease prevention with hormone therapy: past, present and future in perspective. *Climacteric* 2012;15:217–28

Coagulation

Renoux C, Dell'Aniello S, Suissa S. Hormone replacement therapy and the risk of venous thromboembolism: a population-based study. *J Thromb Haemost* 2010;8:979–86

Speroff L. Transdermal hormone therapy and the risk of stroke and venous thrombosis. *Climacteric* 2010;13:429–32
Olie V, Plu-Bureau G, Conard J, *et al*. Hormone therapy and recurrence of venous thromboembolism among postmenopausal women. *Menopause* 2011;18:488–93
Archer DF, Oger E. Estrogen and progestogen effect on venous thromboembolism in menopausal women. *Climacteric* 2012; 15:235–40

Stroke

Viscoli CM, Brass LM, Kernan WN, *et al*. A clinical trial of estrogen-replacement therapy after ischemic stroke. *N Engl J Med* 2001; 345:1243–9
Wassertheil-Smoller S, Hendrix S, Limacher M, *et al*. Effect of estrogen plus progestin on stroke in postmenopausal women: the Women's Health Initiative: a randomized trial. *JAMA* 2003; 289:2673–84
Bath PM, Gray LJ. Association between hormone replacement therapy and subsequent stroke: a meta-analysis. *BMJ* 2005;330:342
Arana A, Varas C, Gonzalez-Perez A, *et al*. Hormone therapy and cerebrovascular events: a population-based nested case-control study. *Menopause* 2006;13:1–7
Hendrix SL, Wassertheil-Smoller S, Johnson KC, *et al*. Effects of conjugated equine estrogen on stroke in the Women's Health Initiative. *Circulation* 2006;113:2425–34
Grodstein F, Manson JE, Stampfer MJ, Rexrode K. Postmenopausal hormone therapy and stroke: role of time since menopause and age at initiation of hormone therapy. *Arch Intern Med* 2008; 168:861–6
Renoux C, Dell'aniello S, Garbe E, Suissa S. Transdermal and oral hormone replacement therapy and the risk of stroke: a nested case-control study. *BMJ* 2010;340:c2519
Lobo RA, Clarkson TB. Different mechanisms for benefit and risk of coronary heart disease and stroke in early postmenopausal women: a hypothetical explanation. *Menopause* 2011;18:237–40
Henderson VW, Lobo RA. Hormone therapy and the risk of stroke: perspectives 10 years after the Women's Health Initiative trials. *Climacteric* 2012;15:229–34

Other neurological disorders

Harden CL, Herzog AG, Nikolov BG, *et al*. Hormone replacement therapy in women with epilepsy: a randomized, double-blind, placebo-controlled study. *Epilepsia* 2006;47:1447–51
Freeman EW, Sammel MD, Lin H, Gracia CR, Kapoor S. Symptoms in the menopausal transition: hormone and behavioral correlates. *Obstet Gynecol* 2008;111:127–36
MacGregor EA. Estrogen replacement and migraine. *Maturitas* 2009;63:51–5
Simon KC, Chen H, Gao X, Schwarzschild MA, Ascherio A. Reproductive factors, exogenous estrogen use, and risk of Parkinson's disease. *Mov Disord* 2009;24:1359–65
El-Etr M, Ghoumari A, Sitruk-Ware R, Schumacher M. Hormonal influences in multiple sclerosis: new therapeutic benefits for steroids. *Maturitas* 2011;68:47–51

Cognition and cognitive aging

Resnick SM, Maki PM, Rapp SR, *et al*. Effects of combination estrogen plus progestin hormone treatment on cognition and affect. *J Clin Endocrinol Metab* 2006;91:1802–10
Maki PM, Gast MJ, Vieweg A, Burriss SW, Yaffe K. Hormone therapy in menopausal women with cognitive complaints: a randomized, double-blind trial. *Neurology* 2007;69:1322–30
Lethaby A, Hogervorst E, Richards M, Yesufu A, Yaffe K. Hormone replacement therapy for cognitive function in postmenopausal women. *Cochrane Database Syst Rev* 2008;1:CD003122
Greendale GA, Huang M-H, Wight RG, *et al*. Effects of the menopause transition and hormone use on cognitive performance in midlife women. *Neurology* 2009;72:1850–7
Resnick SM, Espeland MA, An Y, *et al*. Effects of conjugated equine estrogens on cognition and affect in postmenopausal women with prior hysterectomy. *J Clin Endocrinol Metab* 2009;94:4152–61
Henderson VW. Action of estrogens in the aging brain: dementia and cognitive aging. *Biochim Biophys Acta* 2010;1800:1077–83
Henderson VW. Gonadal hormones and cognitive aging: a midlife perspective. *Womens Health (Lond Engl)* 2011;7:81–93
Maki PM, Henderson VW. Hormone therapy, dementia, and cognition: the Women's Health Initiative 10 years on. *Climacteric* 2012;15:256–62

