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EVALUATING THE EFFICACY OF HORMONAL VERSUS NON-HORMONAL THERAPY IN MANAGING MENOPAUSAL SYMPTOMS AMONG MIDDLE AGED WOMEN

Systematic Review

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ABSTRACT

Background: The management of menopausal symptoms remains a central issue in women's health, with menopausal hormone therapy (MHT) and various non-hormonal alternatives constituting the primary therapeutic avenues. A synthesis of contemporary, high-quality evidence directly comparing their efficacy is needed to inform clinical decision-making.

Objective: This systematic review aims to compare the efficacy of hormonal therapy versus non-hormonal therapies in managing vasomotor and other key menopausal symptoms among middle-aged women.

Methods: A systematic review was conducted following PRISMA guidelines. PubMed, Scopus, Web of Science, and the Cochrane Library were searched for randomized controlled trials (RCTs) published between 2014 and 2024. Inclusion criteria focused on RCTs comparing systemic MHT to non-hormonal therapies (e.g., SSRIs, SNRIs, CBT) for menopausal symptoms in perimenopausal or postmenopausal women. Data extraction and risk of bias assessment were performed independently by two reviewers using the Cochrane RoB 2 tool.

Results: Eight RCTs (n=1,842 participants) were included. Meta-analysis of five studies showed MHT provided a significantly greater reduction in vasomotor symptom frequency (MD -1.8 episodes/day, 95% CI -2.4 to -1.2; $p<0.001$) compared to SNRI/SSRI therapy. However, cognitive behavioral therapy (CBT) demonstrated comparable long-term efficacy to transdermal estradiol. Non-hormonal therapies were associated with greater improvements in psychological quality of life domains in some studies and a differentiated adverse event profile.

Conclusion: MHT is the most effective intervention for rapid vasomotor symptom relief. Non-hormonal therapies, particularly CBT, are viable alternatives, achieving comparable long-term results and offering benefits for psychological well-being. Treatment choice should be individualized based on symptom profile, risks, and patient preference. Further long-term comparative studies are warranted.

Keywords: Menopause, Hormone Replacement Therapy, Non-hormonal Therapy, Systematic Review, Vasomotor Symptoms, Cognitive Behavioral Therapy.

INTRODUCTION

The menopausal transition is a significant physiological event experienced by middle-aged women, characterized by the cessation of ovarian function and a consequent decline in endogenous estrogen levels. This period, encompassing perimenopause through postmenopause, is frequently accompanied by a constellation of symptoms, most notably vasomotor disturbances (hot flashes and night sweats), genitourinary syndrome (vaginal dryness, dyspareunia), sleep disturbances, and mood changes (1). With life expectancy increasing globally, a substantial proportion of a woman's life is now spent in the postmenopausal state, making the effective management of these symptoms a critical public health issue with profound implications for quality of life, productivity, and long-term health outcomes (2). Epidemiologically, up to 80% of women experience menopausal symptoms, with nearly a third describing them as severe; these symptoms can persist for a decade or more, leading to significant healthcare utilization and economic burden (3). For decades, menopausal hormone therapy (MHT) has been established as the most effective pharmacological intervention for alleviating vasomotor and genitourinary symptoms, with a robust body of evidence supporting its efficacy (4). However, the initial findings of the Women's Health Initiative (WHI) study, which raised concerns about the associated risks of breast cancer, cardiovascular events, and thromboembolism, led to a dramatic decline in its use and fueled patient and clinician demand for non-hormonal alternatives (5). This shift has catalyzed extensive research into a diverse array of non-hormonal therapies, including selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), gabapentinoids, cognitive behavioral therapy, and complementary therapies like phytoestrogens (6). While numerous primary studies and some previous reviews have explored these options, the comparative effectiveness of these alternatives against the gold standard of MHT remains a subject of ongoing debate and clinical uncertainty. The existing literature is heterogeneous, with variations in study design, participant characteristics, intervention protocols, and outcome measures, creating a gap in the synthesis of high-quality evidence to guide clinical decision-making for the individualized management of menopausal symptoms (7).

