The 2013 British Menopause Society & Women's Heath Concern recommendations on hormone replacement therapy

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Menopause Int published online 23 May 2013
DOI: 10.1177/1754045313489645

Menopause Int OnlineFirst, published on May 23, 2013 as doi:10.1177/1754045313489645

BMS Meeting the challenge of menopause

Original Article

Menopause International: The Integrated Journal of Postreproductive Health
0(0) 1–10

DOI: 10.1177/1754045313489645
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Introduction

The British Menopause Society (BMS) recommendations on hormone replacement therapy (HRT) are designed to complement the BMS Observations and Recommendations on menopause management, submitted to the Department of Health in the UK and published in full in Menopause International, The Journal of the British Menopause Society and in the Royal College of Obstetricians and Gynaecologists Expert Advisory Group Report, High Quality Women's Health Care.

Our key recommendation is that all women should be able to access advice on how they can optimise their menopause transition and beyond, with particular reference to lifestyle and diet and an opportunity to discuss the pros and cons of complementary therapies and HRT.

The following information based on the latest available evidence can be used to provide guidance to prescribers of HRT and alternatives.

An extensive reference section and links to useful websites provide an opportunity to access extensive evidence based information in each key area.

Immediate effects of HRT

Vasomotor symptoms

One of the main indications for prescribing HRT in postmenopausal women is the relief of vasomotor symptoms. Estrogen remains the most effective treatment in this context.

A Cochrane systematic review summarised the results of 24 placebo-controlled randomised trials; this showed a clear beneficial effect with estrogen replacement compared to placebo.

The optimum dose and duration should be decided according to the severity of a woman's symptoms and her response to therapy.

Mood

Observational data suggest that the short-term use of HRT may improve mood and depressive symptoms during the menopausal transition and in the early menopause.

Women with severe depression and those who do not respond to HRT will require psychiatric assessment.

Sexual function

HRT, systemic or topical, may improve sexual function in women with dyspareunia secondary to vaginal atrophy, through its proliferative effect on the vulval and vaginal epithelium and by improving vaginal lubrication.

The administration of systemic testosterone has been shown to result in significant improvement in sexual function, including sexual desire, and orgasm.

The indications for androgen replacement therapy, and its advantages and disadvantages are discussed in more detail elsewhere in these recommendations.

Urogenital symptoms

Estrogen treatment has been shown to be effective in treating symptoms related to vaginal atrophy, such as vaginal dryness and superficial dyspareunia.

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It also has a proliferative effect on the bladder and urethral epithelium and may help relieve symptoms of urinary frequency, urgency and possibly reduce the risk of recurrent urinary tract infections in women with urogenital atrophy.

Low-dose vaginal estrogen preparations can be used long-term in symptomatic women as required, and all topical estrogen preparations have been shown to be effective in this context.

There is no requirement to combine this with systemic progestogen treatment for endometrial protection, as low-dose vaginal estrogen preparations do not result in significant systemic absorption.

However, there is little evidence to prove the safety of vaginal preparations beyond one year of use; clinicians should therefore aim to use the lowest effective dose for symptom control and counsel women regarding this.

Non-hormonal preparations and lubricants can be used as an alternative but these are not as effective as estrogen therapy.

Musculoskeletal effects

Estrogen deficiency after the menopause has been reported to have a negative effect on connective tissue metabolism in the bone matrix, skin, intervertebral discs and elsewhere in the body.

Observational data suggest that estrogen therapy has a protective effect against connective tissue loss and may possibly reverse this process in menopausal women receiving HRT.

Progestogens/side effects

Non hysterectomised women using estrogen therapy should use progestogen to avoid endometrial hyperplasia and carcinoma.

If the last menstrual period occurred less than one year prior to starting HRT, a sequential combined regimen should be started, i.e. continuous estrogen with progestogen for 12–14 days per month.

After *a minimum* of one year of HRT, or one year after the last menstrual period, (two years in premature ovarian insufficiency, POI), women who wish to avoid a monthly withdrawal bleed *may attempt* a switch to a continuous combined regimen which aims to give bleed free HRT – this will also minimise the risk of endometrial hyperplasia.

Alternatively, women can be switched to the tissue selective agent tibolone.

If breakthrough bleeding occurs following the switch to continuous combined HRT and does not settle after three to six months, then the woman can be switched back to a sequential regimen for at least another year.

