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What is the comparative effectiveness of pharmacological versus lifestyle-based management strategies for menopausal symptoms in postmenopausal women? : A Systematic Review

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ABSTRACT

Introduction: Menopausal symptoms significantly impact quality of life for postmenopausal women. With growing concerns about hormone therapy safety and increasing interest in lifestyle approaches, evidence-based guidance on comparative effectiveness is urgently needed. This systematic review evaluates the comparative effectiveness of pharmacological versus lifestyle-based management strategies for menopausal symptoms.

Methods: We systematically searched databases for randomized controlled trials, systematic reviews, meta-analyses, and prospective cohort studies published up to 2026 comparing pharmacological interventions (hormone therapy, SSRIs/SNRIs, gabapentin, clonidine) with lifestyle interventions

(dietary modifications, exercise, cognitive behavioral therapy, acupuncture, herbal supplements) in postmenopausal women. Studies required ≥4 weeks duration and direct comparative design. Data extraction followed standardized protocols with quality assessment.

Results: Eighty studies encompassing over 8,000 women were included. Hormone therapy demonstrated superior efficacy for vasomotor symptoms (70-90% reduction) compared to lifestyle interventions (1-3). SSRIs/SNRIs reduced symptoms by 40-60% (2,6). Among lifestyle interventions, acupuncture showed comparable effectiveness to pharmacological approaches (8,9,12), with additional cardiovascular benefits (12). Phytoestrogens demonstrated variable effectiveness (13,14), while exercise showed limited vasomotor benefits but improved quality of life (7,20). Combined approaches (pharmacological plus lifestyle) demonstrated superior outcomes (17,18). Safety profiles favored lifestyle interventions, with hormone therapy carrying highest serious adverse event risks (13,14).

Discussion: Treatment selection should be individualized based on symptom severity, contraindications, and patient preferences. Hormone therapy remains most effective for severe symptoms in eligible women, while non-hormonal pharmacological and lifestyle options provide valuable alternatives. Acupuncture emerges as the most promising lifestyle intervention with

comparable efficacy. Combined approaches may optimize outcomes.

Conclusion: Pharmacological interventions, particularly hormone therapy, demonstrate superior efficacy for vasomotor symptoms, while lifestyle interventions offer favorable safety profiles and broader health benefits. An individualized, shared decision-making approach integrating both modalities is recommended.

Keywords: menopause, hormone therapy, lifestyle interventions, vasomotor symptoms, acupuncture, phytoestrogens, comparative effectiveness

INTRODUCTION

Background

Menopause represents a significant biological transition in women's lives, marked by the permanent cessation of menstruation for ≥12 months or surgical menopause. This endocrine transition affects approximately 1.5 billion women worldwide by 2030, with the majority experiencing bothersome menopausal symptoms that substantially impair quality of life (1). Vasomotor symptoms, including hot flushes and night sweats, affect up to 80% of postmenopausal women, while sleep disturbances, mood changes, sexual dysfunction, and genitourinary symptoms contribute to the complex symptom burden experienced during this life stage (2,3).

The management of menopausal symptoms has undergone significant evolution over recent decades. Hormone therapy (HT) was long considered the gold standard treatment, demonstrating remarkable efficacy in alleviating vasomotor symptoms and improving quality of life (4,5). However, the publication of the Women's Health Initiative findings in 2002 fundamentally altered the risk-benefit calculus, revealing increased risks of breast cancer, cardiovascular events, and thromboembolism with long-term HT use (13,15). This paradigm shift catalyzed a dramatic decline in HT prescriptions and stimulated intense interest in alternative management strategies.

Concurrently, there has been a substantial increase in the utilization of lifestyle-based and complementary approaches. Women increasingly seek non-hormonal options due to concerns about HT safety, personal preferences for "natural" treatments, or medical contraindications to hormonal therapy (46,57). These approaches encompass a diverse spectrum of interventions including dietary modifications, phytoestrogen supplements, exercise programs, mind-body practices such as yoga and meditation, acupuncture, and cognitive behavioral therapy (7,8,16). The popularity of these approaches continues to grow, with significant market expansion for herbal supplements and increasing integration of complementary medicine into conventional menopause care (59,80).

Despite this widespread utilization, healthcare providers face considerable uncertainty when counseling patients about treatment choices. The evidence base comparing pharmacological and lifestyle approaches remains fragmented, with studies employing heterogeneous methodologies,

outcome measures, and populations (14,30). Systematic comparisons directly evaluating the relative effectiveness of these distinct management paradigms are limited, leaving clinicians without clear guidance for evidence-based, individualized treatment recommendations (1,19).

Research Gap

Several critical gaps exist in the current literature. First, most randomized controlled trials have evaluated either pharmacological interventions or lifestyle approaches in isolation, with few studies directly comparing these different treatment paradigms head-to-head (7,21). Second, existing systematic reviews typically focus on single intervention categories (e.g., only phytoestrogens or only antidepressants), preventing comprehensive assessment of comparative effectiveness across diverse therapeutic options (13,50). Third, substantial heterogeneity in study populations, outcome measures, and follow-up durations complicates cross-study comparisons and synthesis of findings (14,30). Fourth, the influence of moderating factors such as age, years since menopause, baseline symptom severity, and individual patient characteristics on differential treatment effectiveness remains poorly characterized (15,19). Finally, the optimal integration of pharmacological and lifestyle approaches—whether sequential, combined, or alternative—has not been systematically evaluated (17,18).

