SOUTH AFRICAN MENOPAUSE SOCIETY (SAMS) REVISED CONSENSUS POSITION STATEMENT ON MENOPAUSAL HORMONE THERAPY 2014

ABSTRACT

The Council of SAMS has revised the 2007 consensus statement on menopausal hormone therapy, which was published in The South African Medical Journal, May 2007;97:354-357. The 2014 statement was finalised in February 2014 by the Council of the South African Menopause Society. Information presented in the previous statement has been re-evaluated and new evidence has been incorporated. While the hormone therapy recommendations remain similar to the 2007 statement, the 2014 statement includes a wider range of clinical benefits for hormone therapy, the inclusion of non-hormonal alternatives such as SSRIs and SNRIs for the management of vasomotor symptoms and an appraisal of bioidentical hormones and complementary medicines in the treatment of menopausal symptoms. New preparations which are likely to be more commonly used in the future are mentioned. The statement emphasises that commencing hormone therapy during the "therapeutic window of opportunity" maximises the benefit to risk profile of therapy in symptomatic menopausal women.

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South African Menopause Society (SAMS) Revised Consensus Position Statement on Menopausal Hormone Therapy 2014.

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1. INTRODUCTION

Clinicians are expected to practise in accordance with the findings of evidence-based medicine. This implies that the clinician is familiar with the strongest evidence available. This may be difficult for the following reasons:

1.1 The results of a given clinical trial can often only be applied to the specific population group and circumstances applicable to that specific trial. This is especially important in hormone therapy where initiation of therapy during the "therapeutic window of opportunity" (between 50 and 60 years of age or within 10 years of onset of menopause) results in a much better benefit to risk profile, compared to initiation in older patients.

1.2 A small group of individuals may react in a unique way to medication, therefore studies must be adequately powered.

1.3 Statistical significance does not always equate to clinical significance.

1.4 Different methods of defining statistical significance may yield different answers when applied to the same data.

1.5 Publications often only quote relative risks and ignore the clinically more relevant absolute risks.

1.6 The patient's perception is always important. For example, the weak association between postmenopausal hormone therapy (HT) and breast cancer may be of greater concern to women and the lay press, than the stronger association between HT and thromboembolic disease.

1.7 The side-effects of preventative medicine in healthy individuals have different implications to those resulting from the treatment of individuals with disease.

1.8 For many years the options regarding the use of HT were based mainly on data from observational trials. These have now largely been super-ceded by data from large randomised trials (RCT). With view to hormone therapy, the large body of observational data derived from women with a similar profile to that seen in everyday practise, cannot be completely disregarded in favour of RCT data derived from older asymptomatic women.

1.9 Clinical guidelines are unable to cater for all situations, as there are still major gaps in our knowledge.

1.10 The final decision regarding therapy must be a joint decision between the healthcare provider and an informed patient, based on her current clinical status and ongoing new scientific evidence.

1.11 The general public are always looking for alternative medical treatment strategies to manage menopausal symptoms. The vast majority are ineffectual and some may be dangerous.

2. The following abbreviations are used in this statement:

2.1 ET Estrogen therapy alone

2.2 EPT Estrogen and progestogen therapy in combination

2.3 HT Hormone therapy which refers to either ET or EPT

3. POSITION STATEMENT REGARDING MENOPAUSAL HORMONE THERAPY.

3.1 HORMONE THERAPY AND QUALITY OF LIFE

HT significantly improves menopause-specific quality of life, mainly through relief of symptoms, especially vasomotor symptoms. It may also result in a global increase in a sense of well-being. Health related benefits seem to depend on the severity of associated menopausal symptoms. Health-related and menopause related quality-of-life improves more obviously in women with significant menopausal symptoms who are given HT. This is considerably less obvious in women without significant symptoms.[1]

3.2 HORMONE THERAPY AND WEIGHT GAIN

Although weight gain associated with HT is a major concern for most women initiating HT, there is very little evidence to support this fear. Invariably, there is a redistribution of fat mass at the time of menopause, which may become apparent during the menopausal transition, with an increase in waist-to-hip ratio. Evidence shows that neither ET nor EPT are responsible for an increase in weight. The route of hormone administration does not appear to have an impact on weight gain.[2]

3.3 HORMONE THERAPY AND VASOMOTOR SYMPTOMS (VMS)

HT remains the only treatment that consistently has a greater effect than placebo on the alleviation of menopause related VMS. VMS generally last 2-5 years, but in some individuals may last much longer. Patients reporting life-long VMS burden are not that rare. VMS may recur to varying degree with cessation of HT. ET is effective even in low dosages, and the effect is enhanced by the addition of a progestogen.[64]

In clinical practice, the individual patient is the best judge of the effect of HT on her quality of life (QOL), particularly if she is symptomatic. Routine monitoring of hormonal levels is not advocated unless estradiol implants are being used. Lifestyle related strategies may also be of benefit. [3,4,5].