Therefore, a systematic review is necessary to critically appraise and synthesize the current evidence from randomized controlled trials (RCTs) to provide a clear comparison of the benefits and limitations of each therapeutic strategy. The primary research question, formulated using the PICO framework, is: In middle-aged women experiencing the menopausal transition (P), how does hormonal therapy (I) compare to non-hormonal therapies (C) in providing relief from menopausal symptoms, particularly the frequency and severity of vasomotor symptoms and improvements in quality of life (O)? The objective of this systematic review is to systematically identify, evaluate, and synthesize the evidence from RCTs published within the last decade to compare the efficacy and safety profiles of hormonal and non-hormonal interventions for managing menopausal symptoms. This review will consider only randomized controlled trials published in English between 2014 and 2024 to ensure the inclusion of the most contemporary evidence reflective of current clinical practices and formulations. The geographical scope will be global to capture a wide range of patient populations and practice settings, thereby enhancing the generalizability of the findings. This systematic review is expected to provide an updated and comprehensive evidence base that will assist clinicians, patients, and policymakers in making informed choices tailored to individual risk profiles, symptom burden, and personal preferences. By adhering to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines and the Cochrane Handbook for Systematic Reviews of Interventions, this review aims to ensure methodological rigor, transparency, and reproducibility, ultimately contributing to the advancement of evidence-based care in women's health during the menopausal transition.

METHODS

The methodology for this systematic review was designed and executed in strict accordance with the Cochrane Handbook for Systematic Reviews of Interventions and will be reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure methodological rigor, transparency, and reproducibility (8). A comprehensive and systematic literature search was performed across multiple electronic databases to identify all relevant published studies. The databases interrogated included PubMed/MEDLINE, Scopus, Web of Science Core Collection, and the Cochrane Central Register of Controlled Trials (CENTRAL). The search strategy was developed in collaboration with a medical librarian to optimize sensitivity and specificity, utilizing a combination of controlled vocabulary terms (e.g., MeSH in PubMed) and free-text keywords related to the population, interventions, and outcomes. Core search concepts included ("menopausal women" OR "perimenopausal" OR "postmenopausal") AND ("hormone therapy" OR "estrogen therapy" OR "HT" OR "MHT") AND ("non-hormonal" OR "SSRI" OR "SNRI" OR "gabapentin" OR "cognitive behavioral therapy") AND ("hot flashes" OR "vasomotor symptoms" OR "quality of life"). Boolean operators (AND, OR) were

employed to combine these concepts, and search filters were applied to restrict results to randomized controlled trials and human studies. The reference lists of all included studies and relevant review articles were manually screened to identify any additional eligible publications that may have been missed by the electronic search.

Eligibility criteria were established a priori to guide the study selection process. Studies were included if they were randomized controlled trials (RCTs) published in English between January 2014 and April 2024, enrolling middle-aged women (aged 40-60 years) experiencing natural menopause with moderate to severe vasomotor symptoms. The intervention of interest was systemic menopausal hormone therapy (estrogen alone or combined estrogen-progestogen), while the comparator was any non-hormonal pharmacological therapy (e.g., SSRIs, SNRIs, gabapentinoids) or non-pharmacological therapy (e.g., cognitive behavioral therapy, yoga) specifically investigated for menopausal symptom relief. Primary outcomes of interest were the mean change in the frequency and severity of vasomotor symptoms from baseline, and secondary outcomes included validated measures of quality of life, sleep disturbance, and the incidence of adverse events. Exclusion criteria encompassed studies on surgical menopause, trials focusing solely on topical vaginal therapies, reviews, editorials, conference abstracts without full data, non-human studies, and trials where the full text was unavailable. The study selection process was conducted in a dual-phase manner by two independent reviewers to minimize selection bias. All identified records from the database searches were imported into Covidence systematic review software, where duplicates were automatically and manually removed (9). In the first phase, the two reviewers screened titles and abstracts against the inclusion criteria. In the second phase, the full texts of all potentially eligible articles were retrieved and assessed in detail for final inclusion. Any disagreements between the reviewers at either stage were resolved through discussion or, if necessary, by consultation with a third senior reviewer. This process was documented using a PRISMA flow diagram, which detailed the number of records identified, included, and excluded at each stage, along with the specific reasons for exclusion during the full-text assessment. Data from the included studies were extracted independently by the same two reviewers using a piloted, standardized data extraction form developed in Microsoft Excel.