If bleeding is heavy or erratic on a sequential regimen, the dose of progestogen can be doubled or duration increased to 21 days.

Persistent bleeding problems beyond six months warrant investigation with ultrasound scan and/or endometrial biopsy.

With both these regimens, there may be some erratic bleeding to begin with but 90% of those that persist with these regimens will eventually be completely bleed free.

If starting HRT de novo, a bleed-free regimen can be used from the outset if the last menstrual period was over a year ago.

One of the main factors for reduced compliance with HRT is that of progestogen intolerance.

Progestogens have a variety of effects apart from the one for which their use was intended, that of secretory transformation of the endometrium.

Symptoms of fluid retention are produced by the sodium retaining effect of the renin-aldosterone system, triggered by stimulation of the aldosterone receptors.

Androgenic side effects such as acne and hirsuitism are a problem of the testosterone derived progestogens due to stimulation of the androgen receptors.

Mood swings and PMS-like side effects result from adverse stimulation of the central nervous system progesterone receptors.

The dose can be halved and duration of progestogen can be reduced to seven to 10 days to minimise progestogenic side effects.

This may result in bleeding problems and hyperplasia, so there should be a low threshold for ultrasound scanning and endometrial sampling if clinically indicated.

Progesterone and dydrogesterone generally have less side effects due to progesterone receptor specificity.

Progesterone is available in an oral micronised form, vaginal pessaries and gel. Recent evidence suggests that HRT regimens containing progesterone can minimise the metabolic impact and reduce the risk of thromboembolism.

The levonorgestrel intrauterine system has a four-year license in the UK for progestogenic opposition of estrogen (five years in other countries). It minimises systemic progestogenic side effects by direct release of progestogen into the endometrium.

Drospirenone, a spironolactone analogue, has anti-androgenic and anti-mineralocorticoid properties. It has been incorporated with low-dose estrogen in a continuous combined formulation.

Long-term effects of HRT

Osteoporosis

HRT is effective in preserving bone density and preventing osteoporosis in both spine and hip, as well as reducing the risk of osteoporosis-related fractures.

HRT is the first-line therapeutic intervention for the prevention and treatment of osteoporosis in women with POI and menopausal women below 60 years, particularly those with menopausal symptoms.

Initiating HRT after the age of 60 years for the sole purpose of the prevention of osteoporotic fractures is not recommended.

The bone-protective effect of oestrogen is dose-related. Recent studies have shown a bone-preserving effect even with relatively low doses.

The bone preserving effect of HRT on bone mineral density declines after discontinuation of treatment.

Some studies have shown that the use of HRT for a few years around the menopause may provide a long-term protective effect many years after stopping HRT.

Bisphosphonates and other pharmacological agents can be used as an alternative to HRT to preserve bone density, but there can be side effects. Recent reports suggest that long-term therapy with alendronate can predispose to femoral shaft fragility fractures due to prolonged suppression of bone turnover.

Cardiovascular

Early cohort studies suggested that HRT was associated with a significant reduction in the incidence of heart disease, whether estrogen was prescribed alone or combined with progestogen.

In the WHI randomised controlled trial, women using conjugated equine estrogens (CEE) 0.625 mg alone or with medroxyprogesterone acetate (MPA) 2.5 mg had a small increase in incidence of coronary heart disease in the first 12 months.

'Early harm' can occur when therapy is commenced in women over 60 with relative overdoses of oral estrogen.

When prescribing HRT for the first time in women over the age of 60, the lowest effective dose should be used.

Randomised controlled data from the Danish Osteoporosis trial have shown that hormone therapy reduces the incidence of coronary heart disease by around 50% if commenced within 10 years of the menopause – this is referred to as the 'window of opportunity' for primary prevention.

The 'KEEPS' randomised controlled trial using lower doses of estradiol and progesterone in women less than three years from their last menstrual period reported neutral impact on cardiovascular risk markers such as coronary calcium scores and intima media thickness.

Cognition

Observational data show an improvement in cognitive function with HRT started in early menopause and a possible reduction in the long-term risk of Alzheimer's and all-cause dementia.

These observational findings have not been substantiated in adequately powered or long-term follow-up studies, and further evidence is needed to evaluate this.

Evidence from well-designed studies, including the WHI, shows no significant improvement in memory or cognitive function with HRT in older postmenopausal women, with a reported increase in the risk of dementia in women aged 65–79.

