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RESEARCH REPORT: Menopausal Hormone Therapy—Risks, Benefits and Emerging Options: A Narrative Review

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OVERVIEW

This comprehensive narrative review synthesized contemporary evidence on menopausal hormone therapy (MHT) from peer-reviewed literature published through September 2025. Researchers examined data from major databases, including MEDLINE/PubMed, Embase, and the Cochrane Library, with particular emphasis on studies published in the last 5 years. The review aimed to clarify the evolving understanding of MHT's benefits, risks, and optimal use patterns, particularly addressing how timing, route of administration, dose, and choice of progestogen influence clinical outcomes.

This research matters now because prescribing patterns for MHT dropped sharply after early Women's Health Initiative (WHI) reports highlighted safety concerns, yet subsequent re-analyses have significantly reframed our understanding of risk-benefit profiles. The review addresses critical questions: Which women benefit most from MHT? What formulations, routes, and timing optimize outcomes? How do we individualize therapy to maximize benefits while minimizing risks?

KEY FINDINGS

- MHT provides the most effective relief of vasomotor symptoms: Across randomized trials, estrogen therapy reduces hot-flash frequency by approximately 75% compared with placebo, with symptom relief typically beginning within 2-4 weeks and reaching maximum benefit by 8-12 weeks.

- Timing of initiation significantly impacts outcomes: The "timing hypothesis" is supported by evidence showing that MHT initiated within 10 years of menopause or before age 60 demonstrates a more favorable cardiovascular and overall risk-benefit profile compared to initiation at older ages or longer after menopause.

- Route of administration modifies thrombotic and cardiovascular risk: Transdermal estradiol is not associated with increased venous thromboembolism (VTE) risk, while oral

estrogen—particularly conjugated equine estrogens (CEE)—increases VTE risk by approximately 58%. Oral estrogen also carries a higher stroke risk compared to transdermal formulations.

- Breast cancer associations are regimen-specific: Estrogen-alone therapy after hysterectomy shows neutral to favorable effects (associated with lower breast cancer incidence and mortality in long-term WHI follow-up). In contrast, combined estrogen-progestogen therapy shows duration-dependent increases in risk. Among progestogens, estradiol-dydrogesterone demonstrated the lowest associated increase in breast cancer risk.

- Low-dose vaginal estrogen effectively treats genitourinary syndrome of menopause (GSM): Local vaginal estrogen therapy is highly effective for GSM symptoms with minimal systemic absorption, typically requiring no concurrent progestogen at recommended doses. Approximately 50-70% of postmenopausal women experience GSM symptoms.

- Bone health benefits are well-established: MHT prevents early postmenopausal bone loss and reduces fracture risk in appropriately selected women. Even ultra-low-dose regimens (0.5 mg 17β-estradiol plus 0.1 mg norethisterone acetate) demonstrate protective effects on bone turnover markers.

- Emerging option shows promise: Estetrol (E4), a naturally occurring fetal estrogen, demonstrated anti-VMS efficacy at 15 mg daily dose in phase II trials, with favorable pharmacology including high oral bioavailability, minimal hepatic impact, and promising early safety signals. However, long-term cardiovascular, thrombotic, and breast safety data remain pending.

CLINICAL IMPLICATIONS

This evidence supports a paradigm shift from one-size-fits-all to individualized MHT prescribing. The research confirms that MHT remains the most effective treatment for moderate-to-severe vasomotor symptoms and should be considered first-line therapy for appropriately selected symptomatic women under age 60 or within 10 years of menopause who lack contraindications.

Route selection has emerged as a critical clinical decision point. When cardiometabolic or thrombotic risk factors are present, transdermal estradiol at low-to-moderate doses should be strongly preferred over oral formulations. This is particularly important for women with hypertension, hypertriglyceridemia, migraine with aura, obesity, or personal/family history of VTE.

Progestogen selection matters for women with an intact uterus. The data suggest that micronized progesterone and dydrogesterone offer more favorable breast cancer and cardiovascular profiles compared to medroxyprogesterone acetate, norethisterone, or levonorgestrel when used in combination therapy.

Current protocols may need reconsideration regarding the duration of therapy. The evidence does not support arbitrary discontinuation at a specific age or duration if women remain symptomatic and benefit from therapy, though the lowest effective dose should be maintained with periodic reassessment of risk-benefit balance.

PATIENT IMPACT

For patients, this research validates that effective symptom relief is achievable and that suffering is not mandatory. Women can be reassured that MHT, when appropriately individualized, offers substantial benefits for quality of life beyond just vasomotor symptom control—including improvements in sleep quality, mood regulation, sexual function, and overall well-being.

