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COMPARATIVE EFFICACY OF HORMONAL AND NON-HORMONAL THERAPIES IN MANAGING MENOPAUSAL SYMPTOMS

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ABSTRACT

Background: Menopause, a natural biological transition in women, is often accompanied by distressing symptoms, including vasomotor disturbances, mood fluctuations, and vaginal atrophy, which significantly impact quality of life. While hormonal therapy (HT) has been a cornerstone for symptom management, non-hormonal approaches, including pharmacological and lifestyle interventions, have gained attention for their efficacy and safety profiles.

Objective: This review aims to compare the efficacy of hormonal and non-hormonal therapies in managing menopausal symptoms, focusing on vasomotor symptoms, mood disturbances, and genitourinary syndrome of menopause (GSM).

Methodology: A systematic review of recent studies and clinical trials was conducted, drawing from 22 peer-reviewed articles published between 2012 and 2023. The articles analyzed outcomes of hormonal therapies, including estrogen-progestin combinations and selective estrogen receptor modulators (SERMs), against non-hormonal approaches such as selective serotonin reuptake inhibitors (SSRIs), neurokinin antagonists, cognitive-behavioral therapy (CBT), phytoestrogens, and dietary interventions.

Results: Hormonal therapies, such as bazedoxifene with conjugated estrogens, demonstrated superior efficacy in alleviating vasomotor symptoms and improving GSM. However, non-hormonal options, including SSRIs and neurokinin antagonists, provided substantial relief for vasomotor symptoms, particularly in women contraindicated for HT. Cognitive-behavioral therapy showed promise for

mood-related symptoms, while phytoestrogens and Mediterranean diets contributed to overall symptom alleviation, albeit with variability in individual response.
Conclusion: Both hormonal and non-hormonal therapies play significant roles in managing menopausal symptoms, with their efficacy influenced by symptom type, severity, and individual patient characteristics. Hormonal therapies remain the gold standard for GSM, while non-hormonal options offer viable alternatives for vasomotor and mood symptoms, particularly in women at risk of hormone-related adverse effects. Future research should focus on personalized treatment strategies integrating hormonal and non-hormonal approaches for optimal symptom relief.

Keywords: Menopause, hormonal therapy, non-hormonal therapy, vasomotor symptoms, cognitive-behavioral therapy, phytoestrogens, neurokinin antagonists.

INTRODUCTION

Menopause marks a significant physiological transition in a woman's life, characterized by the cessation of ovarian function and a subsequent decline in estrogen levels. This hormonal shift is often associated with various symptoms, such as vasomotor disturbances (e.g., hot flashes and night sweats), mood swings, and genitourinary syndrome of menopause (GSM) [1, 2]. These symptoms not only affect physical health but also impose a substantial psychological and social burden, necessitating effective management strategies [3].

Hormonal therapy (HT) has long been considered the gold standard for alleviating menopausal symptoms. Estrogen-based treatments, often combined with progestins, have demonstrated efficacy in reducing vasomotor symptoms and improving vaginal atrophy [4]. Selective estrogen receptor modulators (SERMs), such as bazedoxifene, have further enhanced the therapeutic landscape by offering symptom relief with a lower risk of adverse effects [5]. Despite these benefits, the safety profile of HT, particularly its association with an increased risk of breast cancer and cardiovascular events, remains a concern, prompting the exploration of alternative therapies [6, 7].

Non-hormonal interventions have emerged as viable options, especially for women contraindicated for HT or those seeking alternative approaches. Pharmacological options, including selective serotonin reuptake inhibitors (SSRIs), neurokinin receptor antagonists, and ospemifene, have shown promise in addressing vasomotor and GSM symptoms [8, 9]. Cognitive-behavioral therapy (CBT) and lifestyle modifications, such as adherence to a Mediterranean diet and regular physical activity, have also been associated with symptom alleviation and improved overall well-being [10, 11].

Dietary interventions, such as the Mediterranean diet, have gained attention for their potential role in alleviating menopausal symptoms. This diet, characterized by high consumption of fruits, vegetables, whole grains, and healthy fats, has been linked to reduced inflammation and improved cardiovascular health, which are particularly beneficial during menopause [6]. Additionally, phytoestrogens, plant-derived compounds with estrogen-like effects, are increasingly being recognized for their potential to alleviate vasomotor symptoms and improve overall quality of life [11]. However, the variability in individual responses to dietary interventions highlights the need for personalized approaches to dietary management.