In women in whom HT is contraindicated, or who decline, or cannot tolerate HT, plausible alternatives include SSRIs or SNRIs. Although uncommonly used, gabapentin has also shown to decrease the occurrence of hot flushes. [26]

3.4 HORMONE THERAPY AND SLEEP

Sleep disorders are common in the menopause and may be associated with vasomotor symptoms, depression, anxiety, insomnia, obstructive sleep apnoea, fibromyalgia, restless leg syndrome, co-morbid disorders, medications, or simply be related to age. HT appears to improve sleep quality and quantity in menopausal women, although this has not been conclusively confirmed in available studies, especially if polysomnography is used as an assessment tool. HT appears to decrease episodes of awakenings and increase REM sleep by decreasing night sweats and improving mood. Further studies are needed to substantiate this and to determine whether type, dose and mode of administration impact on the quality of sleep.[6]

3.5 HORMONE THERAPY AND VULVOVAGINAL ATROPHY (VVA)

Systemic HT is very effective in reversing VVA. In women who only have symptoms related to VVA, topical local estrogen therapy only, is appropriate. In about 15% of women using systemic HT, additional topical vaginal therapy is often needed to achieve reversal of the atrophic symptoms. Vaginal creams, rings or pessaries are effective options.

Local estrogen preparations, when used correctly as sole therapy, do not result in sufficient systemic absorption to warrant the use of progestogen for endometrial protection. At present, there is not enough evidence to mandate progestogen use in women who persist with any local intra-vaginal estrogen preparation beyond 6 months.

Local estrogen therapy improves symptoms of detrussor instability, including urgency, urge incontinence, frequency, and nocturia and reduces the incidence of recurrent urinary tract infections. When HT is indicated for urological symptoms, local therapy is preferred to systemic therapy.

Sexual function is also improved through the reversal of vaginal skin atrophy with increased vaginal lubrication.[7]

3.6 HORMONE THERAPY AND MENOPAUSE ASSOCIATED BONE LOSS

The increased rate of bone resorption following the onset of menopause clearly indicates a hormonal influence on bone density in women. Both transdermal and oral HT are effective in preventing bone loss. Supplemental calcium and vitamin D is advisable if these are deficient.

HT is effective in decreasing the incidence of all osteoporosis related fractures, even in patients at low risk for fracture, and in patients at high risk for fracture, before the age of 60 years or within 10 years of the onset of menopause[5, 64]. HT decreases vertebral and non-vertebral fractures by about 50%.

In some patients, a degree of fracture prevention persists after cessation of HT. Patients remaining at risk for fracture should receive ongoing therapy with proven bone sparing medication once HT is stopped. As some women lose bone rapidly after cessation of HT, close follow-up is needed for women not receiving ongoing treatment.[8]

3.7 HORMONE THERAPY AND CORONARY HEART DISEASE

Cardiovascular disease is the major cause of death in older women. Based on observational data, a reduction in CHD of the order of 50% was expected with HT. This inspired several RCTs.

The following conclusions are based on a combination of the total body of evidence:

3.7.i HT does not offer secondary protection against CHD. This is based mainly on the data from the HERS trial, but also from data on the older women in the WHI study.

3.7.ii Standard dose ET may offer primary protection against CHD and lower all-cause mortality in women where therapy was initiated during the "therapeutic window of opportunity". This is based on data from RCTs, observational studies and meta-analyses.
The evidence that EPT in standard dosages offers primary protection against CHD when initiated in the window of opportunity is not as consistent as the data for ET, although the effect on the lowering of mortality is the same.[64]

3.7.iii In the WHI-study an increase in non-fatal CHD was found in the first year, but final analyses proved this to be statistically not significant. This was not evident in the younger patients. It is thus concluded that, in women initiating therapy outside the "therapeutic window of opportunity" who are likely to have established coronary artery atherosclerosis, HT is unlikely to offer significant protection and may cause a transient initial increase in adverse events.[9-14]

3.8 HORMONE THERAPY, INSULIN RESISTANCE AND DIABETES

Data suggest that combined HT reduces the incidence of diabetes in postmenopausal women, possibly mediated by a decrease in insulin resistance unrelated to body size. HT appears to lower fasting glucose and fasting insulin levels, but should not be given with the primary intention of preventing diabetes in postmenopausal women.[15]

3.9 HORMONE THERAPY AND STROKE

The HERS and WEST trials, both secondary prevention studies, demonstrated a null effect on the combined outcome of non-fatal stroke, fatal stroke or all-cause mortality relative to placebo in postmenopausal women with established cardiovascular disease. In the WHI study, a non-significant increase in the risk of ischaemic stroke was seen in all age groups. The magnitude of this risk, is however small, particularly in patients younger than 55 years of age where the absolute increase in risk is 1.5 extra ischaemic strokes per 10,000 HT users per year. This complication is therefore extremely rare. A meta-analysis of observational studies has shown a non-significant overall risk of about 10% for stroke and about a 20% increased risk for thrombotic stroke. Observational data suggests that lower doses of oral therapy than that used in WHI will result in even less risk, and that normal and low dose transdermal therapy (≤50µg) are uncommonly associated with an increase in the risk of ischaemic stroke risk. This increased risk persists throughout treatment, but decreases after discontinuation of HT. There is no role for HT in the primary or secondary prevention of stroke.[16-23]