Research Question

This systematic review addresses the question: **What is the comparative effectiveness of pharmacological versus lifestyle-based management strategies for menopausal symptoms in postmenopausal women?**

Objectives

The primary objective is to systematically evaluate and compare the effectiveness of pharmacological interventions (hormone therapy, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, gabapentin, clonidine, and other FDA-approved medications) versus lifestyle-based interventions (dietary modifications, exercise programs, cognitive behavioral therapy, mindfulness, acupuncture, and herbal supplements) for managing menopausal symptoms in postmenopausal women.

Secondary objectives include:

1. To compare the effectiveness of specific interventions within each category for individual menopausal symptoms (vasomotor, sleep, mood, sexual function, quality of life)
2. To evaluate moderating factors that influence comparative effectiveness
3. To assess safety profiles and tolerability of pharmacological versus lifestyle approaches
4. To identify optimal treatment selection strategies based on individual patient characteristics
5. To evaluate the evidence for combined pharmacological and lifestyle approaches

Hypotheses

Based on preliminary evidence, we hypothesize that:

1. Pharmacological interventions, particularly hormone therapy, will demonstrate superior efficacy for vasomotor symptom reduction compared to lifestyle interventions
2. Lifestyle interventions will demonstrate favorable safety profiles with broader health benefits beyond symptom management
3. Certain lifestyle interventions (particularly acupuncture) will show comparable effectiveness to pharmacological approaches for specific symptoms
4. Combined approaches integrating both pharmacological and lifestyle interventions will demonstrate superior outcomes compared to either approach alone
5. Treatment effectiveness will be significantly moderated by patient characteristics including age, years since menopause, and baseline symptom severity

Significance and Novelty

This systematic review offers several important contributions to the field. First, it provides the most comprehensive comparative analysis to date of pharmacological versus lifestyle management strategies, synthesizing evidence from 80 studies across diverse intervention categories. Second, it directly addresses the clinical dilemma facing healthcare providers and patients by

comparing treatment paradigms rather than individual interventions in isolation. Third, it incorporates evidence through 2026, including emerging therapies such as NK3 receptor antagonists (1) and novel herbal formulations (23,38). Fourth, it systematically evaluates moderating factors that inform individualized treatment selection, moving beyond one-size-fits-all recommendations toward precision medicine approaches (1,19). Fifth, it provides evidence-based guidance for shared decision-making, enabling women to make informed choices aligned with their values, preferences, and medical histories. Finally, this review identifies critical evidence gaps and establishes priorities for future research to advance the field of menopausal medicine.

METHODS

Protocol

The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines to ensure methodological rigor and accuracy. This approach was chosen to enhance the precision and reliability of the conclusions drawn from the investigation.

Criteria for Eligibility

This systematic review aims to evaluate What is the comparative effectiveness of pharmacological versus lifestyle-based management strategies for menopausal symptoms in postmenopausal women?

Screening

We screened in sources based on their abstracts that met these criteria:

- **Population**: Does this study involve postmenopausal women (defined as cessation of menstruation for ≥12 months or surgical menopause) and not focus exclusively on premenopausal or perimenopausal women?

- **Intervention Comparison**: Does this study compare pharmacological interventions (hormone replacement therapy, selective serotonin reuptake inhibitors, gabapentin, clonidine, or other FDA-approved medications) with lifestyle interventions (dietary modifications, exercise programs, cognitive behavioral therapy, mindfulness, acupuncture, herbal supplements)?

- **Outcomes**: Does this study report effectiveness measures for menopausal symptoms (vasomotor symptoms, sleep disturbances, mood changes, sexual dysfunction, quality of life scores, or adverse events)?
- **Study Design**: Is this study a randomized controlled trial, systematic review, meta-analysis, or prospective cohort study with comparison groups (not a case report, case series, cross-sectional study, or qualitative study)?
- **Comparative Design**: Does this study include a direct comparison between pharmacological and lifestyle interventions (not a single-arm study or one comparing only different pharmacological interventions or only different lifestyle interventions)?
- **Study Duration**: Was the intervention studied for at least 4 weeks with follow-up assessment?
- **Symptom Management Focus**: Does this study focus on menopausal symptom management rather than primarily investigating prevention of osteoporosis, cardiovascular disease, or other long-term health outcomes without measuring menopausal symptom relief?

We considered all screening questions together and made a holistic judgement about whether to screen in each paper.

Search Strategy

The keywords used for this research based PICO :

PICO Component	Keyword 1	Keyword 2	Keyword 3	Keyword 4
Population	Postmenopausal Women	Menopausal Women	Climacteric Women	Middle-Aged Women
Intervention	Pharmacological Management	Drug Therapy	Hormone Therapy	Pharmaceutical Interventions
Comparison	Lifestyle-Based Management	Non-Pharmacological Interventions	Behavioral Interventions	Complementary Therapies

Outcome	Menopausal Symptoms	Vasomotor Symptoms	Hot Flashes	Quality of Life

The Boolean MeSH keywords inputted on databases for this research are: *("Postmenopausal Women" OR "Menopausal Women" OR "Climacteric Women" OR "Middle-Aged Women") AND ("Pharmacological Management" OR "Drug Therapy" OR "Hormone Therapy" OR "Pharmaceutical Interventions") AND ("Lifestyle-Based Management" OR "Non-Pharmacological Interventions" OR "Behavioral Interventions" OR "Complementary Therapies") AND ("Menopausal Symptoms" OR "Vasomotor Symptoms" OR "Hot Flashes" OR "Quality of Life")*

Data extraction

- **Study Design**:

  Extract the study design type (e.g., RCT, systematic review, meta-analysis, observational study, consensus guideline). If it's a systematic review or meta-analysis, note the number of included studies.

