



## **The South African Menopause Society (SAMS) Statement on Compounded (Bioidentical) Menopausal Hormone Therapy, 18 October, 2023**

Nicole G Jaff, PhD, MSCP, Tobie de Villiers, MBChB (SU), MMed (O&G) FRCOG (UK), FCOG (SA) and members of the SAMS Advisory Group on Compounded (Bioidentical) Menopausal Therapy<sup>a</sup>

This statement from the South African Menopause Society (SAMS) is written as an advisory for healthcare practitioners due to concerns about the widespread use of unregulated compounded bioidentical hormone therapy (CBHT). Since CBHT is unregulated, there is ongoing anxiety about the quality, purity, potency, efficacy, sterility and safety of these products.

Because the word 'bioidentical' is not a scientific term, but one used in marketing to identify CBHT, the consensus for this statement was to use the words 'compounded menopausal hormone therapy' (CMHT) to describe this unregulated treatment, and the accepted global terminology 'menopausal hormone therapy' (MHT), to denote a hormone treatment that has been approved and regulated by government agencies. It is our opinion that by continuing to use the term CBHT in scientific papers and statements, the term 'bioidentical' is given credibility. This also distracts from the fact that the major hormonal content of compounded bioidentical hormone therapy (estradiol and progesterone) is regulatory approved and available for use in practitioner based scripts or in approved fixed combinations. This statement will attempt to identify misinformation about CMHT and to inform healthcare practitioners of the best practice, using an evidence-based approach when prescribing MHT to treat menopausal symptoms in midlife women

### **Key definitions**

**Menopausal hormone therapy (MHT):** Hormonal preparations used to treat menopausal symptoms and consequences.

**Regulated MHT:** Hormone preparations approved and regulated by government agencies.

**Compounded menopausal hormone therapy (CMHT):** Hormone preparations prepared by pharmacists outside the regulatory framework. These are not approved by government agencies for the treatment of menopausal symptoms

**Bioidentical hormones:** 'Bioidentical' is not a scientific term. It is a marketing term used by compounding pharmacists and some healthcare practitioners to describe hormones that have the same molecular structure as endogenous sex steroid hormones. The terms body identical or body similar hormones have the same meaning.

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SAMS Secretariat: Royal House (Alison Shaw)

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## **Regulated MHT**

Major menopause societies recommend MHT as the most effective treatment to alleviate vasomotor symptoms (VMS) and genitourinary syndrome of menopause (GSM), and for prevention of bone loss and fracture<sup>1,2</sup>. The risks of MHT vary for different women, dependent on the type of hormone therapy, the dose, length of use, the way it is administered and when it is first initiated, and whether a progestogen is used. Using transdermal MHT may reduce the risk of venous thromboembolism (VTE) and stroke though there are not comparable randomised controlled trial (RCT) data. A wide variety of government regulated and approved body identical MHT in various dosages and formulations are available<sup>3</sup>. Research suggests that individualized treatment using the most recent evidence-based research helps to increase benefits and decrease risks for the patient. The MHT regimen should be re-assessed periodically<sup>2</sup>.

Key guidelines:

- ☐ The benefits of MHT appear to outweigh the risks when it is not contraindicated, and initiated early in menopause (within 10 years of menopause), or in those women younger than 60
- ☐ There appears to be greater risk of cardiovascular disease (CVD), stroke, VTE and dementia in women, who initiate MHT more than 10 or 20 years after menopause onset
- ☐ There appears to be a lower risk for women using estrogen-only therapy (ET) than for those using an estrogen progestogen therapy (EPT)
- ☐ The wide availability of regulated MHT allows healthcare practitioners to tailor MHT for each individual woman. All MHT regimens should be assessed regularly
- ☐ If symptoms of GSM are not alleviated with nonhormonal therapies, systemic MHT and/or low dose local vaginal estrogen therapy is recommended

## **What is CMHT?**

Traditionally a compounded medicine was one that was formulated for a specific individual by a pharmacist<sup>4,5</sup>. 'Bioidentical' is not a scientific term. It is a marketing term<sup>5</sup>, which an Endocrine Society position statement describes as a term used to define hormones that have "the same molecular [isomolecular] structure as a hormone [estrogen, androgens, progesterone] that is endogenously produced, and circulates in the human bloodstream"<sup>6,7</sup>. 'Bioidentical' hormones may be called body similar or body identical hormones. There is a perception that because they have the same molecular structure as endogenous sex-steroid hormones they are more 'natural' than MHT which is government approved and rigorously regulated. Endogenous hormones may be described as 'natural hormones'<sup>7</sup>. There is often confusion about these hormones because they are available both in regulated MHT, and in CMHT, which is not regulated by a government body.