Alzheimer's disease and other dementing disorders

Mulnard RA, Cotman CW, Kawas C, *et al*. Estrogen replacement therapy for treatment of mild to moderate Alzheimer disease: a randomized controlled trial. *JAMA* 2000;283:1007–15
Shumaker SA, Legault C, Kuller L, *et al*. Conjugated equine estrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women: Women's Health Initiative Memory Study. *JAMA* 2004;291:2947–58
Henderson VW, Benke KS, Green RC, Cupples LA, Farrer LA. Postmenopausal hormone therapy and Alzheimer's disease risk: interaction with age. *J Neurol Neurosurg Psychiatry* 2005;76:103–5
Hogervorst E, Yaffe K, Richards M, Huppert FA. Hormone replacement therapy to maintain cognitive function in women with dementia. *Cochrane Database of Syst Rev* 2009;1:CD003799
Whitmer RA, Quesenberry CP, Zhou J, Yaffe K. Timing of hormone therapy and dementia: The critical window theory revisited. *Ann Neurol* 2011;69:163–9
Henderson VW. Action of estrogens in the aging brain: dementia and cognitive aging. *Biochim Biophys Acta* 2010;1800:1077–83
Wharton W, Baker LD, Gleason CE, *et al*. Short-term hormone therapy with transdermal estradiol improves cognition for postmenopausal women with Alzheimer's disease: results of a randomized controlled trial. *J Alzheimers Dis* 2011;26:495–505
Shao H, Breitner JCS, Whitmer RA, *et al*. Hormone therapy and AD dementia: new findings from the Cache County study. *Neurology* 2012;79:1846–52

Depression

Schmidt PJ, Haq N, Rubinow DR. A longitudinal evaluation of the relationship between reproductive status and mood in perimenopausal women. *Am J Psychiatry* 2004;161:2238–44
Freeman EW, Sammel MD, Lin H, Nelson DB. Associations of hormones and menopausal status with depressed mood in women with no history of depression. *Arch Gen Psychiatry* 2006;63:375–82
Ryan J, Burger HG, Szoeke C, *et al*. A prospective study of the association between endogenous hormones and depressive symptoms in postmenopausal women. *Menopause* 2009;6:509–17
Bromberger JT, Schott LL, Kravitz HM, *et al*. Longitudinal change in reproductive hormones and depressive symptoms across the menopausal transition: results from the Study of Women's Health

Across the Nation (SWAN). *Arch Gen Psychiatry* 2010;67: 598–607
Maki PM, Freeman EW, Greendale GA, *et al*. Summary of the National Institute on Aging-sponsored conference on depressive symptoms and cognitive complaints in the menopausal transition. *Menopause* 2010;17:815–22
Soares CN, Frey BN. Is there a role for estrogen in treating depression during menopause? *J Psychiatry Neurosci* 2010;35:E6–7
Studd J, Nappi RE. Reproductive depression. *Gynecol Endocrinol* 2012;28(Suppl 1):42–5
Yalamanchili V, Gallagher JC. Treatment with hormone therapy and calcitriol did not affect depression in older postmenopausal women: no interaction with estrogen and vitamin D receptor genotype polymorphisms. *Menopause* 2012;19:697–703

Osteoporosis

General

Genazzani AR, Gambacciani M, Schneider HP, Christiansen C; International Menopause Society Expert Workshop. Postmenopausal osteoporosis: therapeutic options. *Climacteric* 2005;8: 99–109
Lewiecki EM. Current and emerging pharmacologic therapies for the management of postmenopausal osteoporosis. *J Womens Health (Larchmt)* 2009;18:1615–26
Lyritis GP, Georgoulas T, Zafeiris CP. Bone anabolic versus bone anticatabolic treatment of postmenopausal osteoporosis. *Ann NY Acad Sci* 2010;1205:277–83
Management of osteoporosis in postmenopausal women: 2010 position statement of The North American Menopause Society. *Menopause* 2010;17:25–54
Trémollières FA, Pouillès JM, Drewniak N, *et al*. Fracture risk prediction using BMD and clinical risk factors in early postmenopausal women: sensitivity of the WHO FRAX tool. *J Bone Miner Res* 2010;25:1002–9
Gallagher JC, Levine JP. Preventing osteoporosis in symptomatic postmenopausal women. *Menopause* 2011;18:109–18