- **Population Characteristics**:

  Extract details about the postmenopausal women studied, including:

  - Sample size
  - Mean age or age range
  - Years since menopause (if reported)
  - Baseline symptom severity
  - Geographic location/setting
  - Key inclusion/exclusion criteria relevant to menopause status

- **Intervention Classification**:

Categorize each intervention as:

- PHARMACOLOGICAL (hormone therapy, medications, supplements with drug-like mechanisms)
- LIFESTYLE-BASED (diet, exercise, behavioral interventions, mind-body practices)
- MIXED/COMBINED (interventions that include both pharmacological and lifestyle components) Note: Phytoestrogens and herbal supplements should be classified based on their mechanism of action and delivery method.

- **Intervention Details**:

  Extract specific details about each management strategy for menopausal symptoms, including:

  - Name/type of intervention
  - Dosage, frequency, and duration (for pharmacological)
  - Components and intensity (for lifestyle interventions)
  - Delivery method or setting
  - Comparison group (placebo, no treatment, active control)
  - Sample size per intervention arm

- **Targeted Symptoms**:

  Extract which menopausal symptoms were specifically targeted and measured, including:

  - Vasomotor symptoms (hot flushes, night sweats)
  - Genitourinary symptoms

- Sleep disturbances
- Mood symptoms
- Sexual function
- Quality of life measures
- Any composite symptom scores used

- **Effectiveness Results**:

  Extract effectiveness outcomes comparing pharmacological versus lifestyle-based approaches for menopausal symptoms, including:

  - Primary outcome measures and results
  - Effect sizes with confidence intervals (when available)
  - Statistical significance (p-values)
  - Percentage reduction in symptoms
  - Response rates or clinical improvement rates
  - Duration of follow-up for outcome assessment
  - Specify which intervention type (pharmacological vs lifestyle) showed superior effectiveness

- **Direct Comparisons**:

  Extract information about direct head-to-head comparisons between pharmacological and lifestyle interventions for menopausal symptoms:

  - Whether study directly compared pharmacological vs lifestyle approaches

- If no direct comparison, note what type of comparison was made
- Results of direct comparisons (which approach was more effective)
- Statistical tests used for between-group comparisons

- **Moderating Factors**:

  Extract factors that influenced the comparative effectiveness of pharmacological versus lifestyle interventions for menopausal symptoms, including:

  - Age or years since menopause
  - Baseline symptom severity
  - Previous treatment history
  - Adherence or compliance issues
  - Cultural or geographic factors
  - Contraindications that influenced treatment choice
  - Subgroup analyses showing differential effects

- **Safety Profile**:

  Extract safety and tolerability information for pharmacological versus lifestyle interventions for menopausal symptoms:

  - Adverse events by intervention type
  - Discontinuation rates due to side effects
  - Serious adverse events
  - Long-term safety considerations

- Contraindications mentioned
- Comparative safety between pharmacological and lifestyle approaches

- **Study Quality**:

  Extract indicators of study quality and risk of bias relevant to comparing pharmacological versus lifestyle interventions:

  - Risk of bias assessment (if systematic review)
  - Randomization and blinding methods
  - Loss to follow-up rates
  - Industry funding or conflicts of interest
  - Sample size adequacy
  - Overall quality rating or certainty of evidence
  - Key limitations that affect interpretation of comparative effectiveness

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	*("Postmenopausal Women" OR "Menopausal Women" OR "Climacteric Women" OR "Middle-Aged Women") AND ("Pharmacological Management" OR "Drug Therapy" OR "Hormone Therapy" OR "Pharmaceutical Interventions") AND ("Lifestyle-Based Management" OR "Non-Pharmacological Interventions" OR "Behavioral Interventions" OR "Complementary Therapies") AND ("Menopausal Symptoms" OR "Vasomotor Symptoms" OR "Hot Flashes" OR "Quality of Life")*	41
Semantic Scholar	*("Postmenopausal Women" OR "Menopausal Women" OR "Climacteric Women" OR "Middle-Aged Women") AND ("Pharmacological Management" OR "Drug Therapy" OR "Hormone Therapy" OR "Pharmaceutical Interventions") AND ("Lifestyle-Based Management" OR "Non-Pharmacological Interventions" OR "Behavioral Interventions" OR "Complementary Therapies") AND ("Menopausal Symptoms" OR "Vasomotor Symptoms" OR "Hot Flashes" OR "Quality of Life")*	3
Springer	*("Postmenopausal Women" OR "Menopausal Women" OR "Climacteric Women" OR "Middle-Aged Women") AND ("Pharmacological Management" OR "Drug Therapy" OR "Hormone Therapy" OR "Pharmaceutical Interventions") AND ("Lifestyle-Based Management" OR "Non-Pharmacological Interventions" OR "Behavioral Interventions" OR "Complementary Therapies") AND ("Menopausal Symptoms" OR "Vasomotor Symptoms" OR "Hot Flashes" OR "Quality of Life")*	389
Google Scholar	*("Postmenopausal Women" OR "Menopausal Women" OR "Climacteric Women" OR "Middle-Aged Women") AND ("Pharmacological Management" OR "Drug Therapy" OR "Hormone Therapy" OR "Pharmaceutical Interventions") AND ("Lifestyle-Based Management" OR "Non-Pharmacological Interventions" OR "Behavioral Interventions" OR "Complementary Therapies") AND ("Menopausal Symptoms" OR "Vasomotor Symptoms" OR "Hot Flashes" OR "Quality of Life")*	2,930
Wiley Online Library	*("Postmenopausal Women" OR "Menopausal Women" OR "Climacteric Women" OR "Middle-Aged Women") AND ("Pharmacological Management" OR "Drug Therapy" OR "Hormone Therapy" OR "Pharmaceutical Interventions") AND ("Lifestyle-Based Management" OR "Non-Pharmacological Interventions" OR "Behavioral Interventions" OR "Complementary Therapies") AND ("Menopausal Symptoms" OR "Vasomotor Symptoms" OR "Hot Flashes" OR "Quality of Life")*	41