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Key guidelines:

- ☐ 'Bioidentical' is not a scientific term
- ☐ The correct terminology is body similar/body identical hormones which have the same molecular and chemical structure as endogenous hormones
- ☐ Government approved and regulated MHT and unregulated CMHT are both widely available

### **Sex steroid hormones used in MHT**

There are a wide range of sex steroid hormones used for MHT which can be divided into four categories: 1) Class A: Steroids found in the natural world that may be formulated without chemical adjustments. Conjugated equine estrogens (CEEs) obtained from the urine of pregnant mare is the only hormone therapy medication that complies with the above definition. 2) Class B: These steroids also derive from the natural world but require chemical amalgamation to be effective as an MHT. 3) Class C: These steroids are also found in the natural world, but they are chemically amalgamated in a process called total synthesis using multiple chemical effects meaning they are not biosynthetic. 4) Class D: This class comprises composites not found in the natural world including levonorgestrel, norethindrone, ethinyl estradiol, and medroxyprogesterone acetate. They can be chemically synthesized, either by total synthesis as in Class D steroids or from plant derived sterols, as explained in Class C<sup>7</sup>.

Classification of steroid hormones used for postmenopausal hormone therapy

Class of steroids	Characteristic of steroid	Description	Example
A	Found in Nature	Formulated into a drug without going through chemical modification	Conjugated equine estrogens
B	Semisynthetic	Found in plant sources such as the Mexican yam and soybean. Exist in nature and are not biosynthesized by the human body. Need to be chemically synthesized from natural starting material	Diosgenin and stigmasterol, which are used as precursors for synthesis of various steroids
C	Synthetic	Synthesized from simple nonsteroidal starting material by a 'total synthesis' process	Estrone, estradiol, equilin, progesterone, etc.
D	Man made/designed	Steroids not found in humans, animals, or plants	Medroxyprogesterone acetate, ethinylestradiol, norethindrone, levonorgestrel, etc.

Stanczyk FZ, Matharu H, Winer SA. Bioidentical hormones. Climacteric. 2021 Feb;24(1):38-45. doi: 10.1080/13697137.2020.1862079. Epub 2021 Jan 6. PMID: 33403887.

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Key guidelines:

- ☐ There are a wide range of steroids available for use in MHT
- ☐ Conjugated equine estrogen is the only hormone therapy medication that is truly 'natural'
- ☐ The main sex-steroid hormones used in bioidentical and regulated hormone therapy are in fact synthesized using plant based precursors
- ☐ Simply taking Mexican yam or soybean products will not be therapeutically effective

### **Salivary assays and urine tests**

There is widespread use of saliva testing for sex steroid hormones, although the data are limited, and the research methodology conflicting<sup>6</sup>. Although there are no dose-response or randomized control trial data available for non-regulated CMHT, healthcare practitioners tend to prescribe CMHT in conjunction with serum, urine, or, more particularly, salivary hormone assays to obtain what the healthcare practitioner has decided should be the appropriate hormone levels<sup>2</sup>. However, as yet, the ideal serum estradiol levels for treatment efficacy have not been determined in menopausal women<sup>8</sup>, nor have optimal levels of hormones been established in menopausal women. As described in the 2022 NAMS position statement: "[CMHT] has been prescribed or dosed on the basis of serum, salivary, or urine hormone testing; however, the use of such testing to guide hormone therapy dosing is considered unreliable because of differences in hormone pharmacokinetics and absorption, diurnal variation, and interindividual and intraindividual variability"<sup>2</sup>. Bleeding patterns as described in STRAW+10 are the gold standard method to determine menopause stage<sup>9</sup>. Major menopause societies do not generally recommend testing of specific serum hormone levels unless it is for a particular reason e.g. to determine fertility, or when a woman does not have a uterus and wants to determine whether she is menopausal<sup>11</sup>

Key guidelines:

- ☐ Although there are very limited data and debatable and conflicting research methodology on this issue, there is widespread use of saliva testing for sex steroid hormones
- ☐ Major menopause societies do not generally recommend testing of serum hormone levels
- ☐ There are no dose-response or randomized control trial data available for non-regulated CMHT
- ☐ Due to wide-ranging inconsistencies in hormone levels, salivary assays do not offer a united basis for assessment of efficacy

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### **What does government approved/regulated mean?**

Globally pharmaceutical grade medications are rigorously regulated to ensure that they are safe, of an approved quality, and efficacious. The regulatory rules apply to both new formulations and those that have already been approved. The regulations also apply to both domestic medicines, and those that are imported into a country. A country will have its own guidelines concerning manufacture, as well as the testing of each medication that includes extensive research, testing, marketing and ongoing oversight in order to ensure patient safety.<sup>8</sup>