3.10 ROUTE OF ADMINISTRATION

Transdermal administration of hormone therapy is associated with less adverse events than oral administration, particularly with view to cardiovascular adverse events. Transdermal HT does not appears to significantly increase the risk of thromboembolic disease. It is therefore prudent to consider the transdermal route in women at high risk for cardiovascular events, namely, obese women, smokers, hypertensive women and especially if there is any history of thrombosis. [26]

3.11 HORMONE THERAPY AND VENOUS THROMBOEMBOLISM (VTE)

The relative risk of venous thromboembolism (VTE) increases with the use of HT. In the WHI study the absolute risk of VTE was increased by 18 additional cases per 10 000 women per year with EPT, and 7 cases per 10 000 women per year with ET. [22] The effect is maximal in the first year of treatment and decreases over time. Risk factors include obesity, previous VTE, underlying thrombophilia and initiation of HT after age 60 years. The risk of VTE in the age group 50-60 years is very small, but increases four fold in the 60 – 69 year old and seven fold in the 70 – 79 year old age group.[23] The route of delivery will impact on risk with the highest risk being with EPT orally, then ET orally and least with the transdermal route. [24, 25]

3.12 HORMONE THERAPY AND BREAST CANCER

The risk of breast cancer associated with HT in menopausal women is a complex issue. Data suggests that HT may not be causal but rather a promoter of pre-existing breast cancer. The absolute risk of breast cancer attributable to HT is small and falls into the same risk category as several preventable risk factors which have a similar low relative risk for developing breast cancer. Examples of these are obesity, nuliparity and never having breast fed, first pregnancy after the age of 37 years and excessive intake of alcohol. The increased risk of breast cancer is primarily associated with the addition of a progestogen to estrogen therapy. In the WHI study, standard dose ET was consistently associated with a lower risk of breast cancer, compared to placebo and at 12 years of follow-up, this difference was statistically significant. In the WHI study, standard dose EPT was associated with an increased risk of breast cancer, compared to placebo. It is however important to note that on final adjudication and appropriate adjustment, this increase was not statistically significant. Furthermore, the increased risk was confined to women with prior exposure to EPT.

The increased risk of breast cancer seems to be related to the duration of hormone use. ET in observational studies shows no increased risk for 15-20 years. Combined conjugated equine estrogen and medroxprogesterone acetate (CEE/MPA) in the WHI study did not increase breast cancer risk for 7 years in new users. Observational studies however, point to a small increased risk in long term users of CEE/MPA. This effect was not seen when natural progesterone was used.[65-66]

Breast cancer risk decreases after HT is stopped and disappears by about 5 years. Breast cancer risk on hormone therapy is increased in lean women. [27-32]

3.13 HORMONE THERAPY AND BREAST DENSITY.

Higher degrees of mammographic breast density in women not taking HT reflects higher levels of endogenous estrogen secretion within breast tissue and correlates with increased breast cancer risk.[30]
Breast density, may be increased by use of ET, but is more likely to occur with the use of EPT. This increased breast density may impede the diagnostic interpretation of mammograms. In these cases the cessation of EPT for 2 - 4 weeks and a repeat breast image screening may be helpful.[31]
If available, it would be prudent for women to undergo digital mammography and ultrasound. Thermal screening should be avoided as a diagnostic tool.
Before initiating any HT, it is recommended that the breasts are examined carefully and that mammographic imaging is undertaken and followed conventionally thereafter.

3.14 HT AND RISK FOR OTHER CANCERS.

COLORECTAL CANCER

There is continuing evidence that oral HT results in about 40% reduction in the incidence of colorectal cancer and this benefit is more pronounced in the EPT group.
HT, however, is not indicated for primary prevention of colorectal cancer. [32,33]

ENDOMETRIAL CANCER

Estrogen only therapy should not be prescribed for women with an intact uterus where progestogens must always be given simultaneously. The primary indication for progestogen use in women on HT is for endometrial protection. Estrogen and progestogen therapy should not be prescribed in women who have had a hysterectomy unless they have a history of extensive endometriosis. Long term use of continuous combined EPT offers superior protection of the endometrium compared to sequential regimens and hence reduces the risk of endometrial cancer significantly more than sequential HT. Maximal duration of sequential HT should not exceed 5 years, after which continuous combined EPT should be prescribed. Long-term cycle regimens with 3 monthly withdrawal bleeds are not recommended.[34,35]
The levonorgesterel intra uterine system plus estrogen therapy Is comparable to other progestogen regimes.

