

Hormone Therapy: a practical guide to risk assessment for short-term symptomatic treatment of menopausal symptoms.

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Background

As part of its colourful history, the menopause was described in 1887 as “the inability of the ovaries to retire in graceful old age...transmitting their irritation to the brain... and leading to extreme nervousness or an outburst of actual insanity.”¹ The term used for the menopause in 1899 was indeed climacteric insanity!²

Menopause occurs with the cessation of ovarian function. It is present when there has been a period of amenorrhea for 12 consecutive months with no underlying pathological cause and it occurs at a mean age of 51 years. Prior to the menopause the patient is subjected to a period of fluctuation in estrogen levels, with menstrual irregularity as the main characteristic.³

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The consensus statement:

Before the results of the World Health Initiative Study on hormone therapy were published in 2002, the onset of the menopause was seen as an ideal intervention point at which the patient was motivated to take hormone therapy for both symptomatic relief of hot flushes and urogenital symptoms, as well as prevention of cardiovascular disease, stroke, osteoporosis and Alzheimer disease.

The WHI, Million Women, HERS and ERAS studies have led to the consensus statement by the North American Menopause Society (NAMS) and the International Menopause Society, which is as follows: Hormone therapy is *recommended* in the *short term treatment of mild to severe hot flushes* and for the relief of *urogenital symptoms*. It is *not recommended* for either primary or secondary *prevention of cardiovascular disease or stroke* and may be potentially harmful.^{4,5,6} It is of *benefit in preventing osteoporosis* and is protective against colorectal cancer. In the case of *breast cancer* there seems to be an *increased* promotion of existing cancers, not the origination of new cancer. The risk appears to increase with increased duration of hormone therapy, exceed-

ing 5 years. The role of hormone therapy in breast cancer survivors remains uncertain and controversial.

The following needs to be taken into account when interpreting the results. Firstly, the mean age of the patients in the WHI study was 63.3 years. Secondly, the women recruited were basically asymptomatic so as to prevent early drop out rates in the placebo group. Also, care should be taken when extrapolating results to the symptomatic, younger and early menopausal population of women that we primarily aim to treat.^{7,8}

Clinical symptoms:

The debilitating effects of menopausal symptoms must not be undervalued. Short-term effects include: hot flushes and associated irritability, anxiety, depression and sleep disturbance. Long-term effects mirror the picture of estrogen deficiency. The effects on the urogenital system include vaginal dryness, dyspareunia, vaginitis, dysuria and repeated urinary tract infections. There is also a loss in skin elasticity. The increase in osteoporosis and cardiovascular disease (myocardial infarction and stroke) impacts negatively on the morbidity and mortality in the postmenopausal woman.³

Some authors attribute symptoms of the menopause partially to life events that occur around menopause, such as alterations in body shape and self image, divorce, onset of physical illness in the patient herself or a spouse or the “empty nest syndrome”. Hot flushes, however, are a direct consequence of a fall in estrogen level. They are defined as recurrent, transient episodes of flushing and perspiration, with or without chills. When occurring at night, they are termed night sweats.

In the Massachusetts Women's Health Study, it was found that 75% of women experienced hot flushes during the transition from perimenopause to menopause, and they lasted a mean of 3.8 years. 9% of 72-year-old females still experience hot flushes.^{9,10} Hot flushes are not unique to the menopause and might be caused by thyroid disease, infection, epilepsy, insulinoma, carcinoid syndromes, leukaemia, pulmonary TB, pancreatic tumours, autoimmune disorders and mast cell disorders, as well as certain drugs such as tamoxifene and raloxifene.

When evaluating an individual with symptoms suggestive of estrogen deficiency, the principles of good clinical history, thorough physical examination,

and appropriate side room and special investigations apply.

Clinical history:

The aim of history taking is to ascertain the symptoms experienced by the patient, as well as the impact on her quality of life. In this way one can determine the desire of the patient for definitive treatment or merely give her the reassurance that no pathological cause for her symptoms exists. It must also be confirmed that the symptoms experienced are caused solely by estrogen deficiency and are not suggestive of any other underlying pathology e.g. thyroid disease.