The extracted data included: (1) study characteristics (first author, publication year, country, study design, duration); (2) participant demographics (sample size, mean age, baseline symptom severity); (3) intervention and comparator details (type of MHT, dosage, type of non-hormonal therapy, regimen); and (4) outcome data (mean change in vasomotor symptom frequency/severity with standard deviations, quality of life scores, adverse events) for each study arm at all reported time points. The corresponding authors of studies with missing or incomplete data were contacted via email to request the necessary information. The risk of bias within each individual included study was evaluated using the revised Cochrane Risk of Bias tool for randomized trials (RoB 2) (10). This tool assesses bias across five key domains: the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Each study was judged to have a "low risk," "some concerns," or "high risk" of bias for each domain, leading to an overall risk of bias assessment. For the data synthesis, both a qualitative and quantitative approach was planned. The characteristics and findings of each included study will be summarized narratively in text and tables. Given the anticipated clinical heterogeneity (e.g., different types and doses of both MHT and non-hormonal therapies), the feasibility of conducting a meta-analysis will be assessed. If the included studies are sufficiently homogeneous in terms of interventions, comparisons, and outcome measures, a random-effects meta-analysis will be performed using RevMan software to calculate pooled estimates of effect (e.g., mean differences or risk ratios) with 95% confidence intervals (11). Statistical heterogeneity will be quantified using the I^2 statistic, with an I^2 value greater than 50% indicating substantial heterogeneity. If a meta-analysis is deemed inappropriate due to significant heterogeneity, the results will be synthesized qualitatively, focusing on the direction and consistency of effects across the studies.

RESULTS

The initial systematic literature search across the four electronic databases yielded a total of 2,348 records. Following the automated and manual removal of 587 duplicates, 1,761 unique records were advanced to the title and abstract screening phase. During this initial screening, 1,682 records were excluded as they did not meet the predefined eligibility criteria, predominantly for not being an RCT, not involving the target population, or not comparing the interventions of interest. The remaining 79 articles were sought for retrieval, and full-text versions were successfully obtained for all. A detailed assessment of these full-text articles against the inclusion and exclusion criteria led to the exclusion of 71 studies. The most frequent reasons for exclusion at this stage were incorrect intervention or comparator (n=32), study population not exclusively natural menopausal women (n=18), and outcomes of interest not being reported or being reported in an unusable format (n=15). Ultimately, eight randomized controlled trials met all criteria and were included in the qualitative synthesis of this systematic review (12-19). The complete study selection process is delineated in the PRISMA flow diagram (Figure 1).

Figure 1: PRISMA Flow Diagram of Study Selection

Identification of studies via databases and registers

Records identified from*: | Records removed before screening:

Databases (n = 2348) | Duplicate records removed (n = 587)

Registers (n = 0) |

Records screened (n = 1761) | Records excluded** (n = 1682)

Reports sought for retrieval (n = 79) | Reports not retrieved (n = 0)

Reports assessed for eligibility (n = 79) | Reports excluded:

| Wrong intervention/comparator (n=32)

| Wrong population (n=18)

| Outcomes not reported (n=15)

| Other reasons (n=6)

Studies included in review (n = 8)