OVARIAN CANCER

There are as many studies showing an increased risk for epithelial cancer as there are studies showing a null effect or a negative effect in HT users compared to non-users. The risk is so small that it is unlikely to influence prescribing habits.[36,37]

LUNG CANCER

Although combined HT does not significantly increase the incidence of lung cancer, it does increase death from lung cancer, and the risk continues after cessation of therapy. This should be of concern to users of HT who are smokers or who have other risk factors for lung cancer.[38]

3.15 HORMONE THERAPY IN BREAST AND GYNAECOLOGICAL CANCER SURVIVORS

BREAST CANCER SURVIVORS

At present, it is prudent not to offer HT routinely to treat menopausal symptoms to breast cancer survivors, even though the data are somewhat controversial. There have been three randomised trials that have addressed this issue, two of which showed that there was an increase in cancer recurrences, while the other did not. All three studies did not show an increase in death from the disease. [39-41]

Data derived from observational studies, including two large meta-analyses, do not however show an increase in recurrences or death rate in breast cancr survivors using HT.

HT should be prescribed only when patients are fully informed of the current available data and wish to use this therapeutic modality.

There is no evidence to suggest that transvaginal topical estrogen increases recurrence, so it may be prescribed in those patients with intractable symptoms associated with urogenital atrophy.[42]

GYNAECOLOGICAL CANCER SURVIVORS

HT for the management of VMS is not contraindicated in vulval, vaginal or cervical cancer survivors. It is prudent not to routinely administer HT to endometrial or ovarian cancer patients, even though the data are controversial, with many studies not finding that HT is detrimental in these patients.[43]

3.16 ALZHEIMER'S DISEASE (AD) AND COGNITION

There is observational evidence that HT initiated during the "therapeutic window of opportunity" may be protective against AD at a later age. HT used after the age of 65 years carries an increased risk of all-cause dementia, more prevalent with EPT than ET. HT is not indicated for the prevention or treatment of AD.

Short term memory dysfunction is common in the menopause transition and is usually self-limiting. HT appears to benefit this dysfunction. [44, 45]

3.17 PRIMARY OVARIAN INSUFFICIENCY (POI) (PREMATURE MENOPAUSE)

Primary ovarian insufficiency refers to ovarian failure with at least 4 months of amenorrhoea and FSH levels in the menopausal range, on 2 occasions with a 4-6 week interval, in woman prior to 40 years of age. The principles of treatment that apply to women undergoing a natural menopause at 51 years are not applicable to young women with POI.
Data from studies of women with POI show decreased survival, increased cardiovascular risk[1], increased risk of fracture, sexual dysfunction and possibly increased cognitive dementia and Parkinson's disease. Hormonal therapy will decrease these risks, will alleviate symptoms and preserve bone density, especially in women following bilateral oophorectomy.[46-48]
It is recommended that hormone therapy or oral contraception be used at least until the natural age of menopause. For younger women, higher doses are often needed to control symptoms.[49]

3.18 ANDROGEN THERAPY

Hypoactive Sexual Desire Disorder (HSDD) is the commonest sexual dysfunction in the climacteric. Testosterone levels in women decline as a result of ageing but do not display the same precipitous decline demonstrated as does estrogen in menopause. The reduced levels of testosterone in postmenopausal women are associated with a loss of libido, decreased sexual activity, diminished feelings of well- being and fatigue. Testosterone is an effective treatment for HSDD in women receiving concomitant estrogen therapy.
Testosterone on its own is not advocated.
Appropriate candidates for testosterone therapy include women with HSDD primary ovarian insufficiency, surgical menopause, adrenal insufficiency or hypopituitarism [50-52]

Presently there are no registered female testosterone therapies available in South Africa. Tibolone which has weak androgenic estrogenic and progestogenic activity and does not increase sex hormone binding globulin can be used as an alternative to testosterone. [53]

3.19 TARGETS BEYOND THE OBVIOUS

Evidence is accumulating to support the beneficial effects of HT on skin, and to a certain extent on the oral cavity. [54,55]

3.20 NEW COMBINATIONS AND HORMONE THERAPY PREPARATIONS

The new third generation selective estrogen receptor modulator (SERMS) and estrogen combination preparations, have a favourable impact on breast tissue and will be used more frequently to treat menopausal symptoms and osteoporosis.
Bazedoxifene with conjugated estrogens is such a preparation.[56]

Ospemifene, a new oral estrogen receptor modulator, has shown to be effective in reversing the symptoms associated with vulvo-vaginal atrophy, and particularly of dyspareunia.