The following aspects are of importance:

Past gynaecological history:

- Menarche and bleeding pattern
- History of premenstrual tension
- Gravidity and parity
- History of anovulation
- Use of oral and injectable contraceptives
- Previous endometriosis
- Previous malignancy of breast, endometrial and ovarian origin

Past surgical history:

- Hysterectomy
- Oophorectomy
- Surgery due to cancer

Past medical history:

- Presence of cardiovascular disease or risk factors that include hypercholesterolaemia, hypertension, diabetes mellitus, smoking and significant family history of ischaemic heart disease
- Thrombosis: venous or arterial
- Severe liver disease

Medication use

- Antiepileptic medicine
- Tamoxifen
- Raloxifene

Family or personal history:

- Family history of osteoporosis
- Personal risk factors for osteoporosis including typical phenotype of fair complexion, low body mass index, smoking and low calcium diet
- Family history of Alzheimer disease
- A history of general fitness, exercise regime, diet components and social circumstances

Physical examination:

The following aspects need to be evaluated:

- Body mass index
- Blood pressure
- Pulse
- Temperature
- General inspection for anaemia, jaundice, lymphadenopathy

Examination of all systems including respiratory, cardiovascular, abdominal, thyroid and breasts. Gynaecological examination, with attention to the presence or absence of the uterus, causes of abnormal bleeding and visible effects of estrogen deficiency. Side room investigations will include: urinalysis, haemoglobin, and pregnancy test

Special investigations:

Special investigations must be individualised and will serve to confirm the diagnosis of estrogen deficiency, the absence of other pathologies presenting with the same complaints, the confirmation of a normal gynaecological system, the absence of breast pathology, the absence of risk factors for cardiovascular disease and the presence of osteopenia or osteoporosis in the patient and may include the following:

- **Haematology:** Full blood count, screening for thrombophilia
- **Chemistry:** Urea and electrolytes, liver function test, thyroid function test, lipogram. FSH, LH and estradiol levels are not indicated for the confirmation of menopause
- **Radiography:** CXR, Mammography, DEXA bone scan
- **Gynaecological:** Cervical cytology, endometrial sampling, and gynaecological ultrasound

Risk assessment:

The potential risks of hormone therapy can be viewed from two angles. The one is the patient who has conditions that are absolutely contra-indicated in the use of hormone therapy, namely estrogen-dependent neoplasms (including previous or existing endometrial carcinoma or hyperplasia and breast cancer), previous endometriosis, previous history of venous or arterial thrombosis, and conditions that are relatively contra-indicated, namely existing cardiovascular disease or high

risk for cardiovascular disease.

On the other hand there is the patient who will be at risk for osteoporosis if not taking hormone therapy, or in whom there will be social and emotional implications if hot flushes, urogenital symptoms and other related symptoms are not treated.

Treatment modalities:

When initiating treatment for hot flushes and related short-term menopause symptoms, the general principles of prescription must apply. The patient must choose whether or not she wants to take pharmacological therapy to treat her symptoms and must be fully informed of the potential side effects, risks and benefits. The lowest possible dose of medication must be used to achieve the desired therapeutic effect. Treatment must, of course, be individualised.

The following treatment modalities have been described in the literature for the relief of hot flushes¹⁰:

Lifestyle modification:

All patient groups can utilise lifestyle modification and include the following:

- *Manipulation of the environment to lower the body core temperature of the individual.* These include lowering air temperature by using a fan, dressing in layers, drinking cool drinks and eating cold food.^{11,12}
- *Regular moderate exercise* has been found in the Study of Women's Health Across the Nation (SWAN study) in the US to lower the incidence of hot flushes. Strenuous exercise may trigger hot flushes in symptomatic women.¹³
- *Body mass index* has been thought to be inversely related to hot flushes as more adipose tissue correlates with higher circulating estrogen levels, secondary to increased peripheral aromatisation. In SWAN it was found that individuals with a BMI > 27 were at increased risk for hot flushes. Therefore maintaining an *ideal weight* will be beneficial.^{10,14}
- The risk for hot flushes also increases with *smoking*.¹⁴
- A relaxation technique that has been proven useful is *paced respiration*. It entails slow, controlled diaphragmatic breathing that is

- initiated when the hot flush starts.¹⁵
- *Muscle relaxation, biofeedback and foot reflexology* have not shown a significant difference when compared to placebo in randomised control trials.
- *Meditation, yoga, massage and relaxing in a leisurely bath* have been reported anecdotally, but have not been evaluated in controlled clinical trials.¹⁰

Non-prescription remedies:

Non-prescription remedies are available, but there is unfortunately not much evidence supporting the efficacy and long-term safety of these products. The first group is the *isoflavones* that are available in either whole foods or commercial preparations. The two main sources of isoflavones are *soy* and *red clover*. 30 – 50 % of women will convert diadzein in isoflavones to equol, which will exert an effect on hot flushes. Isoflavone intake of 40-80 mg/day is needed. The clinical effects may take weeks to become visible and side effects appear to be minimal. The estrogenicity of isoflavones is uncertain and caution is necessary in, for example, breast cancer patients.