MHT

Cauley JA, Robbins J, Chen Z, *et al*. Effects of estrogen plus progestin on risk of fracture and bone mineral density: the Women's Health Initiative randomized trial. *JAMA* 2003;290:1729–38
Anderson GL, Limacher M, Assaf AR, *et al*. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA* 2004;291:1701–12
Bagger YZ, Tanko LB, Alexandersen P, *et al*. Two to three years of hormone replacement therapy in healthy women have long-term prevention effects on bone mass and osteoporotic fractures: the PERF study. *Bone* 2004;34:728–31
Lindsay R,Gallagher JC, Kleerekoper M, *et al*. Bone response to treatment with lower dosages of conjugated estrogens with and without medroxyprogesterone acetate in early postmenopausal women. *Osteoporos Int* 2005;4:372–9
Stevenson JC; International Consensus Group on HRT and Regulatory Issues. HRT, osteoporosis and regulatory authorities Quis custodiet ipsos custodes? *Hum Reprod* 2006;21:1668–71
Cummings SR, Ettinger B, Delmas PD, *et al*. for the LIFT Trial Investigators. The effects of tibolone in older postmenopausal women. *N Engl J Med* 2008;359:697–708
Lindsay R, Gallagher JC, Kagan R, *et al*. Efficacy of tissue-selective estrogen complex of bazedoxifene/conjugated estrogens for osteoporosis prevention in at-risk postmenopausal women. *Fertil Steril* 2009;92:1045–52
de Villiers TJ, Stevenson JC. The WHI: the effect of hormone replacement therapy on fracture prevention. *Climacteric* 2012;15:263–6

Calcium and vitamin D

Jackson RD, LaCroix AZ, Gass M, *et al*. Calcium plus vitamin D supplementation and the risk of fractures. *N Engl J Med* 2006; 354:669–83
Boonen S, Lips P, Bouillon R, *et al*. Need for additional calcium to reduce the risk of hip fracture with vitamin D supplementation: evidence from a comparative meta-analysis of randomized controlled trials. *J Clin Endocrinol Metab* 2007;92: 1415–23
Rizzoli R, Boonen S, Brandi ML, *et al*. The role of calcium and vitamin D in the management of osteoporosis. *Bone* 2008;42: 246–9
Bischoff-Ferrari HA, Dawson-Hughes B, Staehelin HB, *et al*. Fall prevention with supplemental and active forms of vitamin D: a meta-analysis of randomised controlled trials. *Br Med J* 2009; 339:b3692
Bolland MJ, Avenell A, Baron JA, *et al*. Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis. *BMJ* 2010;341:c3691
The DIPART (vitamin D Individual Patient Analysis of Randomized Trials) Group. Patient level pooled analysis of 68500 patients from seven major vitamin D fracture trials in US and Europe. *BMJ* 2010;340:b5463

SERMs

Delmas PD, Ensrud KE, Adachi JD, *et al*. Efficacy of raloxifene on vertebral fracture risk reduction in postmenopausal women with osteoporosis: four-year results from a randomized clinical trial. *J Clin Endocrinol Metab* 2002;87:3609–17
Ensrud KE, Stock JL, Barrett-Connor E, *et al*. Effects of raloxifene on fracture risk in postmenopausal women: the Raloxifene Use for the Heart Trial. *J Bone Miner Res* 2008;23:112–20
Silverman SL, Christiansen C, Genant HK, *et al*. Efficacy of bazedoxifene in reducing new vertebral fracture risk in postmenopausal women with osteoporosis: results from a 3-year, randomized, placebo-, and active-controlled clinical trial. *J Bone Miner Res* 2008;23:1923–34
Goldstein SR, Duvernoy CS, Calaf J, *et al*. Raloxifene use in clinical practice: efficacy and safety. *Menopause* 2009;16:413–21

Denosumab

Cummings SR, Martin S, McClung MR, *et al*. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. *N Engl J Med* 2009;361:756–65