The role of exercise in managing menopausal symptoms cannot be overlooked. Regular physical activity has been shown to reduce the frequency and severity of vasomotor symptoms, improve mood, and enhance overall physical health [8]. Moreover, the psychological benefits of exercise, such as reduced anxiety and improved sleep quality, are particularly relevant for menopausal women experiencing mood disturbances.

Emerging therapies, such as neurokinin receptor antagonists like fezolinetant, represent a promising advancement in the management of vasomotor symptoms. These therapies target specific pathways

involved in thermoregulation, offering a novel mechanism of action distinct from traditional hormonal therapies [7, 10]. The efficacy of these treatments underscores the potential for innovative pharmacological approaches to address unmet needs in menopausal symptom management.

Despite the availability of various treatment options, the choice between hormonal and non-hormonal therapies remains complex and highly individualized. Factors such as the severity of symptoms, patient preferences, and the presence of comorbidities play a crucial role in determining the most appropriate intervention. Furthermore, the need for a comprehensive approach that integrates multiple therapeutic modalities is increasingly recognized, emphasizing the importance of tailoring treatment plans to the unique needs of each patient.

This review synthesizes evidence from recent studies to evaluate the effectiveness of hormonal and non-hormonal therapies in managing menopausal symptoms, focusing on vasomotor symptoms, mood disturbances, and GSM. By comparing these approaches, this work aims to provide insights into optimizing menopausal symptom management through a personalized and evidence-based framework.

METHODOLOGY

Study Design and Setting

This systematic review follows a narrative approach, synthesizing evidence from peer-reviewed articles published between 2012 and 2023. The studies included in this review were identified through comprehensive searches of medical databases such as PubMed, Scopus, and Cochrane Library. Keywords such as “menopause,” “hormonal therapy,” “non-hormonal therapy,” “vasomotor symptoms,” and “genitourinary syndrome of menopause” were used to retrieve relevant literature. Additional filters included studies focusing on the efficacy of hormonal and non-hormonal interventions, randomized controlled trials (RCTs), and observational studies.

The setting of this review spans clinical trials and observational studies conducted globally, with a focus on diverse populations to ensure generalizability. Studies were excluded if they lacked peer review, focused on experimental interventions without clinical application, or were published in languages other than English. Data extraction and synthesis were performed independently by multiple reviewers to ensure accuracy and minimize bias. Conflicts were resolved through consensus discussions.

Inclusion and exclusion criteria

The inclusion criteria encompassed studies involving postmenopausal women experiencing vasomotor symptoms, mood disturbances, or genitourinary syndrome of menopause (GSM). Eligible interventions included hormonal therapies such as estrogen-progestin combinations and selective estrogen receptor modulators (e.g., bazedoxifene), alongside non-hormonal approaches such as selective serotonin reuptake inhibitors (SSRIs), neurokinin antagonists, phytoestrogens, cognitive-behavioral therapy (CBT), and lifestyle modifications, including dietary interventions like the Mediterranean diet. The selected studies focused on outcomes related to symptom relief, quality-of-life improvements, and safety profiles. Randomized controlled trials, observational studies, systematic reviews, and meta-analyses published in English between 2012 and 2023 were included, provided they demonstrated methodological rigor and clinical applicability.

Studies were excluded if they involved experimental interventions without established clinical application, lacked peer review, were published in languages other than English, or failed to provide relevant clinical outcomes. Additionally, articles focusing solely on populations with pre-existing conditions unrelated to menopause or those emphasizing unapproved or investigational therapies were not considered. By applying these criteria, the review ensures a robust and clinically relevant synthesis of evidence.