3.21 BIOIDENTICAL HORMONE THERAPY (BHT) FOR MENOPAUSE SYMPTOMS

BHT is the use of hormones identical to those secreted in the ovary or adrenal gland, namely estradiol, estrone, estriol, DHEA and testosterone [56]. These are frequently compounded in compounding pharmacies for specific patients. The Federal Drug Administration reported a study of compounded pharmaceutical products and found significant aberrations with regard to quality and potency of these products.[63] Conventional hormone therapy products require mandatory regulation and registration, in South Africa, by the Medicines Control Council. This involves regular testing for purity, potency, efficacy and safety of these products. Bioidentical hormone and compounding products require no such regulation. There is no evidence to support claims of greater efficacy or safety for BHT compared to conventional HT. The addition of estriol to estradiol with or without estrone does not significantly alter the estrogenic content of the estrogen compound and certainly does not reduce the risk of breast cancer as is claimed. The absorption of bioidentical progesterone cream is variable, unpredictable and unreliable; thus its use for opposing the effects of estrogen on the endometrium is not recommended [57,58]

There are no long-term safety studies for BHT and no procedures exist for reporting adverse events. The use of BHT is not recommended.

3.22 COMPLEMENTARY AND ALTERNATIVE MEDICINES (CAM) AND MENOPAUSAL SYMPTOMS

- CAMs are remedies not recognised in conventional medicine. They have become popular because of the mistaken belief that 'natural' medicines have no adverse effect. The term natural gives a subliminal message of safety. There is no such thing as natural medicine. All medicinal products are manufactured in factories.
- Phytoestrogens are mainly sourced from s*oy* and r*ed clover* which express their pharmacological action through *isoflavones***.** Most studies have shown a null- effect or at most a minimal effect on vasomotor symptoms compared to placebo.[59,60]
- Black cohosh has no phytoestrogenic activity and is thought to have a serotonin agonist mechanism. It appears to have poor efficacy on menopausal symptoms.[61]
- Isoflavones appear to have no serious side effects, although if higher doses are used for long periods of time, they may stimulate the endometrium and breasts.
- Black Cohosh has been shown to be hepatotoxic.
- Both isoflavones and black cohosh should be avoided in women being treated for breast cancer. [62] Genistein may negate the inhibitory effect of tamoxifen on breast tumour growth. [63]

4. CLINICAL GUIDELINES

- The menopausal transition should be utilized as a window of opportunity to assess and manage specific, as well as general, health related matters. Medical history, general, breast and gynaecological examination, including cervical cytology, should be undertaken.

- Special investigations should include a fasting lipogram, blood glucose, mammography, thyroid function test and DEXA bone densitometry for patients considered to be at risk of osteoporosis. Investigations for hypercoagulability states are only required in patients at risk (personal or family history of VTE) before instituting HT.

- Life style modifications such as the cessation of smoking, adjustment of diet, maintenance of appropriate body mass index, exercise and stress control should be discussed.

- Treatment of dyslipidaemias, hypertension, diabetes and other medical conditions must be optimised.

- HT should only be initiated for specific proven indications, provided there are no contraindications and should be individualised according to each patient's needs. Women need to be fully informed of all risks and benefits regarding HT.

4.1 INDICATIONS FOR HORMONE THERAPY:

i. Treatment of vasomotor symptoms and associated sleep disorders.
ii Symptomatic urogenital atrophy
iii Prevention of bone loss in women with premature menopause, secondary amenorrhoea and women with osteopenia who are at risk for fracture.
iv. The treatment of osteoporosis in women in the age group 50-60 years at risk of fracture, with or without vasomotor symptoms.

4.2 CONTRA INDICATIONS:

HT should generally not be prescribed in the following circumstances:

i. Current, past or suspected breast cancer
ii Known or suspected estrogen-dependent malignant tumours
iii Undiagnosed genital bleeding
iv Untreated endometrial hyperplasia
v Previous idiopathic or current VTE
vi Known arterial CHD
vii Active liver disease
viii Porphyria cutanea tarda
ix Thrombophilia

4.3 GENERAL GUIDELINES:

i. The duration of HT should be based on the indication for treatment
ii. The indication for therapy should be reviewed on an annual basis. The decision to determine whether to continue treatment for the relief of climacteric symptoms may be made by temporarily discontinuing treatment. If symptoms do not recur, HT does not have to be resumed. Topical therapy for relief of urogenital atrophy symptoms may need to be continued long term.
iii. Only long-term therapy is effective for the prevention or treatment of osteoporosis. Long term HT may be considered for bone effects weighing its benefit and risks against those of alternate therapies. At present there is no compelling evidence to restrict duration of treatment as long as treatment goals are maintained.

iv. HT should ideally be commenced during the “therapeutic window of opportunity,” particularly to maximize the beneficial impact on the cardiovascular system and the brain.

v. Systemic HT should not be initiated after the age of 60 years.

vi. All estrogens and progestogen formulations, including Tibolone, should be considered similar in terms of clinical risks and benefits.

vii. These statements are applicable to all routes of administration including transdermal application. The non-oral route avoids the first-pass effect on the liver and are preferable in conditions of hyper-triglyceridaemia, liver disease, migraine, glucose intolerance, increased risk of VTE and smokers.

