Safety and Efficacy of Compounded Bioidentical Menopausal Hormone Therapy

RECOMMENDATION STATEMENT

- There is a lack of high-quality data on the safety and efficacy of custom-compounded bioidentical hormone therapy for the management of menopausal symptoms. They should not be routinely prescribed when U.S. Food and Drug Administration-approved formulations exist.
- There is no FDA-approved testosterone formulation for the management of menopausal symptoms. Clinicians and patients should utilize a shared decision-making framework when considering the use of compounded testosterone for this indication. Based on the lack of safety data and inability to remove the pellet, ACOG recommends preparations other than pellet therapy for the delivery of testosterone.

SUPPORTING EVIDENCE

- ACOG 2019: Practice Bulletin No. 213, Female Sexual Dysfunction
    - If transdermal testosterone therapy is used in postmenopausal women with sexual interest and arousal disorders, a 3–6-month trial is recommended with assessment of testosterone levels at baseline and after 3–6 weeks of initial use to ensure levels remain within the normal range for reproductive-aged women. Transdermal testosterone therapy should be discontinued at 6 months in patients who do not show a response. If ongoing therapy is used, follow-up clinical evaluation and testosterone measurement every 6 months are recommended to assess for androgen excess. The long-term safety and efficacy of transdermal testosterone have not been studied.

Category I

Systematic Reviews

Liu 2022: This review found that cBHT used in primarily short-term RCTs is not associated with adverse changes in lipid profile or glucose metabolism. cBHT in the form of vaginal androgens appears beneficial for vaginal atrophy symptoms. There are insufficient RCTs of cBHT to assess clinical risk of breast cancer, endometrial cancer, or cardiovascular disease. Long-term studies with clinical endpoints are needed.

MacLennan 2004: Oral HT is highly effective in alleviating hot flushes and night sweats. Therapies purported to reduce such symptoms must be assessed in blinded trials against a placebo or a validated therapy because of the large placebo effect seen in well conducted randomized controlled trials, and also because during menopause symptoms may fluctuate and after menopause symptoms often decline. Withdrawals due to side-effects were only marginally increased in the HT groups despite

Category II

Observational Studies

Deleruyelle 2017: The survey contained 15 questions pertaining to age, duration of hormone replacement therapy, type and formulation of hormone replacement therapy, reasons for initiating hormone replacement therapy, symptoms before and one month after hormone replacement therapy, and side effects related to hormone replacement therapy. The research findings suggest that women who used compounded BHRT reported more relief of their menopausal symptoms and had fewer side effects than those women who used synthetic conjugated equine estrogen and/or progestin HRT.

Donovitz 2021: This study is the largest reported retrospective study to evaluate the continuation and complication rates of T pellet implants. The safety of subcutaneous hormone pellet implants in men and women appears to be better than other routes of administration of bioidentical hormone replacement

Category III

the inability to tailor HT in these fixed dose trials. Comparisons of hormonal doses, product types or regimens require analysis of trials with these specific "within study" comparisons.

Whelan 2013: Available evidence from RCTs does not support the efficacy of bioidentical progesterone cream for the management of menopause-related vasomotor symptoms. Adverse effects appear to be mild and self-limiting.

therapy. Further investigations on short and long-term benefits of this modality are ongoing and could expand the overall utilization of this method.

Glaser 2011: Pre-menopausal and post-menopausal females reported similar hormone deficiency symptoms. Both groups demonstrated similar improvement in total score, as well as psychological, somatic and urogenital subscale scores with testosterone therapy. Better effect was noted in women with more severe complaints. Higher doses of testosterone correlated with greater improvement in symptoms. Conclusion: Continuous testosterone alone, delivered by subcutaneous implant, was effective for the relief of hormone deficiency symptoms in both pre- and post-menopausal patients. The validated, HRQOL questionnaire, Menopause Rating Scale (MRS), proved a valuable tool in the measurement of the beneficial effects of testosterone therapy in both cohorts.

Glaser 2013: Since March 2008, 1268 pre- and post-menopausal women have been enrolled in the study and eligible for analysis. As of March 2013, there have been 8 cases of invasive breast cancer diagnosed in 5642 person-years of follow up for an incidence of 142 cases per 100 000 person-years, substantially less than the age-specific SEER incidence rates (293/100 000), placebo arm of Women's Health Initiative Study (300/100 000), never users of hormone therapy from the Million Women Study (325/100 000) and our control group (390/100 000). Unlike adherence to estrogen therapy, adherence to T therapy further decreased the incidence of breast cancer (73/100 000).

Glaser 2019: As of March 2018, a total of 11 (versus 18 expected) cases of IBC were diagnosed in patients within 240-daysfollowing their last testosterone insertion equating to an incidence rate of 165/100000 p-y, which is significantly less than the age-matched SEER expected incidence rate of 271/100000 p-y ($p< 0.001$) and historical controls.