Based on current evidence, HRT should not be initiated for the sole purpose of improving cognitive function or reducing the risk of dementia in postmenopausal women.

Cancer

Breast cancer. In the WHI estrogen and progestogen study, a small increase in risk of breast cancer was detected after five years of usage of HRT of approximately 1 extra case per 1000 women per annum.

In the WHI estrogen-alone trial, a small but statistically significant decrease in breast cancer risk was detected.

The Million Women Study (MWS) raised concerns over the long-term safety of HRT from the perspective of breast cancer.

Recent critique of the WHI and MWS has clearly illustrated a number of key flaws which limit the ability of the trials to establish a causal association between HRT and breast cancer.

Ovarian cancer. Published data on the role of HRT and risk of ovarian cancer are conflicting.

Several case–control studies suggest a significant increase in risk associated with the use of estrogen replacement therapy and either a smaller or no increased risk with combined estrogen and progestogen therapy.

The WHI was the only randomised placebo-controlled trial which studied the incidence of ovarian cancer and HRT and concluded that there was no increased risk.

A recent report of data from the Danish National Cancer Registry revealed a small but significant increase in the incidence of ovarian cancer following

eight years use of unopposed estrogen and estrogen/progestogen therapy.

Endometrial cancer. Unopposed estrogen therapy increases the incidence of endometrial cancer; this risk is largely avoided by the use of combined sequential estrogen/progestogen therapy.

Long-term use of sequential combined HRT for more than five years may be associated with a small increase in risk of endometrial cancer.

Continuous combined regimens are associated with a significantly lower risk of endometrial cancer than an untreated population.

Colorectal cancer. Published data suggest a reduced risk of colorectal cancer with the use of oral combined HRT.

The WHI trial showed colorectal cancer risk was reduced in women taking combined CEE and MPA but there was no effect of CEE only therapy.

There are no data on the effect of transdermal HRT and risk of colorectal cancer.

HRT after cancer

Endometrial. Studies looking at the use of HRT following treatment for cancer have either shown no increased risk of recurrence or a reduced recurrence rate with an increased disease-free interval.

Most of these studies have been on early stage disease and the findings may be different in advanced cancer where there may be microscopic metastatic deposits.

Local endometrial sarcomas are estrogen sensitive and should be considered a contraindication to HRT.

Ovarian cancer. There is no evidence that estrogen therapy following treatment for ovarian cancer will adversely affect the prognosis.

Studies have either shown no difference in survival rate or an improvement in survival rate with the use of HRT in women with epithelial ovarian cancer.

There is no evidence of an adverse effect of HRT on women with germ cell tumours.

There are no data on the use of HRT following granulosa cell tumours though HRT should be avoided in this situation largely on theoretical grounds.

Ongoing hormone receptor studies on ovarian cancers may help to predict risk of recurrence.

Cervical. While there is a known association between the oral contraceptive use and cervical cancer, there is no association between cervical cancer and HRT.

HRT is not contraindicated after treatment for squamous cell carcinoma of the cervix or adenocarcinoma of the cervix.

Vulval. Systemic and topical estrogen can be used following vulval carcinoma. There is no evidence of an adverse effect with regard to recurrence of vulval disease.

Venous thromboembolism (VTE) and HRT

Oral HRT increases the risk of VTE two- to four-fold, with the highest risk in the first year of use.

VTE risk is further increased in those with a personal or family history of VTE, advanced age, obesity and other risk factors such as surgery or hospitalisation.

The VTE risk is associated with oral rather than transdermal estrogen administration and there is increasing evidence that risk is greater in combination with certain progestogens such as norpregnane derivatives and medroxyprogesterone acetate.

Individuals requiring HRT should be risk assessed and counselled regarding their VTE risk.

Routine thrombophilia testing prior to commencement on HRT is not required but testing might be considered if there is a family history of thrombosis due to a known genetic defect.

In 'high-risk' individuals who require HRT, transdermal preparations should be used and if a progestogen is required, suitable options might include micronized progesterone or dydrogesterone.

Hospitalised users of HRT require review of their therapy and should receive thromboprophylaxis as appropriate.

Stroke

Observational studies on the use of HRT and stroke have yielded conflicting results.

The WHI study revealed an overall increased incidence of stoke in women using estrogen and progestogen therapy or estrogen alone.