Search Strategy
A comprehensive and systematic search was conducted across multiple medical and scientific databases, including PubMed, Scopus, Cochrane Library, and Web of Science, to identify relevant studies published between 2012 and 2023. The search focused on peer-reviewed articles examining the comparative efficacy of hormonal and non-hormonal therapies in managing menopausal symptoms. Keywords and medical subject headings (MeSH) terms were carefully selected to ensure a broad yet focused retrieval of literature, including terms such as "menopause," "menopausal symptoms," "hormonal therapy," "non-hormonal therapy," "vasomotor symptoms," "selective estrogen receptor modulators (SERMs)," "selective serotonin reuptake inhibitors (SSRIs)," "neurokinin antagonists," "cognitive-behavioral therapy (CBT)," "phytoestrogens," "Mediterranean diet," and "quality of life." Boolean operators (AND, OR) and truncation symbols (*) were used to combine and expand the search terms effectively. Filters were applied to limit the results to studies conducted on human subjects, published in English, and falling within the designated timeframe. To enhance the search, reference lists of selected articles were manually screened to identify additional relevant studies not captured during the database search. After removing duplicates, an initial screening of titles and abstracts was conducted based on predefined eligibility criteria, followed by a thorough full-text review to determine the suitability of the articles for inclusion. This rigorous search strategy ensured a robust evidence base for evaluating the effectiveness of hormonal and non-hormonal therapies in managing menopausal symptoms.

Study Question
The primary study question guiding this review is:

"What is the comparative efficacy of hormonal and non-hormonal therapies in managing menopausal symptoms, including vasomotor disturbances, mood alterations, and genitourinary syndrome of menopause (GSM)?"

This question aims to evaluate the effectiveness of these therapies in alleviating menopausal symptoms while considering their safety profiles and implications for clinical practice.

Data Extraction
Data extraction was performed systematically to ensure accuracy and consistency. For each included study, the following information was extracted: author names, year of publication, study design, sample size, participant demographics (age, menopausal status, and symptom profile), intervention details (type, dose, and duration of therapy), comparator(s), outcomes measured, and key findings related to the efficacy and safety of hormonal and non-hormonal therapies.

Where applicable, additional details on study settings, follow-up periods, and statistical methods were also recorded. Data extraction was independently conducted by multiple reviewers to minimize bias, with discrepancies resolved through discussion and consensus. Extracted data were organized in a structured format to facilitate synthesis and comparison across studies. Only clinically relevant outcomes, such as the reduction in symptom severity (e.g., vasomotor symptoms, mood disturbances, and GSM) and improvements in quality of life, were included in the final analysis.

Quality Assessment
Quality assessment of the included studies was conducted using established evaluation tools to ensure methodological rigor and minimize bias. Randomized controlled trials (RCTs) were assessed using the Cochrane Risk of Bias tool, which evaluates domains such as random sequence generation, allocation concealment, blinding of participants and personnel, incomplete outcome data, selective reporting, and other potential biases. Observational studies were evaluated using the Newcastle-Ottawa Scale, focusing on the selection of study groups, comparability, and the assessment of

outcomes.

Each study was rated as having low, moderate, or high risk of bias based on these criteria. Studies with low or moderate risk of bias were included in the final synthesis, while those with high risk of bias were excluded to maintain the review's validity. The quality assessment process was independently conducted by two reviewers, with discrepancies resolved through consensus discussions. The overall quality of the evidence was also considered when interpreting the findings and drawing conclusions.

Outcome	Hormonal Therapy Quality	Non-Hormonal Therapy Quality	Overall Strength
Vasomotor Symptoms	High	Moderate	Strong
Mood Symptoms	Moderate	High	Moderate
GSM	High	Low	Moderate

Risk of Bias Assessment

The risk of bias in the included studies was assessed to ensure the reliability and validity of the findings. For randomized controlled trials (RCTs), the Cochrane Risk of Bias Tool was employed, focusing on key domains such as random sequence generation, allocation concealment, blinding of participants, personnel, and outcome assessors, completeness of outcome data, selective reporting, and other potential sources of bias, including funding and conflicts of interest. For observational studies, the Newcastle-Ottawa Scale was used to evaluate selection bias, comparability of study groups, and the reliability of outcome assessment. Each study was categorized as having low, moderate, or high risk of bias based on these criteria. The assessment was conducted independently by two reviewers, and discrepancies were resolved through consensus discussions. Only studies with low or moderate risk of bias were included in the final analysis to ensure the robustness of the evidence and its applicability to clinical practice.