According to this definition regulated MHT contains approved estrogens and progestogens. These products have been rigorously checked for quality, purity and efficacy, and are distributed with appropriate package inserts and extensive evidence-based information from rigorous double-blind RCTS<sup>3</sup>. These inserts have boxed safety warnings and describe potential adverse side effects. Compounded menopausal hormone therapy has not been regulated because it is not a standardised product, and is not obliged to meet the rigorous evaluations demanded by medicine regulatory bodies. Compounded menopausal hormones are prepared by compounding pharmacists/pharmacies using individual prescriptions which may vary widely, both in dose strength and with a broad selection of combinations, that may include several different hormones including estradiol, estrone, estriol, DHEA, testosterone, and progesterone. These may be compounded in combinations and formulations which have not been routinely tested or approved, and given in routes that are not standardized or tested, including creams, patches, vaginal suppositories, pellets and implants. Estriol-alone cream is very common, as are some compounded formulations such as those that contain either estradiol and estriol, or estrone, estradiol, and estriol. Frequently prescribed formulations combine a mix of estradiol, estrone, estriol and progesterone<sup>2,4,7</sup>. Government bodies that regulate MHT worldwide include: The Medicine Control Council (MCC), South Africa; The Food and Drug Administration (FDA), USA; The Medicines and Healthcare Products Regulatory Agency (MHRA), UK; European Medicines Agency (EMA), European Union; and the Therapeutic Goods Administration (TGA), Australia.

Key guidelines:

- ☐ Regulated MHT contains approved amounts of appropriate hormones and are checked for quality, efficacy and purity
- ☐ The formulations of CMHT may vary widely from batch to batch since they are mixed for an individual and are not standardised. There may be safety concerns as far as sterility in the preparation of each formulation
- ☐ CMHT is not standardised or regulated by an approved government body
- ☐ Regulated MHT is distributed with appropriate package inserts and safety warnings

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- ☐ CMHT is not distributed with appropriate package inserts and safety warnings

### **Data and safety concerns with CMHT**

Historically, a compounded medicine was a treatment formulated for a specific individual by a pharmacist and any efficacy evidence was purely anecdotal. However, as medical treatments progressed, clinicians began to examine data describing the safety and efficacy of a medication in treating most patients rather than a single formulation specifically for a single patient<sup>4,5</sup>. Although the medical and scientific community are usually in agreement that CMHT may have the same benefits and risks as standardized MHT, the lack of regulation in CMHT means that there are serious concerns. These include the inconsistent quality of the compounded formulations, and, as data show, the use of serum or salivary assays of hormones levels to prescribe a specific CMHT. Therefore, there is the possibility that levels of estrogen in these formulations may be excessive for symptom control and may include insufficient progesterone to protect against endometrial hyperplasia<sup>4</sup>. There are also safety concerns as far as impurities and insufficient sterility in the preparation of CMHT, as well as efficacy concerns. Individual CMHT formulation may vary from batch to batch leading to over- or under-dosing. In addition, since adverse events with use of CMHT are only reported on a voluntary basis and the information is incomplete, there are little or no peer-reviewed data on the safety of CMHT<sup>2,5</sup>, and major menopause societies do not recommend using CMHT<sup>3</sup>. There are no scientific data available on CMHT to support the unsubstantiated marketing fabrication that it is safer and has a lower risk profile than government approved and regulated MHT<sup>3</sup>. Several clinical guidelines and position statements suggest that CMHT may be considered in those women who may be allergic to ingredients in government regulated MHT, or when specific dosages or formulations are not available in regulated MHT. Data describing explicit allergies that might happen with a regulated MHT are scarce and life-threatening or critical illnesses that required utilization of CMHT have not been identified<sup>2,3,5</sup>.

Key guidelines:

- ☐ Information on efficacy in CMHT is mainly anecdotal
- ☐ Although CMHT and MHT may carry similar benefits and risks there are concerns over the unregulated status of CMHT
- ☐ Batches of CMHT may have inconsistent amounts of hormones leading to over- or under-dosing
- ☐ There are safety concerns over sterility and presence of impurities
- ☐ CMHT may be considered in women who may be allergic to ingredients in regulated MHT
- ☐ There are little or no peer-reviewed data on the safety of CMHT adverse events with use of CMHT

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- Major menopause societies worldwide do not recommend using CMHT

## **Conclusion**

Best practise in prescribing menopausal hormone therapy should take into consideration, efficacy, safety, benefits and risks, patient preference and cost. This can only be done based on high level evidence using hormones that are regulated for strength, purity and quality. Such information is generally lacking for CMHT but freely available for regulated MHT. Individual patient concerns in making an informed decision about MHT should be addressed. Regulated MHT offers body identical hormones in varying doses and regimens that makes individualization of therapy possible. Based on the information we have presented, this SAMS advisory statement recommends that healthcare practitioners use regulated MHT and not compounded products for approved interventions.

<sup>a</sup>DR Malikah Van Der Skyff MBChB (UCT), FCOG (SA), Dr Trudy Smith, MBChB (Wits); FCOG (SA); Cert Gynae Onc, Dr Jacky Searle, MBChB(Wits), FCOG (SA), Dr Phillip Zinn, MBChB (Wits), FRCOG (London) and MMed (O&G) (Cape Town)

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