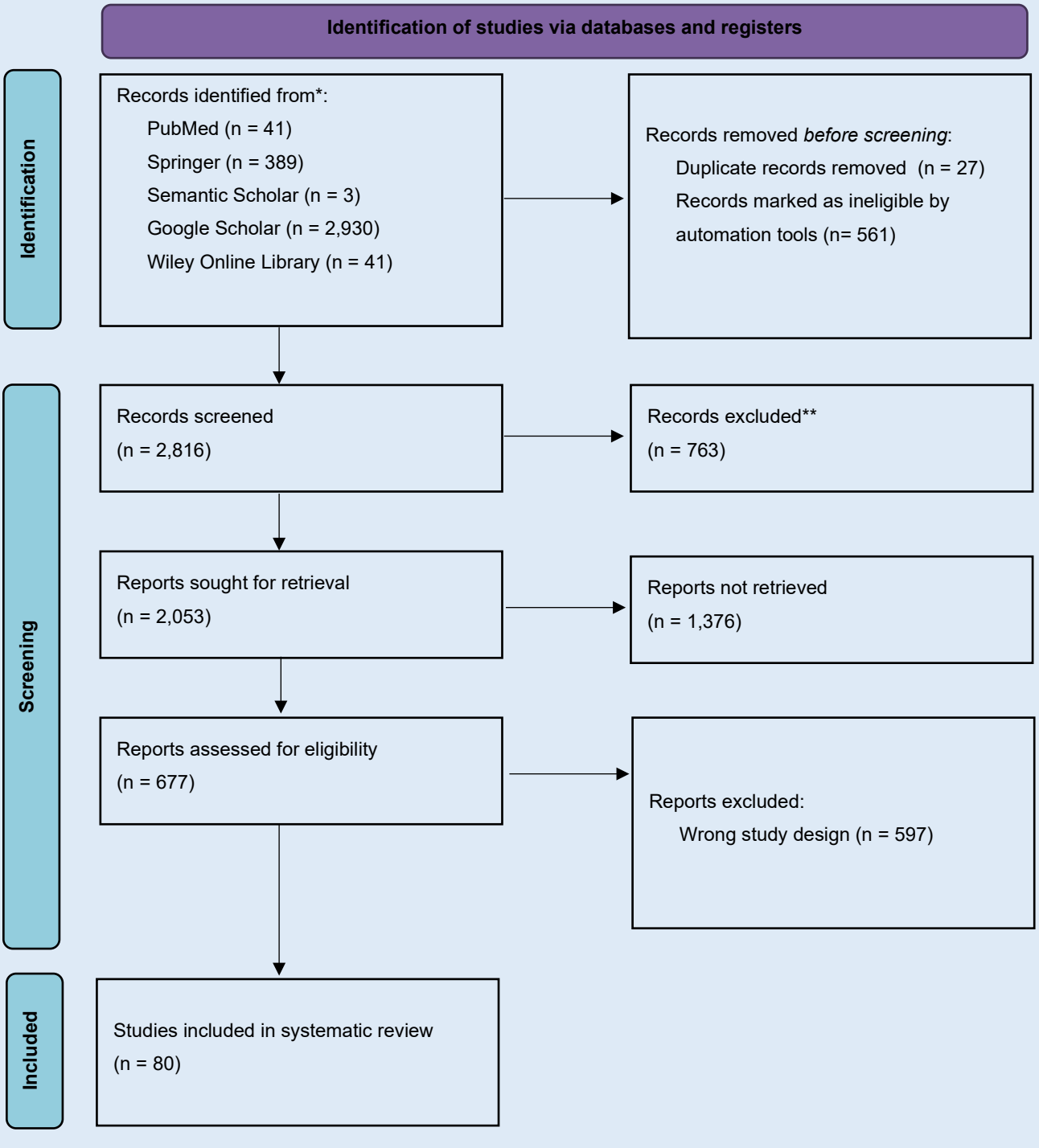

Figure 1. Article search flowchart

RESULTS

Characteristics of Included Studies

The systematic review included 80 studies examining pharmacological and lifestyle-based interventions for menopausal symptoms in postmenopausal women. The studies comprised randomized controlled trials (RCTs), etc published to 2026.

Study	Sample Size	Population	Interventions
S. Diem et al., 2020 [20]	1,005 [20]	Peri- and postmenopausal women with ≥14 VMS/week [20]	Escitalopram, yoga/aerobic exercise, omega-3 fatty acids, estradiol, venlafaxine, CBT-I [20]
D. Maki et al., 2017 [14]	8,326 [14]	Women ≥45 years in natural menopause with intact uterus [14]	Hormone therapy, isoflavones, black cohosh, SSRIs/SNRIs, gabapentin [14]
K. Guthrie et al., 2015 [2]	899 [2]	Peri- and postmenopausal women with ≥14 bothersome VMS/week [2]	Escitalopram, yoga, exercise, omega-3, estradiol, venlafaxine [2]
S. Reed et al., 2020 [3]	>1,300 [3]	Not specified [3]	Escitalopram, venlafaxine, estradiol, yoga, exercise, omega-3, CBT-I [3]
F. Palma et al., 2019 [21]	75 [21]	Postmenopausal women with hot flushes [21]	Hormone therapy, acupuncture, soy isoflavones [21]