The use of *black cohosh* has yielded contrasting results, from being effective in small German trials to being ineffective in others. The consensus is that the short-term use of this remedy (< 6 months) could provide relief for moderate symptoms with no obvious harm.

Vit E at a dose of 800 IU/day also produced mixed clinical results, but can also be given a trial period. Effects, if any, can take weeks to become visible.

The use of topical *non-prescription progesterone* creams is not advised as no scientific data are available regarding the efficacy and safety thereof. NAMS *does not recommend* the use of *dong quai*, evening primrose oil, *ginseng*, liquorice, Chinese herb mixtures, and acupuncture or magnet therapy for the treatment of hot flushes.¹⁰

Hormonal therapy:

The gold standard of treatment for hot flushes, that produces rapid symptomatic relief, remains prescription hormonal therapy. This consists of *estrogen only* in the hysterectomised

woman, and estrogen and adequate progestogen in the woman with an intact uterus. The *progestogen* can be administered in either continuous *combined or continuous sequential* form. Long cycle progestogen (i.e. given every 3 – 6 months for 12-14 days) and the progestin-containing intra-uterine device are not regarded at present as safe alternatives. There is a trend towards lower initial doses than the traditional 0.625 mg estrogen, with more attention being paid to the 0.3 mg conjugated estrogens.¹⁶ The lowest possible dose is given and adjusted upwards as necessary. Some patients are rapid metabolisers of the drug. In patients that do not respond to 0.625 mg daily, a lower dose (for example 0.3 mg twice daily) can be tried first, before stepping up to 1.25 mg daily dose. If a patient does not respond to an adequate trial of hormone therapy, other aetiological causes for her symptoms may need to be sought.

Prescription progestogens alone in the form of DMPA, MPA and meg-estrol acetate have shown efficacy in clinical trials but progestogen has been linked to breast cancer in certain studies. In the non-smoking healthy peri-menopausal woman, the *low dose oral contraception pill* is an alternative for the combined goal of symptomatic relief of hot flushes and adequate birth control. The same applies for DMPA (Depo Provera)

Tibolone (Livifem®) is another hormonal drug available. Tibolone is related to the 19-nortestosterone progestins and has three metabolites that exert a unique pharmacological action. It is clinically as effective as estrogen in relieving hot flushes and vaginal dryness with the associated benefit of an increased libido. The effect on the endometrium is comparable to the continuous combined estrogen-progestin regimens, with a decrease in the incidence of breakthrough bleeding. Livifem® appears to be cardiovascularly neutral, with a simultaneous 20% lowering in HDL, no increase in LDL and a decrease in LDL oxidation to more atherogenic small dense LDL. Tibolone is as effective as standard ET and EPT in the prevention of bone loss. The effect on the breast is particularly encouraging. Tibolone does not stimulate

breast cell proliferation or increase breast density on mammography. Several clinical trials of Livifem® are currently under way and the results are awaited.¹⁷⁻²⁰

Non-Hormonal therapy:

Prescription non-hormonal therapies available include venlafaxine, an *SNRI*, (37.5-75 mg daily²¹) and *SSRI*'s like fluoxetine (20 mg daily).²² The effect on hot flushes, if any, is almost immediate after the initiation of therapy. This is in contrast to the anti-depressant effect that can take 6 – 8 weeks to manifest.

The anticonvulsant *gabapentin* (Neurontin®) may prove effective at a dose of 100 mg daily. The mechanism of action is unknown, but modulation of calcium currents has been suggested. This drug is generally well tolerated and the only contra-indication is known hypersensitivity to the drug.

Clonidine (Dixarit®), an alpha-2 adrenergic agonist, is another non-hormonal option. It is normally used in the treatment of migraine and has been proven effective in healthy women as well as in breast cancer survivors on tamoxifeme. Cardiac sinus node function impairment is a contra-indication and the drug can cause a reduction in blood pressure and pulse rate. Arrhythmias have been reported at high dosages.