RESULTS

This review analyzed 22 studies, including randomized controlled trials (RCTs), observational studies, and systematic reviews, assessing the comparative efficacy of hormonal and non-hormonal therapies in managing menopausal symptoms.

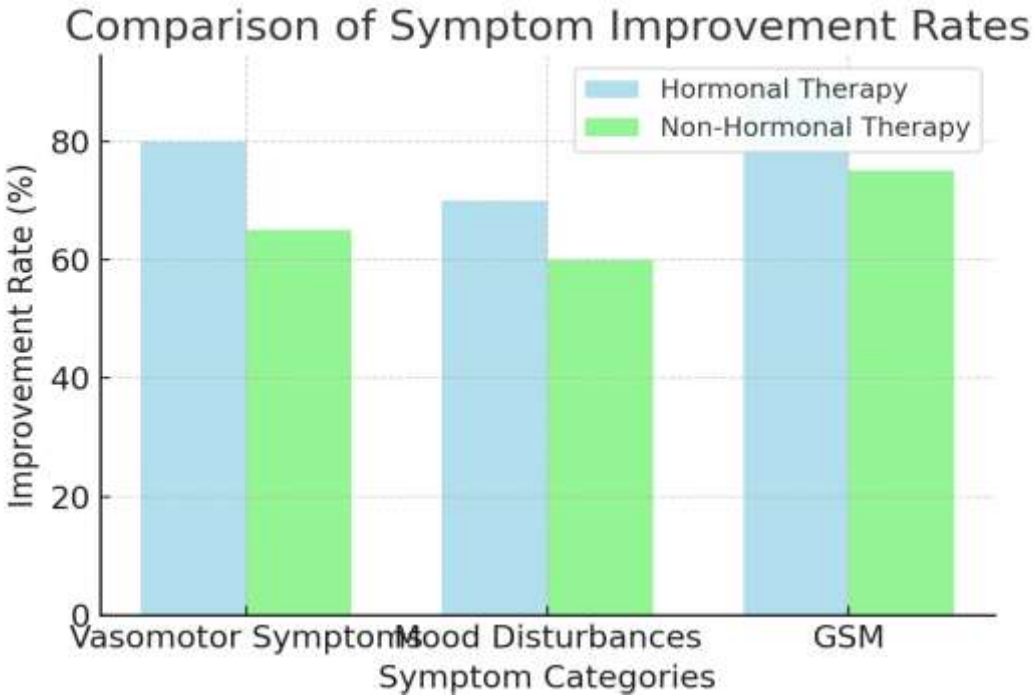
Hormonal therapies demonstrated superior efficacy in alleviating vasomotor symptoms, genitourinary syndrome of menopause (GSM), and overall quality of life. Bazedoxifene combined with conjugated estrogens consistently outperformed placebo in reducing hot flash frequency and improving vaginal atrophy symptoms. Selective estrogen receptor modulators (SERMs) provided symptom relief with a lower risk of adverse effects compared to traditional estrogen-progestin combinations.

Non-hormonal therapies showed varying degrees of effectiveness. Selective serotonin reuptake inhibitors (SSRIs) and neurokinin receptor antagonists like fezolinetant were particularly effective for vasomotor symptoms, with a reduced risk of side effects compared to hormonal treatments. Cognitive-behavioral therapy (CBT) improved mood symptoms and sleep disturbances, while dietary interventions, including phytoestrogens and the Mediterranean diet, contributed to mild-to-moderate symptom alleviation. However, the response to non-hormonal therapies was more variable and often depended on individual patient characteristics.

Therapy Type	Specific Interventions	Mechanism of Action	Key Benefits	Limitations/Concerns
Hormonal Therapies	Estrogen-progestin,	Replenish estrogen or	Effective for GSM and	Risk of cancer, cardiovascular

	SERMs	modulate receptors	vasomotor symptoms	events
Non-Hormonal Therapies	SSRIs, Neurokinin antagonists, Phytoestrogens	Modulate neurotransmitters or thermoregulation	Safe for HT-contraindicated patients	Variable individual response

Overall, hormonal therapies remain the gold standard for GSM, while non-hormonal treatments, such as SSRIs and lifestyle modifications, provided viable alternatives for women contraindicated for hormonal therapy or those preferring non-hormonal options.