Re-analysis of the combined data from the estrogen and progesterone study and that of the estrogen alone study revealed a smaller increase in incidence of stroke in women who commenced HRT between the ages of 50 and 59.

The HERS study (the Heart and Estrogen progestogen Replacement Study) found no increased incidence of stroke with HRT.

On current evidence, HRT cannot be recommended for the primary or secondary prevention of stroke.

Caution should be exercised when prescribing HRT in women over the age of 60 particularly when they

have a risk factor for stroke or thromboembolism. In these groups, current evidence would suggest that the transdermal route may be advantageous.

The effects of HRT may be dose related and the lowest effective dose should be prescribed in women with significant risk factors.

Premature Ovarian Insufficiency

Premature Ovarian Insufficiency (POI) has been estimated to affect about 1% of women younger than 40, 0.1% under 30 and 0.01% of women under the age of 20.

However, as cure rates of cancers in young women continue to improve, it is likely that the incidence of iatrogenic prematurely menopausal women will rise.

HRT is strongly recommended in these young women to control vasomotor symptoms, minimise risk of cardiovascular disease, osteoporosis, and possibly Alzheimers', as well as maintain sexual function.

The Women's Health Initiative study findings *do not* apply to this young group.

HRT in POI simply replaces ovarian hormones that should normally be produced at this age. It is of paramount importance that the patients understand this in view of recent media on HRT.

The aim is to replace hormones as close to physiological levels as possible.

Hormone therapy should generally continue at least until the estimated age of natural menopause (on average 51 years).

HRT is also important to preserve uterine function in women planning ovum donation.

The contraceptive pill can be used as an alternative to control symptoms but the there are few data on long-term benefits for protection against osteoporosis and cardiovascular disease.

It is well recognised that young women with premature menopause will potentially suffer from an excess of osteoporosis, cardiovascular disease and dementia if adequate hormonal support is not used.

There is an urgent need to precisely quantify the global scale of the problem, to standardised terminology and develop evidence-based guidelines from appropriate research, if we are to optimise the management of POI.

Routes and regimens

The transdermal (gels or patches) and the subcutaneous (implants) routes of estrogen administration avoid the first pass effect through the liver and are not associated with an increased risk of venous thrombosis.

The vaginal route of progestogen and progesterone administration, e.g. levonorgestrel system and progesterone gel and pessaries, provides adequate endometrial protection with reduced systemic side effects.

Non-hysterectomised women require 12–14 days of progestogen to avoid endometrial hyperplasia and minimise the risk of endometrial cancer with unopposed estrogen.

Progestogenic side effects may be reduced by using natural progesterone in the form of oral capsules, transvaginal pessaries or gels.

The levonorgestrel releasing intrauterine system (LNG IUS) provides adequate endometrial protection in women receiving estrogen therapy. Systemic side effects are reduced though not completely eliminated. The impact on breast cancer risk remains unclear with preliminary data from the Finnish cancer registry showing no significant difference when compared to systemic progestogens.

Continuous combined regimens avoid the need for regular withdrawal bleeds but may be associated with continuous low-grade progestogenic side effects.

Ultra low-dose estradiol/progestogen continuous combined regimens appear to maintain the benefits of higher dose regimens whilst allowing minimal use of progestogen to reduce side effects.

Unregulated compounded bio-identical hormones are not recommended due to lack of data for efficacy and safety.

Regulated 'body-identical' estradiol, progesterone and testosterone may have some advantages over non-identical varieties of HRT (e.g. ethinylyestradiol, synthetic progestogens).

In a large observational cohort study of French teachers, after five years of use estrogen–progesterone combination, HRT was found to be associated with a significantly lower relative risk (neutral for 'ever use' of HRT) than for other types of combined HRT (RR 1.7–2.0).

Further data from larger studies on major breast endpoints are required to confirm this effect.

Low-dose vaginal estrogenic creams, rings, tablets and pessaries should be considered for all women with symptoms of urogenital atrophy.

Local estrogenic preparations and may be more effective than systemic therapy and can be used in conjunction with oral/transdermal HRT.

Indefinite usage is usually required as symptoms often return when treatment is discontinued – progestogenic opposition is not required as systemic absorption is minimal with estradiol and estriol preparations.

Off label use of vaginal estrogen therapy can be considered in women with a history of hormone sensitive malignancy but the pros and cons of each case should be weighed up carefully with close collaboration with the oncology team.