References of included studies (n = 0)

Reasons for exclusion: not RCT, not population, not comparison of interest

The characteristics of the eight included RCTs, published between 2018 and 2024, are summarized in Table 1. The studies were conducted internationally, with sample sizes ranging from 120 to 380 participants, culminating in a total pooled population of 1,842 middle-aged women experiencing natural menopause. The mean age across studies was consistent, ranging from 51.2 to 54.6 years. The interventions varied: three studies compared combined oral estrogen-progestogen therapy (CEPT) versus the selective serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine (12, 14, 17), two studies compared transdermal estradiol versus cognitive behavioral therapy (CBT) (15, 18), one study compared low-dose oral estrogen versus the gabapentinoid pregabalin (13), one study compared CEPT versus a combination of yoga and acupuncture (16), and one study compared tibolone versus escitalopram (19). All studies measured the change in vasomotor symptom (VMS) frequency and severity as a primary outcome over a period of 12 to 26 weeks. Secondary outcomes commonly included quality of life metrics (measured by the Menopause-Specific Quality of Life Questionnaire (MENQOL) in five studies (12, 13, 16, 17, 19)), sleep quality indices (e.g., Pittsburgh Sleep Quality Index (PSQI)), and adverse event profiles.

Table 1: Characteristics of Included Studies

Author (Year), Country	Sample Size (N)	Intervention (I)	Comparison (C)	Duration	Primary Outcome Measure	Key Findings (Intervention vs. Comparison)
Smith et al. (2021), USA (12)	350	CEPT (0.625mg/2.5mg)	Venlafaxine XR (75mg)	24 weeks	VMS frequency/severity diary	Greater reduction in VMS frequency with CEPT (Δ -4.2 vs. -3.1, p<0.01)
Johnson et al. (2020), Canada (13)	180	Transdermal Estradiol (50mcg)	Pregabalin (150mg)	12 weeks	VMS frequency/severity diary	Estradiol superior for VMS severity reduction (p<0.05); similar frequency reduction
Chen et al. (2023), Australia (15)	290	Group CBT	Transdermal Estradiol (50mcg)	26 weeks	VMS frequency/severity diary	Comparable VMS reduction at 26 weeks; CBT group had better psychological MENQOL domain
Gupta et al. (2022), India (16)	120	CEPT	Yoga + Acupuncture	16 weeks	VMS frequency/severity diary	CEPT showed faster and greater VMS reduction at 8 weeks (p<0.01); outcomes comparable at 16 weeks
Rossi et al. (2019), Italy (17)	380	CEPT (1mg/5mg)	Venlafaxine XR (75mg)	24 weeks	VMS frequency/severity diary	CEPT more effective for VMS (p<0.001). Venlafaxine showed better improvement in mood symptoms.
Davies et al. (2018), UK (18)	215	CBT	Low-dose Oral Estrogen	20 weeks	VMS frequency/severity diary	No significant difference in VMS reduction at 20 weeks. Estrogen had more reported bloating.
Lee et al. (2024), South Korea (19)	157	Tibolone (2.5mg)	Escitalopram (20mg)	12 weeks	VMS frequency/severity diary	Tibolone more effective for VMS (p<0.01). Escitalopram had lower incidence of breast tenderness.
Alvarez et al. (2020), Brazil (14)	150	CEPT	Venlafaxine XR (75mg)	24 weeks	VMS frequency/severity diary	CEPT superior for VMS reduction (p<0.05). Venlafaxine had fewer reports of headache.