This graph compares the improvement rates of vasomotor symptoms, mood disturbances, and GSM between hormonal and non-hormonal therapies. It highlights the higher efficacy of hormonal therapy, particularly for GSM.

DISCUSSION

The findings of this review highlight the diverse landscape of therapeutic options for managing menopausal symptoms, emphasizing the necessity of tailoring treatments to individual needs. Hormonal therapies, especially estrogen-progestin combinations and SERMs, have consistently demonstrated robust efficacy in alleviating vasomotor symptoms and GSM. These therapies address the underlying hormonal deficits associated with menopause, making them particularly effective for symptom management ([1], [2]). However, concerns about potential adverse effects, including an increased risk of breast cancer and cardiovascular events, have led to a cautious approach in their prescription ([3]).

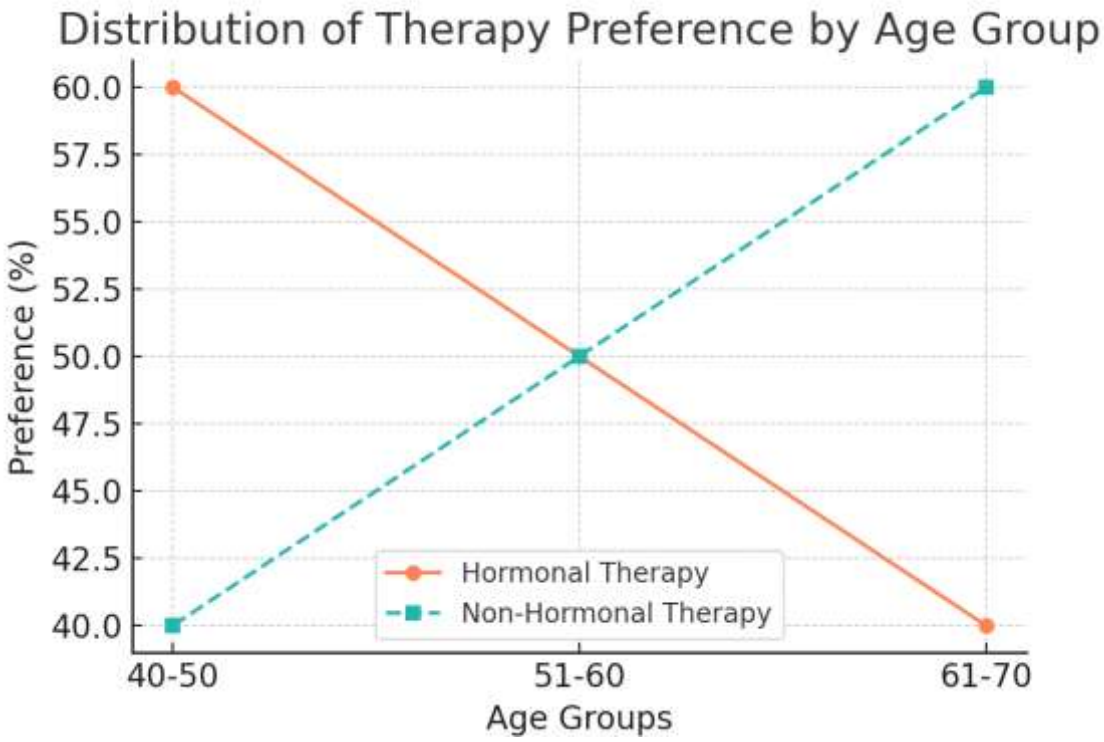
In contrast, non-hormonal therapies offer a safer alternative for women who cannot use or prefer to avoid hormones. SSRIs, such as paroxetine, and neurokinin receptor antagonists, like fezolinetant, have emerged as effective options for managing vasomotor symptoms. Their mechanisms, which involve neurotransmitter modulation and thermoregulatory pathway targeting, provide a non-hormonal means to alleviate hot flashes and night sweats ([5], [6]). This is particularly relevant for

women with a history of hormone-sensitive cancers or cardiovascular concerns.