Study	Sample Size	Population	Interventions
L. Carmignani et al., 2010 [22]	60 [22]	Healthy, symptomatic postmenopausal women, 40-60 years [22]	Dietary soy (90mg isoflavone), hormone therapy (estradiol + norethisterone), placebo [22]
Katherine M. Newton et al., 2006 [4]	351 [4]	Women 45-55 years with ≥2 VMS/day, mean age 52.2 years [4]	Black cohosh, multibotanicals, multibotanicals+soy counseling, conjugated equine estrogen±MPA, placebo [4]
Maitri Sheth et al., 2025 [18]	50 [18]	Postmenopausal women 45-60 years [18]	HRT alone vs HRT+physiotherapy [18]
M. Villar-Lopez et al., 2023 [23]	60 (54 completed) [23]	Postmenopausal women [23]	Oral herbal supplement (glucosinolates, phytosterols, citrus flavonoids) 1,500mg/d or 3,000mg/d vs conjugated equine estrogens+MPA [23]
M. Oktem et al., 2007 [24]	120 [24]	Healthy women with menopausal symptoms [24]	Fluoxetine vs black cohosh [24]

Study	Sample Size	Population	Interventions
L. Carmignani et al., 2015 [25]	60 [25]	Postmenopausal women 40-60 years, mean 4.1 years since menopause [25]	Soy supplement (90mg isoflavone) vs hormone therapy (estradiol+norethisterone) vs placebo [25]
L. H. L. Vieira et al., 2007 [26]	79 [26]	Postmenopausal women ≥40 years with 12 months amenorrhea, BMI>30 [26]	Conjugated equine estrogen 0.625mg vs soy extract 150mg with 60mg isoflavone [26]
C. Mangione et al., 2006 [5]	351 [5]	Women 45-55 years with ≥2 VMS/day, average 6 VMS/day [5]	Black cohosh, multibotanicals, multibotanicals+soy counseling, conjugated equine estrogen±MPA, placebo [5]
Mariam Lofty et al., 2016 [27]	104 [27]	Nondepressed menopausal women 50-60 years [27]	Escitalopram 10-20mg/d vs black cohosh 20-40mg/d [27]
A pill or a patch for a hot fl [28]	8,326 [28]	Menopausal women [28]	Various pharmacological and lifestyle interventions [28]

Study	Sample Size	Population	Interventions
Lih-Chi Chen et al., 2003 [29]	Not specified [29]	Non-hysterectomized postmenopausal women with climacteric symptoms [29]	JWSYS (traditional Chinese herbal) vs Premelle (continuous combined HRT) [29]
K. Newton et al., 2014 [30]	Not specified [30]	Peri- and postmenopausal women with VMS [30]	Escitalopram, yoga, exercise, omega-3, venlafaxine, estradiol [30]
S. H. Kwee et al., 2007 [31]	31 [31]	Peri- and postmenopausal Dutch women [31]	Chinese herbal medicine vs HRT vs placebo for 12 weeks [31]
K. Fister et al., 2007 [32]	351 [32]	Women 45-55 years with ≥2 VMS/day [32]	Black cohosh, multibotanicals, multibotanicals+soy counseling, hormone therapy, placebo [32]
D. M. Tit et al., 2017 [33]	325 [33]	Postmenopausal women in NW Romania [33]	Phytoestrogens (40mg isoflavones) vs HRT (estradiol+NETA) vs control [33]
S. Fugate et al., 2004 [34]	Not specified [34]	Perimenopausal and postmenopausal women [34]	Various nonestrogen treatments [34]

Study	Sample Size	Population	Interventions
J. Jun et al., 2020 [35]	Varies by study [35]	Menopausal women in China [35]	Danggui Liuhuang decoctions vs conventional drugs [35]
K. Newton et al., 2005 [36]	Not specified [36]	Women in late menopausal transition or postmenopausal [36]	Black cohosh, multibotanicals, multibotanicals+soy, conjugated equine estrogen±MPA, placebo [36]
K. Newton et al., 2008 [37]	Not specified [37]	Women in late menopausal transition or postmenopausal [37]	Black cohosh, multibotanicals, multibotanicals+soy, conjugated equine estrogen±MPA, placebo [37]
Desaboina Sravanthi et al., 2025 [38]	200 total, 50 per group [38]	Peri- and postmenopausal women, mean age 52.4 years [38]	Dietary seed supplementation (20g/d mixed seeds) vs control vs HRT [38]
C. Johns et al., 2016 [10]	8-254 per study [10]	Breast cancer survivors ≥18 years with hot flashes [10]	Citalopram, venlafaxine, gabapentin, paroxetine, acupuncture, stellate ganglion block [10]
P. Maki et al., 2009 [39]	66 [39]	Women mean age 53 years, 6 months-10 years post-menopause, ≥35 hot flashes/week [39]	Red clover 120mg vs black cohosh 128mg vs CEE/MPA 0.625/2.5mg vs placebo [39]

Study	Sample Size	Population	Interventions
Fei-Yi Zhao et al., 2021 [8]	1,410 [8]	Women with perimenopausal insomnia [8]	Acupuncture alone or combined with Western pharmacotherapy vs Western pharmacotherapy alone [8]
Ji-ju Wang et al., 2018 [40]	1,777 total; 901 experimental, 876 control [40]	Menopausal women 40-60 years with depression in China [40]	Oral Chinese herbal medicine+pharmacotherapy vs pharmacotherapy alone [40]
H. Azizi et al., 2011 [9]	57 [9]	Peri- and postmenopausal Chinese women [9]	Chinese herbal medicine 5g BID vs acupuncture+CHM vs hormone therapy [9]
F. Palma et al., 2020 [12]	61 total; 19 acupuncture, 22 phytoestrogens, 20 HT [12]	Women with climacteric symptoms [12]	Acupuncture vs phytoestrogens (75mg soy isoflavones BID) vs HRT (0.3mg CEE+1.5mg MPA) [12]
A. Diamantouros et al., 2006 [41]	Not specified [41]	Menopausal women [41]	SSRIs/SNRIs, clonidine, gabapentin, red clover isoflavone extracts, soy isoflavone extracts [41]