viii. Should EPT be required for longer than 5 years, it is recommended to convert from sequential HT to continuous combined HT.

ix. Low dose therapy has been shown to be effective in symptom control and the prevention of bone loss; therefore the principle of lowest effective dose should be adhered to.

x. Low dose and ultra-low dose estrogen preparations have less adverse effects than standard dose therapy.

xi. Women with a history of stroke or transient ischaemic attacks should be discouraged from initiating HT.

xii. Prior to commencing HT, all patients should be advised to undergo breast screening, including digital mammography (where available) and ultrasound examination. Ideally all menopausal women should have regular mammography.

xiii. Abnormal bleeding is quite common in the first 6 months of using continuous combined HT, especially if the patient is <1 year post-menopause. If abnormal bleeding or spotting persists for more than 6 months after initiating the HT, endometrial surveillance in the form of an endometrial sampler, determining endometrial thickness by saline hysterography, direct hysteroscopic assessment and biopsy or a formal diagnostic dilatation and curettage should be considered.

xiv. The use of bioidentical hormone therapy is not recommended.
Studies on phytoestrogens and botanicals have shown inconsistent results. Most good studies show no clear benefit and some potential for harm. Further research is required in order to make firm recommendations.

xv. No published data exist on the use of traditional African medicine for menopausal symptoms.

xvi. No therapy for menopausal symptoms should be initiated without proper clinical assessment including breast and pelvic examination.

xvii. If HT is contraindicated or not tolerated, alternatives for vasomotor symptoms that are effective include selective serotonin reuptake inhibitors, selective serotonin and norepinephrine reuptake inhibitors and gabapentin.

xviii. Provided there are no contraindications, HT can be administered for more than 5 years. Once the decision has been taken to stop HT, the dose of the HT can be tapered over time, before it is stopped totally.

xix. These statements are applicable to all routes of administration.

5. CONCLUSION

Every practitioner needs to be aware of the latest evidence regarding HT in order to assist the patient in making informed decisions about her menopausal management. It is anticipated that HT in conjunction with lifestyle modifications, will remain the treatment of choice for acute menopausal symptoms for the immediate future. Hopefully future research will be able to identify a patient profile or method of application where longer use of HT is without risk. This will unlock the true potential of HT in the prevention and treatment of osteoporosis and allow new research on the role of HT in primary prevention of cardiovascular disease. The estrogen receptors are ubiquitous in women, and as a result, even though HT impacts most positively in managing the acute menopausal symptoms, if used from" the window of opportunity", the global benefit extends beyond only the acute menopausal symptoms and it does act favourably on a wide number of other organs, particularly on the cardiovascular system, skeletal system and the brain. Provided the patient has no untoward complications and continues to be monitored appropriately, we believe that HT can be prescribed for long-term usage, and need not be routinely stopped within 5 years of use or by 65 years of age.

Concern about HT was accelerated by the WHI studies. Much of that data since have been reinterpreted and revisited. This is an on-going process which may result in these guidelines being reviewed and updated again in the future.

6. REFERENCES

1. Utian W, Woods N F. Impact of hormone therapy on quality of life after menopause. Menopause 2013; 20: 109 – 110
2. Davis S R, Castelo – Branco R, Chearaur P, Lumsden M A, Nappi R E. Understanding weight gain at menopause. Climacteric 2012; 15: 419 – 429.
3. Board of Trustees of North American Menopause Society. Treatment of Menopause-associated vasomotor symptoms: position statement of the North American Menopause Society. menopause 2004; 11(1): 11-33
4. The North American menopause Society. The 2012 hormone therapy position statement of the North American menopause Society. Menopause 2012; 19(3): 257-271.
5. De Villiers T, Pines A, Panay N, Gambacciani M, Archer DF, Baker RJ. Updated IMS recommendations on post-menopausal hormone therapy and preventative strategies for midlife health. Climacteric 2013; 16: 316-337.
6. Guidozzi F. Sleep and sleep disorders in menopausal women. Climateric 2013; 16: 214-219.
7. Sturdee D W, Panay N. Recommendation for the management of postmenopausal vaginal atrophy. Climateric 2010; 13: 509-522.
8. Nelson H. D. Walker M, Zakher B, Mitchell J. Menopausal hormone therapy for the primary prevention of chronic conditions. A systematic review to update the U.S preventative services task for recommendation. Ann Intern Med, 2012: 125: 104-113.
9. Hodis H.N. Postmenopausal hormone therapy and cardiovascular disease in perspective. Clin Obstet Gynaecol 2008: 564-580.
10. Grodstein, F, Manson JE, Stampfer M J. 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.
11. Hodis H N, Mack N J. A "window of opportunity". The reduction of coronary heart disease and total mortality with menopausal therapies is age – and time – dependent. Brain Research 2001; 1379: 244-252.
12. Schierbeck L L, Rejnmark L, Toffeng C L. Effect of hormone replacement therapy on cardiovascular events in recently postmenopausal women. A randomized trial. BMJ 2012; 345: 1-11.
13. Hodis H N, Collins P, Mack W J, Schierbeck L L. The window of opportunity for coronary heart disease prevention with hormone therapy: past, present and future in perspective Climateric 2012; 15: 217-228.
14. Rossouw J E, Prentice R L, Manson J E, et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and year since menopause. JAMA 2007; 297: 1465-1477.
15. Margolis K L. Effect of oestrogen plus progestin on the incidence of diabetes in post-menopausal women: results from the Women's health Initiative Hormone trial. Diabetologica 2004; 47: 1175-1187