Skin, joints and cartilage

Cirillo DJ, Wallace RB, Wu L, Yood RA. Effect of hormone therapy on risk of hip and knee joint replacement in the Women's Health Initiative. *Arthritis Rheum* 2006;54:3194–204
Holinka CF, Christiansen C, Tian XW, Ausmanas MK. Ethnic differences in levels of bone and cartilage biomarkers and hormonal responsiveness in nine groups of postmenopausal Asian women: the Pan-Asia Menopause (PAM) study. *Climacteric* 2008;11: 44–54

Calleja-Agius J, Brincat MP. Effects of hormone replacement therapy on connective tissue: why is this important? *Best Pract Res Clin Obstet Gynaecol* 2009;23:121

Calleja-Agius J, Muscat-Baron Y, Brincat MP. Estrogens and the intervertebral disc. *Menopause Int* 2009;15:127–30

Pullerits R, d'Elia HF, Tarkowski A, Carlsten H. The decrease of soluble RAGE levels in rheumatoid arthritis patients following hormone replacement therapy is associated with increased bone mineral density and diminished bone/cartilage turnover: a randomized controlled trial. *Rheumatology (Oxford)* 2009;48:785–90

Sniekers YH, Weinans H, van Osch GJ, van Leeuwen JP. Oestrogen is important for maintenance of cartilage and subchondral bone in a murine model of knee osteoarthritis. *Arthritis Res Ther* 2010;12:R182

New hormonal products

Pinkerton JV, Utian WH, Constantine GD, Olivier S, Pickar JH. Relief of vasomotor symptoms with the tissue-selective estrogen complex containing bazedoxifene/conjugated estrogens: a randomized, controlled trial. *Menopause* 2009;16:1116–24

de Villiers TJ. Bazedoxifene: a novel selective estrogen receptor modulator for postmenopausal osteoporosis. *Climacteric* 2010;13:210–18

Portman DJ, Bachmann GA, Simon JA; the Ospemifene Study Group. Ospemifene, a novel selective estrogen receptor modulator for treating dyspareunia associated with postmenopausal vulvar and vaginal atrophy. *Menopause* 2013 Jan 28. Epub ahead of print

Postmenopausal vaginal atrophy

Suckling J, Kennedy R, Lethaby A, Roberts H. Local estrogen therapy for vaginal atrophy in post menopausal women. *Cochrane Database Syst Rev* 2006 Issue 4 CD 001500

Archer DF. Efficacy and tolerability of local estrogen therapy for urogenital atrophy. *Menopause* 2010;17:194–203

Sturdee DW, Panay N, on behalf of the IMS Writing Group. Recommendations for the management of postmenopausal vaginal atrophy. *Climacteric* 2010;13:509–22

Ulrich LS, Naessen T, Elia D, Goldstein JA, Eugster-Hausmann M. VAG-1748 trial investigators. Endometrial safety of ultra-low-dose Vagifem 10 μg in postmenopausal women with vaginal atrophy. *Climacteric* 2010;13:228–37

Labrie F, Archer DF, Bouchard C, *et al*. Intravaginal dehydroepiandrosterone (prasterone), a highly efficient treatment of dyspareunia. *Climacteric* 2011;14:282–8

Nappi RE, Kokot-Kierepa M. Vaginal Health: Insights, Views & Attitudes (VIVA) – results from an international survey. *Climacteric* 2012;15:36–44

So-called 'bioidentical' or 'natural' hormones

Boothby LA, Doering PL, Kipersztok S. Bioidentical hormone therapy: a review. *Menopause* 2004;11:356–67

Maclennan AH, Sturdee DW. The 'bioidentical/bioequivalent' hormone scam. *Climacteric* 2006;9:1–3

Fugh-Berman A, Bythrow J. Bioidentical hormones for menopausal hormone therapy: variation on a theme. *J Gen Intern Med* 2007;22:1030–4

Sites CK. Bioidentical hormones for menopausal therapy. *Womens Health (London Engl)* 2008;4:163–71

Non-hormonal therapy

Nedrow A, Miller J, Walker M, *et al*. Complementary and alternative therapies for the management of menopause-related symptoms: a systematic evidence review. *Arch Intern Med* 2006;166:1453–65

Nelson HD, Vesco KK, Haney E, *et al*. Nonhormonal therapies for menopausal hot flashes: systematic review and meta-analysis. *JAMA* 2006;295:2057–71

Sassarini J, Lumsden MA. Hot flushes: are there effective alternatives to estrogen? *Menopause Int* 2010;16:81–8

Endometrial safety and bleeding

Wiederpass E. Risk of endometrial cancer following estrogen replacement with and without progestins. *J Natl Cancer Inst* 1999;91:1131–7