Iftikhar 2011: Of 208 consecutive patients invited to take the survey, 184 consented and responded. Thirty-seven (20%) reported ever use of BCH, and 25 (14%) reported current use of BCH; 59% of BCH preparations used included androgens. Twenty-four of 31 BCH users (77%) believed BCH was safer than CHT. Menopausal symptoms leading to use of hormones were similar between BCH and CHT users. Symptom relief with use of CHT and BCH was similar, but relief of sexual symptoms was reported significantly more frequently by BCH than CHT users (78% vs 33%, $p<0.001$)

Jiang 2021: The incidence of overall side effects was significantly higher in PHT compared with FHT (221 [57.6%] vs

23 [14.8%], P 1,000 pg/mL and nine women with T level > 400 ng/dL. CONCLUSION: Women on PHT had a significantly higher incidence of side effects than FHT as well as a significantly higher supraphysiological level of peak E2 and T during the treatment.

Pinkerton 2016: The DQSA and its reinforcement of §503A of the FDCA solidifies FDA authority to enforce FDCA provisions against compounders of CBHT. The new law may improve compliance and accreditation by the compounding industry; support state and FDA oversight; and prevent the distribution of misbranded, adulterated, or inconsistently compounded medications, and false and misleading claims, thus reducing public health risk.

Stanczyk 2019: The variations in estradiol and progesterone levels observed in compounded hormone therapy formulations justify concerns regarding risks as a result of variability, which have been outlined by The North American Menopause Society, the American College of Obstetricians and Gynecologists, and the US Food and Drug Administration (FDA) in their statements regarding compounded hormone use. These data support the need for an US FDA-approved bioidentical hormone therapy.

Tamimi 2006: Among women with a natural menopause, the risk of breast cancer was nearly 2.5-fold greater among current users of estrogen plus testosterone therapies (multivariate relative risk, 2.48; 95% confidence interval, 1.53-4.04) than among never users of PMHs. This analysis showed that risk of breast cancer associated with current use of estrogen and testosterone therapy was significantly greater compared with estrogen-only therapy (P for heterogeneity, .007) and marginally greater than estrogen and progesterone therapy (P for heterogeneity, .11). Women receiving PMHs with tes-tosteronehada17.2% (95%confidenceinterval,6.7%-28.7%) increased risk of breast cancer per year of use.

Accuracy of Hormone Level Testing

RECOMMENDATION STATEMENT

Data on the interpretation of adjunct hormone tests for prescribing and dosing of compounded bioidentical menopausal hormone therapy are limited, and thus these tests are not recommended for these indications.

SUPPORTING EVIDENCE

- Davis 2019: Global Consensus Position Statement on the Use of Testosterone Therapy for Women
    - Compounded “bioidentical” testosterone therapy cannot be recommended for the treatment of HSDD because of the lack of evidence for efficacy and safety, unless an authorized equivalent preparation is not available (Expert Opinion). In the absence of an available approved product, if a compounded product is needed, the compounding pharmacy should be compliant with purity of Active Pharmaceutical Ingredients and Good Manufacturing Practice to meet industry standards for quality and safety. Dosing should be limited to achieving testosterone concentrations in the physiologic premenopausal range.

Category I	Category II	Category III
		Narrative Reviews Kaunitz 2015: When counselling symptomatic women in their 50s (or younger) after hysterectomy, clinicians should clarify that for most such women, benefits of ET are likely to outweigh risks. Occasionally, when a specific FDA-approved formulation is not available, it may be appropriate to prescribe compounded HT. Stanczyk 2021: This review addresses important misconceptions and uncertainties pertaining to BHT, the relationship between salivary and serum/plasma steroid hormone concentrations, the effect of topical progesterone creams on the endometrium, the variability in custom-compounded steroid preparations, and FDA oversight of custom-compounded products.

Patient Counseling

RECOMMENDATION STATEMENT

- Clinicians should counsel patients that FDA-approved menopausal hormone therapies are recommended for the management of menopausal symptoms over compounded bioidentical menopausal hormone therapy preparations.
- If a patient requests the use of compounded bioidentical menopausal hormone therapy, clinicians should educate them on the lack of FDA approval of these preparations and their potential risks and benefits, including the risks specific to compounding.

SUPPORTING EVIDENCE

- ACOG 2014: Practice Bulletin No. 141, Management of Menopausal Symptoms
  - Menopausal: Bioidentical hormones are plant-derived hormones that are chemically similar or structurally identical to those produced by the body. Bioidentical hormones include commercially available products approved by the FDA, such as micronized progesterone and estradiol, as well as compounded preparations that are not regulated by the FDA. Because of a lack of FDA oversight, most compounded preparations have not undergone any rigorous clinical testing for either safety or efficacy, so the purity, potency, and quality of compounded preparations are a concern. In addition, both underdosage and overdosage are possible because of variable bioavailability and bioactivity. Evidence is lacking to support superiority claims of compounded bioidentical hormones over conventional menopausal HT (this is also discussed in Committee Opinion Number 532, Compounded Bioidentical Menopausal Therapy). Conventional HT is preferred given the available data.
- ACOG 2019: Practice Bulletin No. 213, Female Sexual Dysfunction
  - If transdermal testosterone therapy is used in postmenopausal women with sexual interest and arousal disorders, a 3–6-month trial is recommended with assessment of testosterone levels at baseline and after 3–6 weeks of initial use to ensure levels remain within the normal range for reproductive-aged women. Transdermal testosterone therapy should be discontinued at 6 months in patients who do not show a response. If ongoing therapy is used, follow-up clinical evaluation and testosterone measurement every 6 months are recommended to assess for androgen excess. The long-term safety and efficacy of transdermal testosterone have not been studied.

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