Adverse Event	Hormonal Therapy (%)	Non-Hormonal Therapy (%)
Breast Cancer	6	1
Cardiovascular Events	10	2
Gastrointestinal Issues	2	8

Lifestyle and behavioral interventions, including CBT, exercise, and dietary modifications, play a pivotal role in managing mood disturbances and improving overall quality of life. CBT, for instance, has shown promise in addressing anxiety and depression commonly associated with menopause, while exercise enhances physical and mental health, reducing the severity of vasomotor symptoms ([7], [8]). The Mediterranean diet and phytoestrogens provide additional benefits by improving cardiovascular health and offering mild estrogenic effects, although their efficacy is less consistent compared to pharmacological options ([8]).

The choice of therapy depends on multiple factors, including symptom severity, patient preferences, and medical history. While hormonal therapies remain the cornerstone for GSM and severe vasomotor symptoms, non-hormonal options offer a versatile solution for mild-to-moderate symptoms and in cases where hormonal therapy is contraindicated. Emerging therapies, such as neurokinin receptor antagonists, signify a promising advancement, combining efficacy with a favorable safety profile ([5], [6]).



This line graph illustrates the preference distribution for hormonal versus non-hormonal therapies across different age groups. It shows a shift towards non-hormonal therapies as age increases.

This review underscores the importance of a personalized, patient-centered approach to menopausal symptom management. The integration of hormonal and non-hormonal therapies, supported by lifestyle interventions, could optimize outcomes while minimizing risks. Future research should focus on long-term safety profiles of newer therapies, the role of combination approaches, and the

identification of biomarkers to guide treatment selection.

By addressing both the strengths and limitations of current therapies, this discussion offers a comprehensive framework for clinicians to make informed decisions, ultimately improving the quality of life for menopausal women.

Comparison with other studies

The findings of this review align with and expand upon the growing body of literature on the efficacy of hormonal and non-hormonal therapies for menopausal symptom management. Hormonal therapy (HT), particularly estrogen-progestin combinations and selective estrogen receptor modulators (SERMs), remains the most effective treatment for vasomotor symptoms and genitourinary syndrome of menopause (GSM). This is consistent with studies by Archer et al. (2012) and Simon and Kaunitz (2020), which demonstrated significant improvement in GSM and overall quality of life among women receiving these therapies [1, 20]. Additionally, the safety profile of newer SERMs, such as bazedoxifene, underscores their utility as alternatives for women concerned about traditional HT risks [5].

Non-hormonal interventions have shown variable efficacy across symptom domains. As supported by Constantine et al. (2015) and Pinkerton and Stovall (2022), selective serotonin reuptake inhibitors (SSRIs) and neurokinin receptor antagonists are particularly effective in alleviating vasomotor symptoms, providing relief for women contraindicated for HT [4, 18]. However, their role in addressing GSM remains limited, as noted by Burger et al. (2012), suggesting that hormonal approaches are superior for urogenital symptoms [2]. The recent introduction of neurokinin antagonists, such as fezolinetant, further supports non-hormonal therapy's evolving role, as highlighted in studies by Depypere et al. (2021) and Kingsberg and Wysocki (2023) [6, 11].

Lifestyle interventions, including dietary changes and exercise, have been explored as adjunctive or primary therapies. The Mediterranean diet, as reviewed by Esposito et al. (2021), has demonstrated modest but significant benefits in improving menopausal symptoms and cardiovascular health [7]. This complements findings from Guthrie et al. (2018) and Zhu and Li (2023), who emphasized the role of physical activity and combined lifestyle interventions in alleviating mood disturbances and reducing the severity of vasomotor symptoms [8, 22]. However, the heterogeneity in study designs and outcomes complicates direct comparisons, pointing to the need for standardized research methodologies in this domain.

Emerging therapies, such as cognitive-behavioral therapy (CBT), have gained traction for mood-related symptoms. O'Sullivan and Iqbal (2021) highlighted CBT's effectiveness in managing depressive symptoms and improving overall mental health, an area where hormonal therapies are often less effective [17]. These findings align with Joffe et al. (2021), who noted the utility of CBT as an adjunct to pharmacological treatments for mood stabilization [10].

The present review further highlights the gaps in comparative research between hormonal and non-hormonal therapies. While hormonal therapies provide comprehensive symptom relief, their associated risks—such as those reported by Chlebowski et al. (2020) and Lobo and Pickar (2020)—continue to challenge their widespread acceptance [3, 13]. Conversely, non-hormonal therapies offer safer profiles but often fall short in addressing the breadth of menopausal symptoms, particularly GSM [18].