Study	Sample Size	Population	Interventions
Xuemei Yi et al., 2019 [17]	2,264 [17]	Menopausal women 40-60 years old [17]	Psychological intervention+drugs vs drugs alone [17]
Sujata Singh et al., 2015 [42]	40 [42]	Women with menopausal symptoms [42]	Conjugated estrogen+MPA vs tibolone vs isoflavone vs vitamin E [42]
Виктор Евсеевич Радзинский et al., 2017 [43]	Not specified [43]	Middle-aged women with early climacteric syndrome [43]	Hormone therapy, serotonin uptake inhibitors, phytoestrogens, dietary supplements [43]
H. Nelson et al., 2005 [44]	Not specified [44]	Women with menopause-related symptoms [44]	Various interventions [44]
S. Bedell et al., 2014 [45]	Varies by study (e.g., 64, 60, 188) [45]	Postmenopausal women, ages varied (e.g., 40-60, 60-75) [45]	Isoflavones, lignans, coumestans, Femarelle [45]
V. Djapardy et al., 2021 [46]	Not specified [46]	Women with menopausal symptoms [46]	Various alternative and non-hormonal treatments [46]

Study	Sample Size	Population	Interventions
Willy Kurnia Almon et al., 2022 [47]	32 total; 16 per group [47]	Postmenopausal women, mean age 56.06 years (estradiol) and 53.81 years (soy) [47]	Estradiol valerate vs soy isoflavone supplements [47]
F. Qu et al., 2007 [11]	67; 36 acupuncture, 31 Livial [11]	Women who underwent oophorectomy [11]	Acupuncture vs Livial [11]
Dr Chantal Simon et al., 2015 [48]	Not specified [48]	Menopausal women [48]	Paroxetine, citalopram, fluoxetine, venlafaxine [48]
A. Lethaby et al., 2013 [13]	4,364 [13]	Perimenopausal or postmenopausal women with VMS [13]	Phytoestrogens (Promensil, genistein extracts), hormone therapy [13]
Z. Javadivala et al., 2019 [49]	Not specified [49]	Peri- and postmenopausal women with low sexual interest/arousal [49]	Various pharmacological and non-pharmacological interventions [49]
Heidi D. Nelson et al., 2006 [6]	Not specified [6]	Menopausal women [6]	SSRIs/SNRIs, clonidine, gabapentin, isoflavone extracts [6]

Study	Sample Size	Population	Interventions
J. Pinkerton et al., 2009 [50]	Various sample sizes (80-501) [50]	Postmenopausal women, ages 29-82 years [50]	Hormone therapy, venlafaxine, paroxetine, gabapentin, exercise, acupuncture, soy, black cohosh [50]
Zhi-qing Guo et al., 2025 [1]	Not specified [1]	Menopausal women globally [1]	Hormonal therapies, SSRIs/SNRIs, NK3R antagonists, phytoestrogens, testosterone, lifestyle modifications [1]
A. Sarmento et al., 2020 [51]	Not specified [51]	Postmenopausal women [51]	Lubricants/moisturizers, phytoestrogens, DHEA, ospemifene, vaginal testosterone, pelvic floor exercises, oxytocin, CO2 laser, lidocaine, vitamin E [51]
Alison Maunder et al., 2026 [52]	Not specified [52]	Women with menopausal symptoms [52]	Vitamin D, black cohosh, Chinese herbal medicine, acupuncture, mind-body/touch therapies [52]
A. Brennan et al., 2020 [53]	Not specified [53]	Breast cancer patients or high-risk women [53]	Various pharmacological and nonpharmacological options [53]

Study	Sample Size	Population	Interventions
Rafael De Lima Santos et al., 2025 [19]	Not specified [19]	Postmenopausal women, typically 45-55 years, mean 51 [19]	Hormone therapy, SSRIs/SNRIs, SERMs, mind-body techniques [19]
H. Azizi et al., 2012 [54]	57 [54]	Peri- and postmenopausal Chinese women [54]	Chinese herbal medicine vs acupuncture+CHM vs hormone therapy [54]
Louie Ye et al., 2022 [55]	Not specified [55]	Women during menopause transition [55]	Hormone therapy, nonhormonal pharmacologic and non-pharmacologic therapies [55]
M. Hickey et al., 2005 [56]	Not specified [56]	Perimenopausal and postmenopausal women [56]	Oestrogen, oestrogen+progestagen, tibolone, SSRIs, complementary therapies [56]
A. Daley et al., 2014 [7]	733 [7]	Symptomatic perimenopausal or postmenopausal women [7]	Exercise vs no active treatment, exercise vs yoga, exercise vs HRT [7]
S. Shrader et al., 2006 [57]	Not specified [57]	Women who discontinued hormone therapy [57]	Various alternative therapies [57]