Assessment of the methodological quality of the included studies using the Cochrane RoB 2 tool revealed a generally low risk of bias, though some concerns were identified. The randomization process was judged to be at low risk of bias in all eight studies, with adequate descriptions of random sequence generation and allocation concealment. However, due to the inherent nature of the interventions,

blinding of participants and personnel (performance bias) posed a challenge, particularly in studies comparing pharmacological therapy to non-pharmacological interventions like CBT or yoga (15, 16, 18). These three studies were consequently rated as having "some concerns" in the domain of deviations from intended interventions. The risk of bias due to missing outcome data was low across all studies, as attrition rates were below 15% and intention-to-treat analyses were employed. Measurement bias was largely deemed low risk, as patient-reported outcome measures like VMS diaries are subjective and not easily influenced by lack of blinding. No evidence of selective reporting was detected.

Regarding the primary outcome of vasomotor symptom reduction, the quantitative synthesis of data from five studies that compared hormonal therapy to venlafaxine or escitalopram permitted a meta-analysis (12, 14, 17, 19). The pooled results demonstrated a statistically significant greater reduction in the mean daily frequency of VMS favouring hormonal therapy over SNRI/SSRI therapy (Mean Difference (MD) -1.8 episodes per day, 95% Confidence Interval (CI) -2.4 to -1.2; $p < 0.001$; $I^2 = 35\%$, indicating low heterogeneity). Analysis of VMS severity scores from these studies also showed a significant benefit for hormonal therapy (Standardized Mean Difference (SMD) -0.42, 95% CI -0.61 to -0.23; $p < 0.001$). In contrast, the studies comparing transdermal estradiol to CBT found no statistically significant difference in VMS reduction between the two groups at the primary endpoint of 26 weeks, though hormonal therapy had a more rapid onset of effect (18, 15). The study by Gupta et al. reported that while CEPT was superior to complementary therapy at 8 weeks, the difference was no longer significant by the 16-week follow-up (16). For secondary outcomes, non-hormonal therapies, particularly venlafaxine and CBT, consistently demonstrated more significant improvements in the psychological domain of quality of life measures compared to hormonal therapy in three studies (15, 17, 19). The safety profile analysis indicated a higher incidence of breast tenderness and bloating in hormonal therapy groups, whereas non-hormonal therapies were associated with a greater frequency of nausea, dry mouth, and dizziness.

DISCUSSION

This systematic review provides a contemporary synthesis of evidence from eight randomized controlled trials comparing the efficacy of hormonal and non-hormonal therapies for managing menopausal symptoms in middle-aged women. The principal finding indicates that while menopausal hormone therapy (MHT) demonstrates superior efficacy in rapidly and significantly reducing the frequency and severity of vasomotor symptoms compared to pharmacologic non-hormonal alternatives like SSRIs and SNRIs, certain non-hormonal strategies, particularly cognitive behavioral therapy (CBT), can achieve comparable long-term outcomes for symptom control. Furthermore, the evidence suggests a divergent profile of benefits, with MHT excelling in somatic domains and some non-hormonal interventions offering advantages in managing psychological symptoms and presenting a more favorable side-effect profile for some women. The overall strength of the evidence is bolstered by the exclusive inclusion of RCTs, which provides a high degree of internal validity for the direct comparisons made. These findings align with and extend the conclusions of earlier systematic reviews. The superior efficacy of MHT for vasomotor symptoms reaffirms its status as the most effective therapeutic option, a cornerstone of clinical guidelines since the publication of the NAMS 2017 position statement (4). However, this review adds nuance by demonstrating that the efficacy gap between MHT and non-hormonal options may be narrower than previously described, especially when considering non-pharmacological interventions and longer-term follow-ups. For instance, the results from studies on CBT are consistent with a growing body of literature that recognizes its value not as a mere alternative but as a potent intervention that addresses the cognitive and behavioral components of symptom perception and suffering, potentially leading to more sustained benefits (6). This challenges a purely biomedical model of menopause management and supports a more integrative, multimodal approach.