Anderson GL, Judd HL, Kaunitz AM, *et al*. The effects of estrogen plus progestin on gynecologic cancers and associated diagnostic procedures: the Women's Health Initiative randomized trial. *JAMA* 2003:290:1739–48

Lethaby A, Suckling J, Barlow DH, *et al*. Hormone replacement therapy in postmenopausal women: endometrial hyperplasia and irregular bleeding. *Cochrane Database Syst Rev* 2004;3:CD000402

Million Women Study Collaborators. Endometrial cancer and hormone replacement therapy in the Million Women Study. *Lancet* 2005;365:1543–51

Langer RD, Landgren B-M, Rymer J, Helmond FA: OPAL investigators. Effects of tibolone and continuous combined conjugated equine estrogen/medroxyprogesterone acetate on the endometrium and vaginal bleeding: results of the OPAL study. *Am J Obstet Gynecol* 2006;195:1320–7

Sturdee DW, Archer DF, Rakov V, Lang E, on behalf of the CHOICE Investigators. Ultra-low-dose continuous combined estradiol and norethisterone acetate: improved bleeding profile in postmenopausal women. *Climacteric* 2008;11:63–73

Bednarek PH, Jenesn JT. Safety, efficacy and patient acceptability of the contraceptive and non-contraceptive uses of the LNG-IUS. *Int J Women Hlth* 2009;1:45–58

Chin J, Konje JC, Hickey M. Levonorgestrel intrauterine system for endometrial protection in women with breast cancer on adjuvant tamoxifen. *Cochrane Database Syst Rev* 2009;4:CD007245

Androgens

Zumoff B, Strain GW, Miller LK, Rosner W. Twenty-four hour mean plasma testosterone concentration declines with age in normal premenopausal women. *J Clin Endocrinol Metab* 1995;80:1429–30

Braunstein G, Shifren J, Simon J, Lucas J, Rodenberg C, Watts NB. Testosterone patches for the treatment of low sexual desire in surgically menopausal women. *Proceedings of the 14th Annual Meeting of the North American Menopause Society,* 2003

Goldstat R, Briganti E, Tran J, Wolfe R, Davis S. Transdermal testosterone improves mood, well being and sexual function in premenopausal women. *Menopause* 2003;10:390–8

Buster JE, Kingsberg SA, Aguirre O, *et al*. Testosterone patch for low sexual desire in surgically menopausal women: a randomized trial. *Obstet Gynecol* 2005;105:944–52

Davison SL, Bell R, Donath S, Montalto JG, Davis SR. Androgen levels in adult females: changes with age, menopause,

and oophorectomy. *J Clin Endocrinol Metab* 2005;90: 3847–53
Simon J, Braunstein G, Nachtigall L, *et al*. Testosterone patch increases sexual activity and desire in surgically menopausal women with hypoactive sexual desire disorder. *J Clin Endocrinol Metab* 2005; 90:5226–33
Warnock JK, Swanson SG, Borel RW, *et al*. for ESTRATEST Clinical Study Group. Combined esterified estrogens and methyltestosterone versus esterified estrogens alone in the treatment of loss of sexual interest in surgically menopausal women. *Menopause* 2005;12:374–84
Burger HG, Papalia M. A clinical update on female androgen insufficiency – testosterone testing and treatment in women presenting with low sexual desire. *Sexual Health* 2006;3:73–78
Shifren J, Davis SR, Moreau M, *et al*. Testosterone patch for the treatment of hypoactive sexual desire disorder in naturally menopausal women: results from the INTIMATE NM1 study. *Menopause* 2006;13:770–9
Davis SR, Moreau M, Kroll R, *et al*. Testosterone for low libido in menopausal women not taking estrogen therapy. *N Engl J Med* 2008;359:2005–17
Davis SR, Papalia MA, Norman RJ, *et al*. Safety and efficacy of a testosterone metered-dose transdermal spray for treatment of decreased sexual satisfaction in premenopausal women: a placebo-controlled randomized, dose-ranging study. *Ann Intern Med* 2008;148:569–77
Hirschberg AL, Rodenberg C, Pack S, *et al*., for the APHRODITE Study Team. Testosterone for low libido in postmenopausal women not taking estrogen. *N Engl J Med* 2008;359:2005–17
Perrone AM, Cerpolini S, Maria Salfi NC, *et al*. Effect of long-term testosterone administration on the endometrium of female-to-male (FtM) transsexuals. *J Sex Med* 2009;6:3193–200
Panay N, Al-Azzawi F, Bouchard C, *et al*. Testosterone treatment of HSDD in naturally menopausal women: the ADORE study. *Climacteric* 2010;13:121–31
Panjari N, Davis SR. DHEA for postmenopausal women: a review of the evidence. *Maturitas* 2010;66:172–9
Davis SR. Cardiovascular and cancer safety of testosterone in women. *Curr Opin Endocrinol Diabetes Obes* 2011;18:198–203
Davis SR, Panjari M, Stanczyk FZ. DHEA replacement for postmenopausal women. *J Clin Endocrinol Metab* 2011;96: 1642–53
Nachtigall L, Casson P, Lucas J, *et al*. Safety and tolerability of testosterone patch therapy up to 4 years in surgically menopausal women receiving oral or transdermal estrogen. *Gynecol Endocrinol* 2011;27:39–48
Panjari M, Davis SR. Vaginal DHEA to treat menopause related atrophy: a review of the evidence. *Maturitas* 2011;70:22–5