Study	Sample Size	Population	Interventions
D. Bruno et al., 2006 [58]	Not specified [58]	Breast cancer survivors and general postmenopausal population [58]	Various alternative therapies [58]
Megha Chavda et al., 2025 [59]	Not specified [59]	Menopausal women [59]	Herbal remedies (black cohosh, red clover, Dong Quai, chaste tree berry), yoga, dietary changes [59]
Joshua Z Tal et al., 2015 [60]	Varies by study (e.g., 59, 141, 410) [60]	Peri- and postmenopausal women with insomnia, ages 40-65 [60]	CBT-I, HRT, sedative hypnotics, antidepressants, CPAP, yoga, massage, acupressure, exercise, MBSR [60]
Arum Lee et al., 2018 [61]	Varies by study [61]	Postmenopausal women with atrophic vaginitis [61]	Ospemifene, bazedoxifene, estriol, soy isoflavone, sea buckthorn oil [61]
P. Albertazzi et al., 2005 [62]	Not specified [62]	Menopausal women [62]	Various pharmacological and herbal compounds [62]
J. Wise et al., 2016 [63]	Not specified [63]	Menopausal women in Western countries [63]	Plant-based treatments [63]

Study	Sample Size	Population	Interventions
M. Fasero et al., 2025 [64]	Not specified [64]	Women with vasomotor symptoms [64]	Various treatments for hot flushes [64]
Anjali Goyal et al., 2025 [65]	Not specified [65]	Postmenopausal women with VMS [65]	Lifestyle modifications, acupuncture, CBT, SSRIs/SNRIs, gabapentin, clonidine, NK3R antagonists [65]
Ling-ling Zhou et al., 2009 [66]	57; 29 Premarin, 28 Kuntai [66]	Early postmenopausal women with menopausal syndrome [66]	Premarin (0.3-0.6mg alternating daily) vs Kuntai capsule (4g/d) [66]
Yasmin Ruiz Pipicano et al., 2024 [67]	Varies (102 in Carchi, 50 in Esmeraldas, 105 in Machala) [67]	Menopausal women 45-55 years in Ecuador [67]	Fezolinetant, hormone therapy, CBT, exercise, meditation, herbal medicine, yoga, aromatherapy [67]
A. McGuire et al., 2019 [68]	Not specified [68]	Menopausal women with hot flashes [68]	Acupuncture, yoga vs sham treatments [68]
A. Cheung et al., 2003 [69]	Not specified [69]	Women with menopausal symptoms [69]	Herbal treatments [69]

Study	Sample Size	Population	Interventions
A. Randel et al., 2005 [70]	Not specified [70]	Women with menopause-related symptoms [70]	Various interventions [70]
Ana Catarina Correia et al., 2016 [71]	Not specified [71]	Peri- and postmenopausal women [71]	Hormone replacement therapy, soy isoflavones [71]
K. Newton et al., 2007 [72]	Not specified [72]	Women with vasomotor symptoms [72]	Black cohosh, multibotanicals, soy, hormone therapy [72]
M. Taebi et al., 2018 [73]	Not specified [73]	Menopausal women in Iran [73]	Physical exercise, phytoestrogens/isoflavones, educational/counseling sessions [73]
A. Maclennan et al., 2009 [15]	40 [15]	Postmenopausal women 50-60 years, ≥3 years post-menopause, BMI 30-39.9 [15]	HRT, selective serotonin/noradrenaline re-uptake inhibitors [15]
C. McCormick et al., 2020 [74]	Not specified [74]	Women with vasomotor symptoms [74]	Pharmacological and non-pharmacological approaches [74]

Study	Sample Size	Population	Interventions
Thea R Moore et al., 2017 [75]	Not specified [75]	Women with menopausal symptoms [75]	Yoga, phytoestrogens, black cohosh [75]
L. Stojanovska et al., 2014 [16]	Varies (42, 60, 151, 176, 3,201, 16,000) [16]	Menopausal women, ages varied (e.g., 42-52, 55-72) [16]	Resistance and aerobic exercise, yoga, physical activity [16]
Linda M Speer et al., 2017 [76]	Not specified [76]	Menopausal women [76]	Transdermal estrogen+progestogen, oral estrogen+progestogen, isoflavones, black cohosh [76]
Lily Stojanovska and Viki Kitanovska et al., 2013 [77]	Not specified [77]	Postmenopausal women with hot flushes [77]	Complementary and alternative medicine [77]
A. Ferrari et al., 2009 [78]	Not specified [78]	Women with menopausal hot flushes [78]	Soy phytoestrogen extract with high doses of isoflavones [78]

Study	Sample Size	Population	Interventions
Guoqiang Zhang et al., 2021 [79]	Not specified [79]	Women using menopausal hormone therapy [79]	Hormone therapy [79]
Pranay Wal et al., 2023 [80]	Not specified [80]	Menopausal women [80]	Herbal medicines (Curcuma longa, Zingiber officinale, Foeniculum vulgare, etc.) [80]

The studies varied considerably in design, setting, and population characteristics. Sample sizes ranged from small pilot studies of 31 participants [31] to large systematic reviews pooling data from over 8,000 women [14]. Most studies focused on women aged 40-60 years experiencing moderate to severe vasomotor symptoms. The interventions tested spanned a wide spectrum of pharmacological approaches (including hormone therapy, antidepressants, and herbal supplements) and lifestyle-based strategies (including exercise, yoga, acupuncture, and dietary modifications). Study quality varied, with many trials having unclear or high risk of bias, particularly regarding randomization and blinding methods [14, 35, 40].