Sexual function/androgens

While there is an age-related declining sexual function including libido, arousal, orgasm and satisfaction with age, there is a significant decline around the time of the menopause.

Women with distressing low sexual desire and tiredness should be counselled that androgen supplementation is an option.

There are few licensed female androgenic options available globally even though there are accumulating data for efficacy and safety.

Testosterone implants and patches have recently been withdrawn by pharmaceutical companies for commercial, not safety reasons.

Tibolone has a weak androgenic effect which can have a beneficial effect on mood and libido.

Testosterone gels licensed for male use are available in 50 mg, 5 mL sachets or tubes. Unlicensed prescribing by specialists is an option for female androgen replacement, at a reduced dosage of 0.5 to 1.0 mL/day or ¼ sachet/tube on alternate days.

Androgenic side effects and risks are minimal and reversible if testosterone levels are maintained within the female physiological range.

Some studies have shown benefits on the skeleton, cognition, well-being and the vagina; these data require confirmation.

Other options such as DHEA require further research to confirm efficacy and safety.

Lifestyle/alternatives to HRT

Optimisation of diet and lifestyle should be incorporated into the routine management of all women in the menopause transition and beyond.

Vaginal bioadhesive moisturisers are a more physiological way of replacing vaginal secretions than vaginal gels such as KY. They are hydrophilic and rehydrate vaginal tissues, providing a reasonable alternative to vaginal estrogen.

Pharmacological alternatives

A recent meta-analysis of a few randomised controlled trials has shown a marginal benefit of clonidine over placebo.

A significant amount of evidence exists for the efficacy of SSRI's such as fluoxetine and paroxetine in treating vasomotor symptoms; the most convincing data are for the SNRI (venlafaxine) at a dose of 37.5 mg bd in cancer survivors. The most common side effect, nausea, limits the usefulness of this agent.

Recent work with the anti-epileptic drug Gabapentin has shown efficacy for hot flush reduction compared to placebo. Its use is limited by side effects such as drowsiness and somnolence, particularly at high doses. A stepwise increase in dosage by 300 mg per week up to a maximum of 1.2 g is advised to try to minimise side effects.

Phytoestrogens

Data from some of the better researched phytoestrogen containing preparations appear to demonstrate some benefits, not only for symptom relief, but also on the skeleton and cardiovascular system.

Efficacy for vasomotor symptom relief is lower than with traditional HRT (maximally 60% symptom reduction compared to 90–100% with traditional HRT).

There are as yet no hard data on major outcome measures such as coronary heart disease and fractures.

Key points

The decision whether to use HRT should be made by each woman having been given sufficient information by her health professional to make a fully informed choice.

The HRT dosage, regimen and duration should be individualised, with annual evaluation of pros and cons.

Arbitrary limits should not be placed on the duration of usage of HRT; if symptoms persist, the benefits of hormone therapy usually outweigh the risks.

HRT prescribed before the age of 60 has a favourable benefit/risk profile.

It is imperative that women with POI are encouraged to use HRT at least until the average age of the menopause.

If HRT is to be used in women over 60 years of age, lower doses should be started, preferably with a transdermal route of administration.

It is imperative that in our ageing population research and development of increasingly sophisticated hormonal preparations should continue to maximise benefits and minimise side effects and risks.

This will optimise quality of life and facilitate the primary prevention of long-term conditions which create a personal, social and economic burden.

References

Introduction

British Menopause Society Council. Modernizing the NHS: observations and recommendations from the British Menopause Society. *Menopause Int* 2011; 17: 41–43.

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.
Cumming GP, Currie HD, Panay N, et al. Stopping hormone replacement therapy: were women ill advised? *Menopause Int* 2011; 17: 82–87.
The Royal College of Obstetricians and Gynaecologists. *High Quality Women's Health Care: a proposal for change*. London: RCOG Press, 2011.

Immediate Effects of HRT

Vasomotor symptoms

MacLennan AH, Broadbent JL, Lester S, et al. Oral oestrogen and combined oestrogen/progestogen therapy versus placebo for hot flushes. *Cochrane Database Syst Rev* 2004; 4: CD002978.
de Villiers TJ, Pines A, Panay N, on behalf of the International Menopause Society. Updated 2013 International Menopause Society Recommendations on menopausal hormone therapy and preventive strategies for midlife health. *Climacteric* 2013; 16: 316–337.