The breast cancer data requires nuanced patient conversations. Women who have undergone a hysterectomy can be counseled that estrogen-alone therapy is associated with favorable breast outcomes in long-term data. For women with an intact uterus requiring combined therapy, the duration-dependent increase in breast cancer risk must be balanced against individual symptom burden and quality of life impact, with the understanding that risk is more evident in normal-weight than obese women and varies by progestogen choice.

Patients with cardiovascular risk factors need not be categorically excluded from MHT. Rather, these women may be excellent candidates for transdermal estradiol formulations, which demonstrate a neutral VTE profile and lower stroke risk compared to oral preparations. This expands treatment options for women previously thought to have contraindications.

Women experiencing GSM symptoms can be offered highly effective local vaginal estrogen therapy with confidence in its safety profile and minimal systemic absorption at recommended doses. The research supports vaginal estrogen as appropriate, even in women with prior ischemic stroke (vaginal estradiol tablets were not linked to higher recurrence rates) when used appropriately.

IMPLEMENTATION CONSIDERATIONS

Clinical Considerations:

- Screen for contraindications: active or recent VTE, stroke, breast cancer, unexplained vaginal bleeding, active liver disease
- Assess individual VTE risk factors: obesity, thrombophilia, immobility, smoking status
- Evaluate cardiovascular risk profile: blood pressure, lipids, diabetes, family history
- Consider patient preferences regarding route of administration and dosing schedule
- For women with a uterus, ensure adequate endometrial protection proportional to estrogen dose

Practical Considerations:

- Transdermal formulations may have higher out-of-pocket costs than generic oral options
- Insurance coverage varies significantly by formulation and indication
- Patient adherence differs by route—patches require regular changing, gels daily application
- Compounded "bioidentical" preparations lack FDA oversight and standardized dosing
- Generic oral estradiol and micronized progesterone offer cost-effective alternatives to branded products

Communication Considerations:

- Frame discussions around individual risk-benefit analysis rather than population statistics
- Distinguish absolute risk from relative risk when discussing safety data
- Acknowledge legitimate patient concerns about breast cancer and cardiovascular risks
- Present MHT as one tool in a comprehensive menopause management approach
- Emphasize that therapy can be adjusted, discontinued, or changed if needed
- Provide written materials to support informed decision-making

LIMITATIONS & CONTEXT

The review acknowledges several important limitations. As a narrative rather than a systematic review, it involved qualitative synthesis rather than formal meta-analysis, which limits the statistical precision of effect estimates. Most safety data derive from observational studies subject to confounding and selection bias, though findings generally align with randomized trial results where available.

The majority of high-quality randomized data comes from studies of oral conjugated equine estrogens with medroxyprogesterone acetate (the WHI regimens), limiting generalizability to other formulations, routes, and progestogens. Contemporary practice increasingly favors transdermal estradiol with micronized progesterone, combinations for which long-term randomized outcome data remain more limited.

Questions that remain unanswered include: What is the optimal duration of therapy for individual women? How do genetic factors influence individual response and risk? What are the long-term outcomes of newer formulations like estetrol? Can biomarkers better identify women who will benefit most from therapy? How do different progestogen regimens (continuous versus sequential) compare in large, long-term studies?

Areas requiring additional research include head-to-head comparisons of different MHT regimens in randomized trials, long-term safety and efficacy data for estetrol, optimal approaches for women with premature ovarian insufficiency, effects on cognitive function and dementia risk in appropriately timed therapy, and strategies to personalize therapy based on individual risk profiles and preferences.

RECOMMENDED NEXT STEPS

Based on this evidence synthesis, healthcare providers should consider the following actions:

- Update clinical protocols to emphasize individualized prescribing based on timing (age, years since menopause), route (transdermal preferred for higher-risk patients), dose (lowest effective), and progestogen choice (favor micronized progesterone or dydrogesterone when possible).

- Implement systematic screening for VTE and cardiovascular risk factors before MHT initiation to guide route selection and identify women who would benefit most from transdermal formulations.

- Develop patient education materials that accurately communicate current evidence on timing hypothesis, route-specific risks, and regimen-specific breast cancer associations to support informed decision-making.

- Establish practice patterns for ongoing monitoring and periodic reassessment rather than arbitrary discontinuation at predetermined ages or durations, allowing continuation when benefits outweigh risks for individual patients.

- Stay informed about emerging evidence on estetrol and other novel formulations as longer-term safety and efficacy data become available from ongoing trials.

RESEARCH SOURCE CITATION

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