



Full length article



Expert opinion by the Italian Society of Gynecology of the Third Age (SIGiTE) and the Italian Society of Menopause (SIM) on hormone therapy with bioidentical hormones

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ABSTRACT

The publication of the study WHI (Women's Health Initiative) represented a critical moment for the management of menopause considering the alarming results about breast cancer and cardiovascular risks. Anyway, several further studies progressively clarified over time the effective clinical impact of hormone replacement therapy (HRT) among post-menopausal women if adequately started before the age of sixty and no more than ten years after the last menstrual cycle and properly customized according to the major international recommendations. Robust evidence exists on different approved bioidentical HRT (abHRT) but data about galenic composed bioidentical hormone therapy (cbHRT) remain poor. The purpose of this expert opinion is to elucidate the position on Hormone Therapy with Bioidentical Hormones of the major Italian societies dealing with menopause, that is the Italian Society of Gynecology of the Third Age (SIGiTE) and the Italian Society of Menopause (SIM), in order to aware physicians about the suitability of their use.

Introduction

After the publication of The Women's Health Initiative [1] many years ago, the fear of hormones in treating menopausal syndrome has led to reduced prescriptions of this kind of therapy and to different strategies to help women in menopausal period.

The main objectives of the present position paper are the following:

- Evaluating the differences between the "composed" bioidentical hormone replacement therapy (cbHRT) realized in galenic formulations and the "approved" bioidentical HRT (abHRT).
- Assessing and clarifying the issues that may cause confusion regarding the prescription and the regulation of these therapies.
- Identifying and discussing the scientific rationale because of the potential advantages, if available, of cbHRT in comparison with abHRT.

This position paper has been realized considering the following levels of evidence:

- Level I: evidence based on good and consistent scientific data.
- Level II: evidence based on limited scientific data.
- Level III: evidence based on consensus and expert opinions.

The definition of bioidentical hormones

"Bio-identical hormones" stay for hormones that are the same as those produced by the human body and, more specifically, by the ovary, adrenal gland and thyroid, such as Estradiol (E2), Estriol (E3), Estrone (E1), Progesterone (P4), Dehydroepiandrosterone (DHEA), Testosterone (T) and Levothyroxine (LT4).

Nowadays, with regards DHEA, there is a ban on prescription for systemic use by doctors as well as on galenic preparation created for the same purposes by pharmacists in Italy (Gazzetta Ufficiale della

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Anyway, the use of the adjective “bioidentical” is usually employed in an inappropriate manner in marketing language, especially when one tends to propose the benefits of cbHRT. Indicating the abHRT as the HRT realized with hormones that are similar (“Body identical”) to those directly produced by human body should be preferred, in order to better distinguish abHRT from cbHRT.

Types of cbHRT

First, it is worth remembering that the “raw material” to produce both acHRT and cbHRT – i.e., hormones such as estradiol, progesterone and testosterone – is always obtained through industrial methods by large manufacturing companies, which then either resell it to those who prepare the drug (pharmacists or pharmaceutical companies) or, in the case of large pharmaceutical companies, prepare the final product themselves. The manufacturing process takes place from components of plant origin which undergo laboratory transformations to become “bio-identical hormones”. It is clear, therefore, that they cannot be defined as “natural agents”.

While abHRT is only marketed when clinical studies have assessed its pharmacokinetics, safety and efficacy, the same does not apply to bcHRT. In the field of bcHRT, several hormonal combinations emerged without any scientific support.

Based on the notion that E1 and E3 can behave as competitive inhibitors of E2 because they act on the same receptor, in cbHRT E2 is often prescribed together with E1 and E3 to balance its activity on the target organs, and overall have a supposedly physiological hormonal action.

Therefore, several formulations are available on the international market with combinations of E2 + E3 (in a 20/80 ratio) or E1 + E2 + E3 (in a 10/10/80 ratio), in ratios whose pharmacological or pathophysiological basis is unclear. For example, that in the female organism, E1 and E2 are continuously inter-converted into each other by the two forms of 17beta-hydroxysteroid dehydrogenase (17beta-HSD). Combinations of these elements with estrogenic activity are usually combined with progesterone and/or DHEA.