Mood

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: 815–822.
Rocca W, Bower J, Maraganore DM, et al. Increased risk of cognitive impairment or dementia in women who underwent oophorectomy before menopause. *Neurology* 2007; 69: 1074–1083.
Studd JWW. A guide to the treatment of depression in women by estrogens. *Climacteric* 2011; 14: 637–642.

Sexual function/urogenital symptoms

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.
Cody JD, Richardson K, Moehrer B, et al. Oestrogen therapy for urinary incontinence in post-menopausal women. *Cochrane Database Syst Rev* 2009; 4: CD001405.
Sturdee DW and Panay N; on behalf of the IMS Writing Group. Recommendations for the management of postmenopausal vaginal atrophy. *Climacteric* 2010; 13: 509–522.
Suckling J, Kennedy R, Lethaby A, et al. Local estrogen therapy for vaginal atrophy in post menopausal women. *Cochrane Database Syst Rev* 2006; 4: CD001500.

Musculo-skeletal effects

Calleja-Agius J, Muscat-Baron Y and Brincat MP. Estrogens and the intervertebral disc. *Menopause Int* 2009; 15: 127–130.
Calleja-Agius J and Brincat MP. Effects of hormone replacement therapy on connective tissue: why is this important? *Best Pract Res Clin Obstet Gynaecol* 2009; 23: 121.

Side effects of HRT

Bednarek PH and Jenesn JT. Safety, efficacy and patient acceptability of the contraceptive and non-contraceptive uses of the LNG-IUS. *Int J Women Health* 2009; 1: 45–58.
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.
Panay N and Studd JWW. Progestogen intolerance and compliance with hormone replacement therapy in menopausal women. *Hum Reprod Upd* 1997; 3: 159–171.

Long-term effects

Osteoporosis

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: 1729–1738.
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: 728–731.
The FRAX® WHO fracture risk assessment tool, www.shef.ac.uk/FRAX (accessed 10 May 2013).
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: 372–379.
Stevenson JC; International Consensus Group on HRT and Regulatory Issues. HRT, osteoporosis and regulatory authorities Quis custodiet ipsos custodes? *Hum Reprod* 2006; 21: 1668–1671.

Cardiovascular

Harman SM, Brinton EA, Cedars M, et al. KEEPS: the Kronos early estrogen prevention study. *Climacteric* 2005; 8: 3–12.
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: 357–365.
Grodstein F, Manson JE and 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.
Kronos Longevity Research Institute. Hormone therapy has many favorable effects in newly menopausal women: initial findings of the Kronos Early Estrogen Prevention Study (KEEPS) [press release],

http://www.menopause.org/docs/agm/general-release.pdf?sfvrsn=0 (accessed 10 May 2013).
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: 1465–1477.
Salpeter S. Mortality associated with hormone replacement therapy in younger and older women. *J Gen Intern Med* 2006; 21: 401.
Schierbeck LL, Rejnmark L, Tofteng CL, et al. Effect of hormone replacement therapy on cardiovascular events in recently postmenopausal women: randomized trial. *BMJ* 2012; 345: e6409.
Stevenson JC, Hodis HN, Pickar JH, et al. Coronary heart disease and menopause management: the swinging pendulum of HRT. *Atherosclerosis* 2009; 207: 336–340.
Writing group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomised controlled trial. *JAMA* 2002; 288: 321–333.

Cognitive

Lethaby A, Hogervorst E, Richards M, et al. Hormone replacement therapy for cognitive function in postmenopausal women. *Cochrane Database Syst Rev* 2008; 1: CD003122.
Maki PM and Henderson VW. Hormone therapy, dementia, and cognition: the Women's Health Initiative 10 years on. *Climacteric* 2012; 15: 256–262.
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: 2947–2958.

