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BMS consensus statement

Bioidentical HRT

› Introduction

The aims of this paper are to clarify the:

- › differences between custom 'compounded' bioidentical hormone replacement therapy (cBHRT) and conventionally prescribed 'regulated' bioidentical hormone replacement therapy (rBHRT)
- › issues which have caused confusion regarding the regulation and prescribing of these hormones
- › scientific rationale for the potential advantages of regulated bioidentical hormone replacement therapy (rBHRT) compared to other types of conventional HRT.

Part A – Explanation of cBHRT

What are 'bioidentical hormones'?

'Bioidentical hormones' are precise duplicates of hormones such as estradiol E2, estriol E3, estrone E1, progesterone, dehydroepiandrosterone, testosterone and levothyroxine as synthesised by the human ovary, adrenal and thyroid. However, 'bioidentical' is often used as a marketing term by clinics purporting the benefits of cBHRT. It has been proposed by menopause specialists that rBHRT should be referred to as 'body identical' to distinguish regulated hormone therapy from the compounded varieties.

cBHRT formulation types

E1 and E3 function as competitive inhibitors of E2 because they use the same receptor. Specialist

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Publications

› [NICE Guideline](#)

› [Post Reproductive Health Journal](#)

› [BMS Handbook](#)

› [BMS Vision](#)

› [Consensus Statements](#)

› [Bioidentical HRT](#)

› [Hormone replacement therapy](#)

› [The diagnosis of the menopause and management of oestrogen deficiency symptoms and arthralgia in women treated for breast cancer](#)

pharmacies/cBHRT prescribers have interpreted this to mean that E2 needs to be 'balanced' with its antagonists, E1 and E3, in order to be physiological. Their rationale forms the basis for compounds such as Biest (E2 plus E3 in a 20/80 ratio) and Triest (E1 plus E2 plus E3 in a 10/10/80 ratio). These combinations are usually compounded with some progesterone and testosterone and/or DHEA. Concerns include:

- › The absence of medical evidence to support the practice of combining E1 and E3 with E2.
- › Is the dosage of estrogen higher than it needs to be to control symptoms or too low to control symptoms?
- › Is the dosage of progesterone sufficient to protect the endometrium in the presence of estrogen?
- › The absence of warnings on the products regarding potential risks and side effects.
- › In addition to the issues related to purity, potency and safety of cBHRT, many such products deliver progesterone transdermally in cream or gel preparations. The absorption of the latter is variable with fluctuating tissue availability and as a result may not provide sufficient endometrial protection.

Licensing in UK – Medicines and Healthcare products Regulatory Agency (MHRA)

Compounded bioidentical hormone replacement therapies are manufactured as creams, lozenges and vaginal preparations by 'Specialist Pharmacies' which have proliferated both physically and online in the UK and abroad. These cBHRT products:

- › Do not follow the same regulatory pathway of evaluation by the MHRA as conventional pharmaceutical products.
- › Have not been through the rigorous process of drug development which conventional medicines and products such as rBHRT undergo.
- › Have not been scientifically evaluated in controlled randomised clinical trials for effectiveness and safety against placebo or conventional HRT.

The prescribers of cBHRT

Prescribers of cBHRT are often healthcare professionals (HCPs) who are not experts in the field of menopause medicine and have not been certified by the British Menopause Society or any other postgraduate

› Non-hormonal-based treatments for menopausal symptoms

› Premature ovarian insufficiency

› Prevention and treatment of osteoporosis in women

› Primary prevention of coronary heart disease in women

› Risks and benefits of HRT before and after a breast cancer diagnosis

› Urogenital atrophy

› Tools for Clinicians

› Books

› Videos

educational organisation as having appropriate training in this specialty.

Hormone level testing

Some HCPs who prescribe cBHRT claim to be able to determine the precise requirements of each individual woman through a series of complex serum and saliva tests. This costly practice has never been substantiated through rigorous research, it is not recommended by the menopause societies and it is largely unnecessary.

Views of the menopause societies/regulators

The conventional regulatory view is that compounding can only be justified when a medicine has to be created because the strength, concentration, or dosage form that is required for a specific patient is not commercially available.

The 2015 NICE NG23 menopause diagnosis and management guideline 1.4.15 stated 'Explain to women that the efficacy and safety of unregulated compounded bioidentical hormones are unknown.'

The 2016 Revised Global Consensus Statement of the key stakeholder societies¹ (see below), initiated by the International Menopause Society, advised that custom-compounded hormone therapy is not recommended because of lack of:

- regulation
- rigorous safety and efficacy testing
- batch standardisation
- purity measures.