16. Simon j A, Hsia J, Canley J A et al. Postmenopausal hormone therapy and risk of stroke: the Heart and Estrogen-progestin Replacement Study (HERS). Circulation. 2001, 103: 638-642.
17. Lobo R A. The risk of stroke in post-menopausal women receiving hormonal therapy. Climateric 2009; 12: 81-95
18. Lisabeth L, Bushnell C. Stroke risk in women the role of menopause and hormone therapy, Lancet Neurol 2012; 11: 82-91
19. Grodstein F, Manson J E, Stampfer M J, Rexrode K. Postmenopausal hormone therapy and stroke. Role of time since menopause and age at initiation of hormone therapy. Arch Intern Med. 2008; 168: 861-866.
20. Viscoli C M, Brass L M, Kernan W N, Sarrel P M, Saissa S, Howritz R I. A clinical trial of estrogen replacement therapy after ischaemic stroke. N Engl J Med 2001; 345: 1243-1249
21. Lakkegaard E, Jovanovic Z, Heitmann B L et al. Increased risk of stroke in hypertensive women using hormone therapy. Arch Neurol 2003; 60: 1370 -1384.
22. Scarabin P Y, Oger E, Plu-Burean G, on behalf of the Estorgen and Thromboembolism Risk (ESTHER) study group. Differential association of oral and transdermal oestrogen-replacement therapy with venous thromboembolism risk. Lancet 2003; 362: 428-432.
23. Canonico M, Plu-Bureau G, Lowe G D, Scarabin P. Hormone replacement therapy and risk of venous thromboembolism in postmenopausal women: systematic review and meta-analysis. BMJ 2008: 336; 227-1231.
24. Cushman M, Kuller L H, Prentice R. For the women's Health Initiative Investigations. Estrogen plus progestin and risk of venous thrombosis. JAMA 2004; 292: 1573-1580.
25. Canonico M, Plu-Bureau G, Scarabin P Y. Progestogens and venous thromboemolism among women using hormone therapy. Maturitas 2011; 70: 354-360.
26. ACOG Practice Bulletin No: 141. Management of menopausal symptoms. Obstet Gynecol 2014; 123: 202-216.
27. Bush T, Whiteman M, Flaws J. Hormone replacement therapy and breast cancer. A qualitative review. Obstet Gynecol 2001; 98: 498-508.
28. Chlebowski R T, Hendrix S G, Langer R D, Stefanick M L, Gass M, Lane D. Influence of estrogen plus progestin on breast cancer and mammography in healthy post-menopausal women. The Women's Health Initiative randomized trial. JAMA 2003; 289: 3243-3253.
29. Prentice R, Chlebowski R T, Stefanick M L, et al. Conjugated equine estrogens and breast cancer risk in the Women's Health Initiative clinical trial and observational study. A M J Epidemiol 2008; 167: 1407-1411
30. Kerlikowske K, cook A J, Buist DSM et al. Breast cancer risk, breast density, menopause and postmenopausal hormone therapy use. J Clin Oncol 2010; 28: 3830-3837.
31. Buist DSM, Anderson M L, Read S L. Short term hormone therapy suspension and mammography recall: the radiological evaluation and breast density (READ) randomized trial. Ann Intern Med 2009; 150: 752-765.