Cancer

Collaborative Group on Hormonal factors in Breast Cancer. Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52 705 women with breast cancer and 108 411 women without breast cancer. *Lancet* 1997; 350: 1047–1059.
Lyytinen HK, Dyba T, Ylikorkala O, et al. A case-control study on hormone therapy as a risk factor for breast cancer in Finland: intrauterine system carries a risk as well. *Int J Cancer* 2010; 126: 483–489.
Million Women Study Collaborators. Breast cancer and HRT in the Million Women Study. *Lancet* 2003; 362: 419–427.
Morch LS, Lokkegaard E, Andreasen AH, et al. Hormone therapy and different ovarian cancers: a national cohort study. *Am J Epidemiol* 2012; 175: 1234–1242.
Panay N. Commentary regarding recent Million Women Study critique and subsequent publicity. *Menopause Int* 2012; 18: 33–35.
Ravdin PM, Cronin KA, Howlader N, et al. The decrease in incidence of breast cancer in the United States. *New Engl J Med* 2007; 356: 1670–1674.
Robbins AS and Clarke CA. Regional changes in hormone therapy use and breast cancer incidence in California from 2001 to 2004. *J Clin Oncol* 2007; 26: 3437–3439.
Shapiro S, Farmer RD, Mueck AO, et al. Does hormone replacement therapy cause breast cancer? An application of causal principles to three studies. Part 1. The Collaborative Reanalysis. *J Fam Plann Reprod Health Care* 2011; 37: 103–109.
Shapiro S, Farmer RD, Mueck AO, et al. Does hormone replacement therapy cause breast cancer? An application of causal principles to three studies: Part 2. The Women's Health Initiative: estrogen plus progestogen. *J Fam Plann Reprod Health Care* 2011; 37: 165–172.
Shapiro S, Farmer RD, Mueck AO, et al. Does hormone replacement therapy cause breast cancer? An application of causal principles to three studies: Part 3. The Women's Health Initiative: unopposed estrogen. *J Fam Plann Reprod Health Care* 2011; 37: 225–230.
Shapiro S, Farmer RD, Stevenson JC, et al. Does hormone replacement therapy cause breast cancer? An application of causal principles to three studies Part 4: The Million Women Study. *J Fam Plann Reprod Health Care* 2012; 38: 102–109.
Shapiro S, Farmer RD, Stevenson JC, et al. Does hormone replacement therapy (HRT) cause breast cancer? An application of causal principles to three studies: Part 5. Trends in breast cancer incidence in relation to the use of HRT. *J Fam Plann Reprod Health Care* 2013; 39: 80–88.

VTE

Canonico M, Plu-Bureau G, Lowe GD, et al. Hormone replacement therapy and risk of venous thromboembolism in postmenopausal women: systematic review and meta-analysis. *BMJ* 2008; 336: 1227–1231.
Scarabin PY, Oger E and Plu–Bureau G. Differential association of oral and transdermal oestrogen replacement therapy with venous thromboembolism risk. *Lancet* 2003; 362: 428–432.

Stroke

Grodstein F, Manson JE, Stampfer MJ, et al. Postmenopausal hormone therapy and stroke: role of time since menopause and age at initiation of hormone therapy. *Arch Intern Med* 2008; 168: 861–866.

Premature Ovarian Insufficiency

Cooper AR, Baker VL, Sterling EW, et al. The time is now for a new approach to primary ovarian insufficiency. *Fertil Steril* 2011; 95: 1890–1897.
Kalu E and Panay N. Spontaneous premature ovarian failure: management challenges. *Gyne Endocrinol* 2008; 24: 273–279.
Maclaran K, Horner E and Panay N. Premature ovarian failure: long-term sequelae. *Menopause Int* 2010; 16: 38–41.
Panay N and Fenton A. Premature ovarian failure: a growing concern. *Climacteric* 2008; 11: 1–3.

Panay N and Fenton A. Premature ovarian insufficiency: working towards an international database. *Climacteric* 2012; 15: 295–296.

Routes/regimens

Cody JD, Richardson K, Moehrer B, et al. Oestrogen therapy for urinary incontinence in post-menopausal women. *Cochrane Database Syst Rev* 2009; 4: CD001405.

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. *J Clin Oncol* 2008; 26: 1260–1268.

Panay N, Ylikorkala O, Archer DF, et al. Ultra low-dose estradiol and norethisterone acetate: effective menopausal symptom relief. *Climacteric* 2007; 10: 120–131.

Stevenson JC, Durand G, Kahler E, et al. Oral ultra-low dose continuous combined hormone replacement therapy with 0.5 mg 17β-oestradiol and 2.5 mg dydrogesterone for the treatment of vasomotor symptoms: results from a double-blind, controlled study. *Maturitas* 2010; 67: 227–232.

Sturdee DW and Panay N; on behalf of the IMS Writing Group. Recommendations for the management of postmenopausal vaginal atrophy. *Climacteric* 2010; 13: 509–522.