This phenomenon raises some questions:

- cbHRT formulations have not been subjected to efficacy and safety evaluation with appropriate randomized, placebo-controlled studies, rigorous observational studies or adequate comparison studies with other known abHRT. There is no solid evidence of scientific, pre-clinical and clinical data that could clearly support the practice of using hormone combinations such as E1 with E2 and with E3.
- The optimal dosage of the various estrogens administered in this way to control symptoms and prevent long-term conditions associated with the menopausal state (e.g., osteoporosis) is not known.
- The optimal dosage of progesterone to protect the endometrium in the presence of estrogen administered in this way is not known. Furthermore, progesterone in cbHRT is generally administered in transdermal or gel formulations. The degree of absorption of transdermal progesterone is not adequately constant, with possible insufficient and/or significantly variable absorption [2–4], and, in any case, such that safe endometrial protection cannot be guaranteed.
- With these preparations, in the absence of ministerial authorization and package leaflets, it is the doctor writing the prescription who assumes full responsibility for adequately informing the patient also about possible side effects, assessing indications and contraindications, and explaining how to report adverse events.
- The degree of purity, potency and safety of this type of therapy are still not clear.
- From a regulatory perspective, cbHRT is produced in the form of creams, tablets or galenic preparations. Without prejudice to the right of pharmacists to formulate galenic preparations as established

by law, SIGITE and SIM had already expressed themselves in a recommendation published in 2019 [5], on galenic preparations in the context of bio-identical menopausal therapies, advising against that kind of prescription.

- CbHRT is prescribed in a way that is touted as ‘customized’, often based on the result of complicated and expensive hormone assays performed on saliva, urine or blood, the validity of which is not supported by scientific evidence [6]

The position of the different international scientific societies on bioidentical compounds for the treatment of menopausal symptoms

In 2016, the Revised Global Consensus Statement [7] warned that cbHRT was not recommended due to lack of: regulatory aspects, adequate safety and efficacy testing, batch standardization and purity measurement. This document was shared by The International Menopause Society (IMS), The North American Menopause Society (NAMS), The Endocrine Society, The European Menopause and Andropause Society (EMAS), The Asia Pacific Menopause Federation, The International Osteoporosis Foundation (IOF), The Federation of Latin American Menopause Societies.

The Endocrine Society in 2016 [8], concluded that the availability of FDA-approved bioidentical hormones (abHRT) produced in modalities that are routinely monitored, demonstrating a high quality of safety and efficacy in clinical trials. Thus, there is no rationale in routinely prescribing unregulated, untested and potentially dangerous “customized” galenic bioidentical hormone therapies; furthermore, physicians are encouraged to prescribe FDA-approved products in accordance with package insert directions and to avoid customized compounded hormones.

The North American Menopause Society (NAMS) in its Position Statement of December 2022 [6], regarding cbHRT, stated that:

1. CbHRT is associated with safety problems, such as minimal regulation and monitoring by government authorities, possibility of overdose or underdose, presence of impurities and lack of sterility, lack of scientific data on efficacy and safety, and absence of a package leaflet outlining the risks (Level 1).
2. Salivary and urinary tests to determine the dosage are unreliable and are not recommended. Blood tests are rarely necessary (Level II/III).
3. Shared decision-making is important, but patient preference alone does not justify the use of cbHRT preparations, especially when bioidentical hormone-containing preparations with government regulation (Level III) are available.
4. Situations in which the prescription of a cbHRT could be considered include allergies to ingredients in government-approved formulations or unavailable dosages in government-approved products (Level III).
5. CbHRT prescribers should document the medical indications for which they prescribed cbHRT instead of government-approved and regulated therapies.
6. Pharmacists preparing cbHRT should provide standardized information on the content of cbHRT, including warnings of potential adverse events, specifying that it is a formulation without governmental approval; in addition, it should be reported how any adverse events occurring as a result of taking HRT are reported.

The position of SIGITE and SIM

The position of SIGITE and SIM, also in agreement with that of the major international scientific societies working in the field of menopause, is the following:

1. in the field of Hormone Therapy with so-called Bioidentical Hormones, better defined as ‘natural’ because they are the same as those

- produced by the female body, regulated, approved and controlled by regulatory bodies formulations (abHRT) are to be preferred. (Level I).
- Hormone assays performed on saliva and urine are unreliable and they are not recommended. Hormone tests on blood are also rarely needed in clinical practice (Level II/III).
 - The combinations of hormones (E2, E1, E3, DHEA, testosterone, progesterone) found in some cbHRT preparations are without scientific basis as they are not supported by pharmacokinetic, safety and efficacy studies. (Level II). Moreover, these formulations are often administered by non-standardized or untested routes (subcutaneous implants, gels, creams) [8–13] (Level I).
 - There is no evidence that cbHRT, has any kind of advantage in all respects over abHRT (Level I).
 - On the contrary, cbHRT may present problems regarding the safety and efficacy profile, due to insufficient scientific data on it and on the lack of a package leaflet describing the risks and possible side effects [14–17]. (Level I).
 - It is therefore recommended that doctors use standardized, government-approved treatments for HRT in order to prescribe products with certain quality and quantity standards to postmenopausal women.