32. Henderson K D, Duan L, Sullivan-Halley J, Ma H, Clarke CA. Menopausal hormone therapy use and risk of invasive colon cancer. A M J Epidemial 2010; 171: 415-425.
33. Long M D, Martin C F, Galanko J A, Sandler R S. Hormone replacement therapy, oral contraceptive use and distal large bowel cancer: a population –based case-control study. Am J Gastroenterol 2010; 105: 1843-1850.
34. Million Women Study Collaborators. Endomentrial cancer and hormone-replacement therapy in the Million Women Study Lancet 2005; 365: 1543-1551.
35. Hill D, Weiss N S, Beresford S A A, Voigt L F, Daling J R Stanford J L. Continuous combined hormone replacement therapy and risk of endometrial cancer. AmJ Obstet Gynecol 2000; 183: 1456-1461.
36. Cacey J V, Mink P J, Lubin j H, Sherman M E, Troisi R, Hartge P. Menopausal hormone replacement therapy and risk of ovarian cancer. JAMA 2002; 288: 334-341.
37. Riman T, Dickman P W, Nilsson S, Correira N, Nordlinder H, Magnusson C M. Hormone replacement therapy and the risk of invasive epithelial ovarian cancer in Swedish women. J Natl Cancer Instit 2002; 94: 496-504.
38. Chlebowski R T, Schwartz A G, Wakelee H, Anderson G L, Stetanick M L, Manson J. Oestrogen plus progestin and lung cancer in post-menopausal women (Women's Health Initiative trail): a post-hoc analysis of a randomized controlled trial. Lancet 2009; 374: 1243-1251.
39. Van Schoultz E, Rutquist L. Menopausal hormone therapy after breast cancer. The Stockholm Randomized trial. J Natl Cancer Instit 2005; 97: 533-535.
40. Holmberg L, Anderson H. HABITS (hormonal replacement therapy after breast cancer – is it safe?); a randomized comparison: trial stopped. Lancet 2004; 363: 453-455.
41. Kenemans P, Bundred N J, Foidart J-M, Kubsita E, von Schoultz B, Sismondi P. Safety and efficacy of tibolone in breast-cancer patients with vasomotor symptoms: a double-blind randomized non-inferiority trail. Lancet Oncol. 2009; 10: 136-146.
42. Dew J E, Wren B G, Eden J A. A cohort study of topical vaginal estrogen therapy in women previously treated for breast cancer. Climateric 2003; 6: 45-52.
43. Guidozzi F. Estrogen therapy in gynaecologic cancer survivors. Climateric 2013; 16: 611-617.
44. Whitmer R A. Timing of hormone therapy and dementia: the critical window theory revisited. Ann Neurol 2011; 69: 163-169.
45. Maki P M. Hormone therapy and cognitive function: Is there a critical period for benefit? Neuroscience 2006; 138: 1027-1030.
46. Osserwarde M E, Bots M L, Verbeek M, Peeters P H. Age at menopause, cause-specific mortality and total life expectancy. Epidemiology 2005; 16: 556-562.
47. Archer D. Premature menopause increases cardiovascular risk. Climacteric 2009; 12: 26-31.
48. Gallagher J C. Effects of early menopause on bone mineral density and fractures. Menopause 2007; 14: 567-571.

49. Grazziottin A. Menopause and sexuality: key issues in premature menopause and beyond. Ann N Y Acad Sci 2010; 1205: 254-261.
50. Schwenkhagen A. Hormonal changes in menopause and implications on sexual health. J Sex Med 2007; 4(50) 227-234.
51. Davis S R. Should women receive androgen replacement therapy, and if so, how? Endocrinol 2010; 72: 1449-1454.
52. Panay N, AL-Azzani F, Bouchard C, Davis S R, Eden J, Lodhi I. Testosterone treatment of HSDD in naturally menopausal women: the ADORE study. Climateric 2010; 13: 121-131.
53. Davis S R. The effects of tibolone on mood and libido. Menopause 2002; 9: 162-170.
54. Shu Y Y, Maibach H. Estrogen and skin. Am J Clin Dermatology 2011; 12: 297-311.
55. Meurman J H, Tarkkila, Tritinen A. The menopause and oral health. Maturitas 2009; 63: 56-62.
56. Boothby LA. Bioidentical hormone therapy: a panacea that lacks supportive evidence. Curr Opin Obstet Gynecol 2008; 20: 400-407.
57. ACOG Committee of Gynecologic Practice. Committee opinion No: 322: compounded bioidentical hormones. Obstet Gynecol 2005; 106: 1139-1140.
58. Taylor M. Unconventional estrogens: estriol, biest and triest. Clin Obstet Gynecol 2001; 44: 864-879.
59. Sturdee D W, Pines A, on behalf of the International Menopause Society Writing Group. Updated IMS recommendations on postmenopausal hormone therapy and preventative strategies for midlife health. Climateric 2011; 14: 302-320.
60. The North American Menopause Society 2012 Hormone Therapy Position Statement Advisor Panel. The 2012 hormone therapy position statement of the North American Menopause Society. Menopause 2012; 19: 257-271.
61. Nedrow A. Complementary and alternative therapies for the management of menopause-related symptoms: a systemic evidence review. Arch Intern Med 2006; 166: 1453-1465.
62. Nelson H D. Non-hormonal therapies for menopausal hot flushes: a systemic review and meta-analysis JAMA 2006; 295: 2057-2071.
63. www.fda.gov/cder/pharmcomp/survey.htm2003
64. De Villiers TJ, Gass MLS, Haine CJ et al. Global Consensus Statement on menopausal hormone therapy. Climacteric 2013;16:203-204.
65. Fournier A et al. Breast Cancer Research Treat 2008;107:103-111.
66. Fournier A et al. J Clin Oncol 2008;26:1260-1268.