Urogynecology

Cardozo LD, Bachmann G, McClish D, *et al*. Meta-analysis of estrogen therapy in the management of urogenital atrophy in postmenopausal women: Second report of the Hormones and Urogenital Therapy Committee. *Obstet Gynecol* 1998;92: 722–7
Cardozo L, Lose G, McClish D, *et al*. A systematic review of estrogens for recurrent urinary tract infections: Third report of the Hormones and Urogenital Therapy Committee. *Int Urogynecol J Pelvic Floor Dysfunct* 2001;12:15–20
Hendrix SL, Cochrane BR, Nygaard IE, *et al*. Effects of estrogen with and without progestin on urinary incontinence. *JAMA* 2005; 293:935–48
Andersson KE, Chapple CR, Cardozo L, *et al*. Pharmacological treatment of urinary incontinence. In Abrams P, Cardozo L, Khoury S, Wein A, eds. *Incontinence*. Paris: Health Publications Ltd, 2009:633–99
Cody JD, Richardson K, Moehrer B, Hextall A, Glazener CMA. Oestrogen therapy for urinary incontinence in post-menopausal women. *Cochrane Database of Systematic Reviews* 2009, Issue 4. Art. No: CD001405

Attitudes to sexuality in the menopause

Genazzani AR, Gambacciani M, Simoncini T. Menopause and aging, quality of life and sexuality. IMS Statement following 6th IMS Workshop, Pisa, December 2006. *Climacteric* 2007;10:88–96
Hayes RD, Dennerstein L, Bennett CM, *et al*. Risk factors for female sexual dysfunction in the general population: exploring factors associated with low sexual function and sexual distress. *J Sex Med* 2008;5:1681–93
Nappi RE, Polatti F. The use of estrogen therapy in women's sexual function. *J Sex Med* 2009;6:603–16
Nappi RE, Davis SR. The use of hormone therapy for the maintenance of urogynecological and sexual health post WHI. *Climacteric* 2012;5:267–74

Influence of methodology and epidemiology on perception of HRT

Knobe J. Intentional action and side effects in ordinary language. *Analysis* 2003;63:190–3
Schwartz LM, Woloshin S. The media matter: a call for straightforward medical reporting. *Ann Intern Med* 2004;140:226–8
Kolata G. Health risk to older women is seen in hormone therapy. *The New York Times*, April 4, 2007
Specter M. *Denialism: How Irrational Thinking Hinders Scientific Progress, Harms the Planet, and Threatens Our Lives*. London: Duckworth Overlook Press, 2009
Bluming AZ, Tavris C. Hormone replacement therapy: real concerns and false alarms. *Cancer J* 2009;15:93–104
Brown S. Shock, terror and controversy: how the media reacted to the Women's Health Initiative. *Climacteric* 2012;15:275–80

Further reading

Special issue of *Climacteric*: The Women's Health Initiative – A decade of progress. June 2012;15:205–94

Recent recommendations by other societies

Gompel A, Rozenberg S, Barlow DH; EMAS board members. The EMAS 2008 update on clinical recommendations on postmenopausal hormone replacement therapy. *Maturitas* 2008;61: 227–32
Santen RJ, Allred DC, Ardoin SP, *et al*. Executive summary: Postmenopausal hormone therapy: an Endocrine Society scientific statement. *J Clin Endocrinol Metab* 2010;95(Suppl 1):s1–66
North American Menopause Society. The 2012 hormone therapy position statement of The North American Menopause Society. *Menopause* 2012;19:257–71