Authors' contributions

All authors read and approved the final version of the manuscript.

CRedit authorship contribution statement

Stefano Lello: Conceptualization, Project administration, Supervision, Writing – original draft. **Anna Capozzi:** Data curation, Writing – original draft, Writing – review & editing. **Angelo Cagnacci:** Conceptualization, Validation. **Marco Gambacciani:** Conceptualization, Validation. **Lino Del Pup:** Data curation, Validation. **Costantino Di Carlo:** Validation.

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Declaration of competing interest

The authors declare that they have no known competing financial

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References

- 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 randomized controlled trial. *JAMA* 2002;288:321–33.
- Wren BG, McFarland K, Edwards L. Micronized transdermal progesterone and endometrial response. *Lancet Infect Dis* 1999;354(9188):1447–8.
- Carey BJ, Carey AH, Patel S, Carter G, Studd JW. A study to evaluate serum and urinary hormone levels following short- and long-term administration of two regimens of progesterone cream in postmenopausal women. *BJOG* 2000;107(6):722–6.
- Burry KA, Patton PE, Hermsmeyer K, Weiderman WC, Caillouette JC, Plaut MM, et al. Percutaneous absorption of progesterone in postmenopausal women treated with transdermal estrogen. *Am J Obstet Gynecol* 1999;180(6):1504–11.
- Cagnacci A, Gambacciani M, Gallo M, Lello S, on behalf of the Executive Committee of the Italian Society of Menopause (SIM) and of the Italian Society of Gynecology of the Third Age (SIGiTE). *Minerva Ginecol* 2019;71(6):395–403.
- The 2022 hormone therapy position statement of The North American Menopause Society. *Menopause* 2022; 29(7): 767-794.
- De Villiers TJ, Hall JE, Pinkerton JV, et al. Revised global consensus statement on menopausal hormone therapy. *Climacteric* 2016;19(4):313–5.
- Santoro N, Butts CL, Martin KA, McDermott M, Pinkerton JV. Compounded bioidentical hormones in endocrinology practice: an endocrine society scientific statement. *JCEM* 2016;101:1318–43.
- Cirigliano M. Bioidentical hormone therapy: a review of the evidence. *J Womens Health (Larchmt)* 2007;16:600–31.
- Files JA, Ko GM, Pruthi S. Bioidentical hormone therapy. *Mayo Clin Proc* 2011;86:673–80.
- Sites CK. Bioidentical hormones for menopausal therapy. *Womens Health (Lond Engl)* 2008;4:163–71.
- Bhavnani BR, Stanczyk FZ. Misconception and concerns about bioidentical hormones used for custom-compounded hormone therapy. *J Clin Endocrinol Metab* 2012;97:756–9.
- Stanczyk FZ, Matharu H, Winer SA. Bioidentical hormones. *Climacteric* 2021;24:38–45.
- Committee on Gynecologic Practice and the American Society for Reproductive Medicine Practice Committee. Committee opinion No. 532: compounded bioidentical menopausal hormone therapy. *Obstet Gynecol* 2012; 120:411-415.
- National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Health Sciences Policy; Committee on the Clinical Utility of Treating Patients with Compounded Bioidentical Hormone Replacement Therapy, Jackson LM, Parker RM, Mattison DR (eds). In: *The Clinical Utility of Compounded Bioidentical Hormone Therapy: A Review of Safety, Effectiveness, and Use*. Washington, DC: National Academies Press; 2020.
- Pinkerton JV. Concerns about safety and efficacy of compounded bioidentical hormone therapy. *Menopause* 2021;28(8):847–9.
- Xuezhai J, Bossert A, Parthasarathy KN, Leaman K, Minassian SS, Schnatz PF, et al. Safety assessment of compounded non-FDA-approved hormonal therapy versus FDA-approved hormonal therapy in treating postmenopausal women. *Menopause* 2021;28(8):867–74.