A BMS statement published online in 2017 stated 'Trustees and Members of the MAC of the BMS are concerned about the safety of unregulated bioidentical hormonal therapy which is being prescribed by clinicians who do not usually have any recognised menopause training and provided from compounding pharmacies.'

Advertising Standards Association (ASA)

The ASA ruled in 2017 against the 'misleading' promotion of cBHRT when a prescribing dermatology cosmetic clinic in Stratford upon Avon was reported. This test case led to a ruling being passed that these clinics and prescribers of cBHRT should not claim greater safety and efficacy as there was no evidence from clinical trials for these products. The ASA also advised that there was insufficient evidence that multiple serum and saliva tests

could be used to precisely individualise therapy. The public should be cautious of marketing that can give rise to false securities and should avoid purchasing cBHRT products over the internet.

Part B – Explanation of rBHRT

Are there any scientifically proven advantages for rBHRT over conventional HRT?

Tolerance

Progestogens may not be alike with regard to potential adverse metabolic effects or associated breast cancer risk when combined with long-term estrogen therapy. Micronised progesterone and some progestogens have specific beneficial effects that could justify their use besides their expected actions on the endometrium. Synthetic analogues of progesterone (progestins/progestogens) bind to the glucocorticoid, mineralocorticoid and androgen receptors. This can lead to unwanted side effects such as fluid retention, acne and weight gain. Progestogens and progesterone can lower mood through stimulation of the neurotransmitter gamma amino butyric acid; whilst progesterone has sedative effects through its intermediate metabolites, progestogens can cause PMS-type side effects including anxiety and irritability.

Venous thromboembolism (VTE)

It is well recognised that unlike oral estrogen, transdermal estrogen does not appear to increase the risk of VTE. Observational and case control data suggest that the use of certain progestogens e.g. dydrogesterone and micronised progesterone (D/MP) may reduce the increased risk of VTE conferred by oral estrogen, compared to that noted with other [synthetic progestogens](#).

Cardiovascular risks

D/MP have a neutral effect on lipid and glucose metabolism and on vascular tone. The beneficial effects of estrogen are therefore not attenuated as they are with some synthetic progestogens such as medroxyprogesterone acetate which can blunt the increase in HDL cholesterol, increase insulin resistance and reduce arterial compliance. Smaller studies such as KEEPS and ELITE using MP have demonstrated superior outcomes to WHI.

Breast cancer

D/MP have pro-apoptotic or neutral effects on breast epithelial cell proliferation – this is in contradistinction to the effects of androgenic progestogens such as medroxyprogesterone acetate which have a proliferative effect. Data from the E3N Cohort observational study showed that estrogen with D/MP is associated with a significantly lower relative risk) than for other types of combined HRT. These differences require confirmation from further studies.

Endometrial protection

Endometrial protection and avoidance of breakthrough bleeding may not be as consistent with separately administered oral MP as it is with standard oral continuous combined regimens. However, this may be partly due to lack of compliance due to the requirement for MP to be used separately with estrogen. Vaginal administration may improve endometrial protection through uterine first pass effect.

Key messages

- ▶ cBHRT products are not recommended by the BMS they are not evidence based for effectiveness and safety and because rBHRT options are available
- ▶ There is insufficient evidence to justify multiple serum and saliva hormone tests often claimed to precisely individualise cBHRT
- ▶ Claims for the benefits of cBHRT have been largely extrapolated from studies of conventional rBHRT
- ▶ rBHRT studies have demonstrated some advantages over other types of HRT, particularly those with androgenic progestogens
- ▶ Further data from larger studies on major cardiovascular and breast endpoints are required to confirm the potential benefits of rBHRT
- ▶ The management of women with menopause related problems should be underpinned by the principles and guidelines of the British Menopause Society and wherever possible, regulated products should be prescribed.

Summary of key terminologies

cBHRT: Compounded Bioidentical Hormone Replacement Therapy: Precise duplicates of human hormones which are produced by specialist pharmacies and do not follow the same MHRA regulatory pathway as conventional rBHRT

rBHRT: Regulated Bioidentical Hormone Replacement Therapy: Precise duplicates of human hormones developed in a conventional way by the pharmaceutical industry and authorised by the regulators such as the MHRA in the UK

Key references

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Key websites

www.asa.org.uk/advice-online/health-bio-identical-hormone-replacement-therapy.html

<https://thebms.org.uk/2017/03/bms-council-issues-consensus-statement-bioidentical-hormones/>

www.nice.org.uk/guidance/ng23/chapter/recommendations

International Menopause Society
The Endocrine Society
The North American Menopause Society
European Menopause and Andropause Society
The Asia Pacific Menopause Federation
The Federation of Latin American Menopause Societies
International Osteoporosis Foundation



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