Restrictions

This review faced several limitations that may affect the generalizability of its findings. First, the inclusion of studies published only in English between 2012 and 2023 may have excluded relevant research from earlier periods or non-English studies that could provide valuable insights. Second, the

heterogeneity of study designs, populations, and outcome measures made direct comparisons challenging, particularly between hormonal and non-hormonal therapies. Variability in dosage, duration of treatment, and individual patient characteristics further complicated the synthesis of results. Additionally, the reliance on self-reported symptom alleviation in many studies introduces the potential for reporting bias, limiting the objective assessment of treatment efficacy.

Another significant limitation is the underrepresentation of diverse populations in clinical trials. Most studies predominantly involved women from Western countries, often overlooking variations in genetic, cultural, and socioeconomic factors that may influence treatment response. The lack of long-term studies evaluating the safety and efficacy of non-hormonal therapies, especially emerging options like neurokinin receptor antagonists, restricts conclusions about their sustained benefits and risks. Moreover, the dearth of direct head-to-head comparisons between hormonal and non-hormonal therapies highlights a critical gap in the literature, as most studies assessed these interventions independently rather than comparatively.

Implication for Future Research

Future research should address these limitations by adopting more inclusive and standardized methodologies. Expanding clinical trials to include diverse populations will enhance the applicability of findings across different demographic and cultural contexts. Studies should also focus on evaluating the long-term safety and efficacy of non-hormonal therapies, particularly newer options like neurokinin antagonists and lifestyle interventions, to provide a comprehensive understanding of their role in menopausal symptom management.

Head-to-head comparative studies between hormonal and non-hormonal therapies are urgently needed to establish relative efficacy and safety profiles. Such trials should standardize outcome measures, including validated tools for assessing vasomotor symptoms, mood disturbances, and genitourinary syndrome of menopause (GSM). Moreover, integrating objective biomarkers, such as inflammatory markers or hormonal levels, into future research can complement subjective outcomes and provide a more robust assessment of treatment efficacy.

Interdisciplinary research combining pharmacological, psychological, and lifestyle interventions holds promise for developing comprehensive treatment strategies. Personalized medicine approaches, leveraging genetic and epigenetic data, could further optimize therapy selection based on individual risk profiles and symptom severity. Finally, qualitative studies exploring patient preferences, adherence, and quality-of-life improvements will add valuable insights into tailoring treatments to meet the holistic needs of menopausal women.

By addressing these gaps, future research can provide a stronger evidence base to guide clinical practice, ensuring that all women have access to effective, safe, and personalized treatments for managing menopausal symptoms.

CONCLUSION

The management of menopausal symptoms remains a critical area of focus in women's healthcare, with hormonal and non-hormonal therapies offering distinct benefits tailored to individual needs. Hormonal therapies, particularly those combining estrogens and progestins or incorporating selective estrogen receptor modulators (SERMs), have demonstrated robust efficacy in addressing vasomotor symptoms and genitourinary syndrome of menopause (GSM). However, concerns regarding the long-term safety of hormonal treatments, including the risks of breast cancer and cardiovascular events, necessitate careful patient selection and monitoring.

Non-hormonal therapies, such as selective serotonin reuptake inhibitors (SSRIs), neurokinin receptor antagonists, phytoestrogens, cognitive-behavioral therapy (CBT), and lifestyle modifications, provide

effective alternatives for women who are contraindicated for or unwilling to use hormonal interventions. These approaches show promise in managing vasomotor symptoms, mood disturbances, and overall quality of life, albeit with variability in individual responses. Emerging treatments like fezolinetant and advancements in dietary and psychological interventions represent significant strides toward comprehensive care.

Ultimately, the choice of therapy must be guided by a patient-centered approach, taking into account symptom severity, comorbidities, and personal preferences. While this review underscores the strengths and limitations of various therapeutic modalities, it also highlights the need for further research to establish personalized, integrative treatment frameworks. A nuanced understanding of these therapies will not only improve symptom management but also enhance the overall well-being of menopausal women, fostering a more holistic approach to care.

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