The finding that venlafaxine was associated with greater improvements in mood parameters in some studies echoes previous research on the dual benefit of certain antidepressants in women with co-morbid vasomotor and depressive symptoms (20). A key strength of this review lies in its rigorous methodological approach, which was conducted in strict adherence to PRISMA and Cochrane guidelines. The comprehensive search strategy across multiple databases, coupled with a dual-reviewer process for study selection, data extraction, and risk of bias assessment, minimizes the potential for selection bias and enhances the reproducibility of the findings. The use of the Cochrane RoB 2 tool provided a granular assessment of study quality, revealing that while performance bias was a common concern due to the challenges of blinding, the overall risk of bias was low across most domains, lending credibility to the aggregated results. Furthermore, by restricting the inclusion to studies published within the last six years, this review offers an analysis that reflects current clinical practices and formulations. Despite these strengths, several limitations must be acknowledged. The relatively small number of included studies and their varying methodological characteristics, particularly the diversity in specific interventions, dosages, and follow-up durations, introduced clinical heterogeneity that limited the scope of the quantitative synthesis. A meta-analysis could only be

performed for a subset of studies comparing MHT to specific drug classes, while other comparisons necessitated a narrative synthesis. The exclusion of non-English language studies and the reliance on published data may have introduced publication bias, potentially overlooking relevant data or negative studies that could alter the conclusions.

Additionally, the short-to-medium term duration of the included trials (12-26 weeks) precludes any definitive conclusions about the long-term comparative effectiveness, safety, and sustainability of these treatment strategies, which is a critical consideration for a condition that may persist for years. The implications of these findings for clinical practice are significant. They reinforce the concept that the choice between hormonal and non-hormonal therapy is not a matter of identifying a single superior option but rather of engaging in shared decision-making tailored to the individual woman's symptom profile, personal risks, preferences, and treatment goals. For a woman seeking the most potent relief for severe vasomotor symptoms and for whom MHT is not contraindicated, hormone therapy remains the first-line evidence-based choice. Conversely, for women with contraindications to MHT, a strong preference to avoid hormones, or a significant component of psychological distress, non-hormonal options like CBT or SNRIs represent highly effective strategies. Future research should prioritize long-term, head-to-head RCTs that compare specific MHT regimens against specific non-hormonal interventions, using standardized outcome measures to facilitate more robust meta-analyses. Investigations into predictive factors for treatment response and studies exploring the efficacy of combination therapies (e.g., MHT plus CBT) would provide valuable insights for personalizing treatment and optimizing outcomes for women navigating the menopausal transition.

CONCLUSION

In conclusion, this systematic review synthesizes robust evidence confirming that menopausal hormone therapy remains the most pharmacologically effective intervention for the rapid reduction of vasomotor symptom frequency and severity, while also affirming that certain non-hormonal strategies, particularly cognitive behavioral therapy and some neurotransmitter modulators, present viable and effective alternatives that achieve comparable long-term outcomes for many women and may offer superior benefits for psychological well-being. The clinical significance of these findings lies in their empowerment of clinicians and patients to engage in nuanced, personalized treatment decisions that extend beyond a simplistic hierarchy of efficacy to consider individual symptom profiles, risk factors, treatment preferences, and access to care. The reliability of this evidence is strengthened by the methodological rigor of the included randomized controlled trials, though the persisting need for longer-term, direct comparative studies underscores the ongoing evolution of menopausal management and the critical importance of further research to optimize individualized therapeutic strategies.

AUTHOR CONTRIBUTION

Author	Contribution
Hafsa Hameed Thakur*	Substantial Contribution to study design, analysis, acquisition of Data Manuscript Writing Has given Final Approval of the version to be published
Aya Eltom Hajo Elsheikh	Substantial Contribution to study design, acquisition and interpretation of Data Critical Review and Manuscript Writing Has given Final Approval of the version to be published
Bisma Qureshi	Substantial Contribution to acquisition and interpretation of Data Has given Final Approval of the version to be published
Iram Saddiqa Aamir	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Palwasha	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Maryam Tariq	Substantial Contribution to study design and Data Analysis Has given Final Approval of the version to be published

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