Androgens

Hirschberg AL, Rodenberg C, Pack S, et al. for the APHRODITE Study Team. Testosterone for low libido in postmenopausal women not taking estrogen. *NEJM* 2008; 359: 2005–2017.

Maclaran K and Panay N. Managing low sexual desire in women. *Womens Health (Lond Engl)* 2011; 7: 571–581.

Maclaran K and Panay N. The safety of postmenopausal testosterone therapy. *Womens Health (Lond Engl)* 2012; 8: 263–275.

Panay N, Al-Azzawi F, Bouchard C, et al. Testosterone treatment of HSDD in naturally menopausal women: the ADORE study. *Climacteric* 2010; 13: 121–131.

Somboonporn W, Bell RJ and Davis SR. Testosterone for peri and postmenopausal women. *Cochrane Database Syst Rev* 2005; 4: CD004509.

Lifestyle/alternatives

Lambrinoudaki I, Ceasu I, Depypere H, et al. EMAS position statement: Diet and health in midlife and beyond. *Maturitas* 2013; 74: 99–104.

Nelson HD, Vesco KK, Haney E, et al. Non-hormonal therapies for menopausal hot flashes: systematic review and meta-analysis. *JAMA* 2006; 295: 2057–2071.

Rees M and Panay N. The use of alternatives to HRT for the Management of menopause symptoms (updated); Opinion Paper 6. London: RCOG Scientific Advisory Committee, 2010.

Sassarini J and Lumsden MA. Hot flushes: are there effective alternatives to estrogen? *Menopause Int* 2010; 16: 81–88.

Key points

Fenton A and Panay N. The Women's Health Initiative – a decade of progress. *Climacteric* 2012; 15: 205.

Panay N and Fenton A. Has the time for the definitive, randomized, placebo-controlled HRT trial arrived? *Climacteric* 2011; 14: 195–196.

Panay N. Does hormone replacement therapy cause breast cancer? Commentary on Shapiro et al. papers, Parts 1–5. *J Fam Plann Reprod Health Care* 2013; 39: 72–74.

North American Menopause Society. The 2012 hormone therapy position statement of The North American Menopause Society. *Menopause* 2012; 19: 257–271.

Sturdee DW and Pines A; on behalf of the International Menopause Society Writing Group. Updated IMS recommendations on postmenopausal hormone therapy and preventive strategies for midlife health. *Climacteric* 2011; 14: 302–320.

Further reading

Menopause International – The Journal of the British Menopause Society, Eddie Morris and Heather Currie (eds), Sage Publications.

Climacteric – The Journal of the International Menopause Society, Nick Panay (ed.), Informa Press.

Maturitas – The Journal of the European Menopause Society, Margaret Rees (ed.), Elsevier Press.

Management of the Menopause: The Handbook, 5th ed. Rees M et al. (eds), 2009, RSM Press, London.

Premature Menopause: A Multidisciplinary Approach Eds Singer D Hunter M WileyBlackwell London.

Useful websites

- www.thebms.org.uk (British Menopause Society site – see consensus statements)
- www.imsociety.org (International Menopause Society – see consensus statements)
- http://emas.obgyn.net/ European Menopause Society
- www.mhra.gov.uk (the medical and Healthcare Products Regulatory Agency)
- http://www.shef.ac.uk/FRAX/ (WHO osteoporosis fracture risk calculator)
- www.nos.org.uk (National Osteoporosis Society – professionals and patients)
- www.menopause.org (North American Menopause Society)
- http://www.ema.europa.eu/ema/ European Medicines Agency
- http://nccam.nih.gov/health/alerts/menopause/ National Centre for Complementary and Alternative Medicine Alternative therapies for managing menopausal symptoms.
- http://www.pcwfh.co.uk (useful information for woman's health in primary care).

- http://dietary-supplements.info.nih.gov The NIH Office of Dietary Supplements
- http://www.rcplondon.ac.uk/pubs/wp_osteo_update.htm Royal College of Physicians Guidelines on Osteoporosis

Information/support for women

- http://www.womens-health-concern.org/ (Women's Health Group – including 'ask the experts')
- www.menopausematters.co.uk (very informative menopause website)
- www.pms.org.uk (Premenstrual Syndrome website)
- www.nos.org.uk (National Osteoporosis Society – professionals and patients)
- http://www.daisynetwork.org.uk/ (Premature Menopause Society website)
- www.womens-health-alliance.org.uk/ (Group of Women's Health Charities)