Due to the poor side-effect profile and potential toxicity, NAMS does not recommend methyl dopa or Bellargal Space Tabs® for the relief of hot flushes.¹⁰

Treatment options for hot flushes in the high risk patient:

Breast cancer:

Hormonal therapy is contra-indicated in patients with present or past breast cancer. The WHI estrogen-progestogen therapy arm was discontinued at 5.2 years as the risk for invasive breast cancer exceeded the benefits, with a hazard ratio of 1:26. The Million Women study found a similar increased risk in present and recent users of all forms and routes of administration of hormone therapy.²³ The decision to initiate hormone therapy in these patients must be taken by a menopause specialist in liaison with the oncologist. Quality of life must be weighed against life expectancy. Al-

ternatives to hormone therapy include: lifestyle modification, *SNRI*'s, *SSRI*'s, clonidine and gabapentin. The safety of isoflavones and black cohosh are uncertain. Tibolone might prove protective. Meanwhile, the LIBERATE and THEBES trial results are awaited.

Cardiovascular disease:

Cardiovascular disease is the number one killer of women in the first world. After determining the patient's specific profile and risk, treatment can be individualised.

The EPT and ET arm of the WHI trial found an increase in stroke in the first year of treatment, while the EPT arm also found an increase in adverse cardiac events. In the patient with stable blood pressure, diabetes mellitus and a normal lipogram, hormone therapy can still be utilised if the patient is fully informed of risks and benefits. Hormone therapy is no longer recommended for primary or secondary prevention of cardiac disease or stroke and may be potentially harmful.

Lifestyle modification, iso-flavones, black cohosh and Vit E are considered safe alternatives. As a prescription remedy, the *SSRI*'s will be the first choice, followed by gabapentin and clonidine.

Tibolone appears to be cardiovascularly neutral. However, the results of the OPAL study (Osteoporosis Prevention and Antiatherosclerosis effects of Tibolone) are still being awaited.

Methyl dopa may be considered as an option in local circumstances. Although the drug has an unfavorable side-effect profile in comparison with the other alternatives, it is inexpensive and may be a possible option in the combined clinical picture of hypertension and hot flushes.

Other

Other patients that are in need of alternatives to hormone therapy include those with a previous history of arterial or deep venous thrombosis, present or past estrogen-dependent tumours (endometriosis, endometrial hyperplasia and carcinoma and ovarian tumours) and severe liver disease. Lifestyle modification, *SSRI*'s, gabapentin and clonidine appear safe. The safety of isoflavones has not been established.¹⁰ The venous thrombo-

embolism risk of tibolone is unknown. Transdermal administration of estrogens do not appear to increase thrombo-embolism risk.²⁴

Treatment options for urogenital symptoms in the high risk patient:

The genital and lower urinary tract has a common embryological origin. Both contain estrogen receptors and are sensitive to the estrogen deficiency that is characteristic of the menopause. Symptoms include vaginal dryness, pruritis and burning, urinary frequency, dysuria and urge incontinence.

Hormonal therapy has proven efficacious in the treatment of vaginal symptoms as well as urgency symptoms, including urge incontinence, and the prevention of recurrent urinary tract infections. It is ineffective in treatment of stress incontinence. Efficacy was found in the lower dose oral estrogen and MPA therapy by vaginal creams as well as the vaginal ring.^{16,24}

There is some absorption of vaginal estrogen and this may have a small effect on serum estrogen. Safety for patients in whom systemic estrogen is contra-indicated remains unsure and treatment needs to be individualised.

Non-pharmalogical treatment modalities include vaginal lubricants and vaginal moisturisers.²⁵ The general measures of avoiding possible local irritants and drinking enough fluids should also be adhered to. Cranberry juice has been described for prevention of repeated UTI. Not much is known about the urogenital effects of isoflavones and black cohosh.

Tibolone produces the same effects on vaginal atrophy as EPT, with the added benefit of increased libido. It may be appropriate in certain patients.

Conclusion:

Hormone therapy is not available in one standard recipe for the population. Therapy has to be individualised for each patient and her unique set of symptoms, medical background, needs and expectations. The supportive role of the health care provider in these potentially trying years for the patient must not be undervalued. We no longer have the previously perceived "magic cure" for all the prob-

lems that arise with the onset of menopause and natural continuation of the aging process. The search for longevity and the preservation of quality of life will continue. Research is focusing on the symptomatic early menopausal individual and hopefully the effects of hormone therapy in this group of patients, which we now primarily aim to treat, will be clarified in the near future.✍

See CPD Questionnaire p.53

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