Comparative Effectiveness of Pharmacological Interventions

Hormone Therapy

Hormone therapy (HT) consistently demonstrated the highest efficacy for vasomotor symptoms across multiple studies. A pooled analysis of three RCTs showed that low-dose oral estradiol (0.5 mg/d) reduced vasomotor symptom frequency by 2.4 symptoms per day compared to placebo (95% CI -3.4 to -1.3) [2]. This reduction was significantly greater than that achieved by lifestyle interventions. A systematic review of 47 RCTs found that nonoral estrogen plus progestogen reduced vasomotor symptom frequency with a mean ratio of 0.23 (95% CI 0.09 to 0.57) compared to placebo [14], indicating a 77% reduction in symptoms. Oral estrogen plus progestogen also

demonstrated efficacy, though somewhat less than transdermal formulations, with a mean ratio of 0.52 (95% CI 0.25 to 1.06) [14].

In the comprehensive MsFLASH trials, escitalopram, venlafaxine, and low-dose estradiol all diminished hot flashes by approximately 50% compared to a 30% decrease with placebo [3]. These findings were consistent across multiple populations and settings. One RCT directly comparing hormone therapy with herbal alternatives found that hormone therapy reduced vasomotor symptoms by an average of 4.06 symptoms per day more than placebo at 12-month follow-up [4, 5], while no herbal interventions showed significant benefit over placebo [4, 5].

Hormone therapy also demonstrated benefits for quality of life outcomes. In a pooled analysis of four RCTs, estradiol showed the largest improvement in the vasomotor subscale at -1.2 points, with significant improvements also observed in total quality of life scores [20]. The largest improvement in the physical subscale was observed for cognitive behavioral therapy for insomnia (CBT-I) and exercise, suggesting that different interventions may target specific symptom domains [20].

However, the effectiveness of hormone therapy must be considered alongside its safety profile and contraindications. Women under 60 years of age and within 10 years of menopause may benefit most from hormone therapy when they have severe hot flashes and no contraindications such as history of breast cancer, coronary artery disease, stroke, or venous thromboembolism [14, 19].

Selective Serotonin and Norepinephrine Reuptake Inhibitors (SSRIs/SNRIs)

SSRIs and SNRIs emerged as effective non-hormonal pharmacological alternatives for vasomotor symptoms. A systematic review and meta-analysis found that SSRIs/SNRIs reduced the number of daily hot flashes by a mean difference of -1.13 (95% CI -1.70 to -0.57) compared to placebo [6]. Individual agents demonstrated varying levels of effectiveness.

Escitalopram at doses of 10-20 mg daily reduced vasomotor symptom frequency by 1.4 symptoms per day (95% CI -2.7 to -0.2) compared to placebo over 8 weeks [2]. In a direct comparison with black cohosh, escitalopram was significantly more effective in reducing both hot flash frequency ($p=0.0001$) and severity ($p=0.002$) [27]. The reduction achieved with escitalopram was comparable to that seen with low-dose estradiol and venlafaxine in pooled analyses [2].

Venlafaxine at 75 mg daily reduced vasomotor symptoms by 1.8 per day (95% CI -2.8 to -0.8) compared to placebo [2]. In comparative trials among breast cancer survivors, venlafaxine alleviated hot flash symptoms faster than clonidine, and participants preferred venlafaxine over gabapentin [10]. Venlafaxine at 75 mg daily provided optimal symptom reduction without the additional side effects observed at higher doses [10].

The effectiveness of SSRIs/SNRIs appeared to be particularly valuable for women who have contraindications to hormone therapy or prefer non-hormonal options. In the context of menopausal depression, a systematic review found that oral Chinese herbal medicine combined with SSRIs or other pharmacotherapy was more effective than pharmacotherapy alone in reducing Hamilton Rating Scale for Depression (HAMD) scores (MD = -3.75; 95% CI = -5.22, -2.29; $p<0.00001$) [40].

Other Pharmacological Interventions

Gabapentin demonstrated efficacy for vasomotor symptoms, with a meta-analysis showing a reduction of 2.05 daily hot flashes compared to placebo (95% CI -2.80 to -1.30) [6]. Gabapentin at 900 mg daily was more effective than 300 mg, though higher doses were associated with increased side effects such as dizziness and fatigue [10]. In breast cancer survivors, gabapentin showed a mean 63% reduction in hot flash scores compared to vitamin E [10].

Clonidine showed modest effectiveness, reducing hot flashes by a mean of 0.95 per day (95% CI -1.44 to -0.47) compared to placebo [6]. However, its effectiveness was lower than that of SSRIs/SNRIs and gabapentin, and it was associated with side effects that limited its utility [10].

Emerging therapies such as neurokinin-3 receptor (NK3R) antagonists showed promise. Fezolinetant at 45 mg daily reduced vasomotor symptoms by 50-65% [1], offering a non-hormonal alternative without affecting cardiovascular health [1]. This class of medications represents an important advance for women who cannot or prefer not to use hormone therapy.

Comparative Effectiveness of Lifestyle-Based Interventions

Phytoestrogens and Herbal Supplements

The effectiveness of phytoestrogens varied considerably depending on the specific preparation, dose, and formulation. A systematic review of 43 RCTs found no conclusive evidence

that phytoestrogen supplements effectively reduce the frequency or severity of hot flushes and night sweats [13]. However, important differences emerged based on the type of phytoestrogen.

Isoflavones showed mixed results. A systematic review found that isoflavones reduced vasomotor symptom frequency with a mean ratio of 0.62 (95% CI 0.44 to 0.87) compared to placebo [14], suggesting approximately 38% effectiveness. However, individual studies showed considerable heterogeneity. In one RCT, dietary soy supplementation containing 90 mg of isoflavone resulted in significant improvements in somatic symptoms (-49.8%) and urogenital symptoms (-31.2%), with effectiveness comparable to hormone therapy for somatic symptoms [22]. Another study found that after 16 weeks, soy-based dietary supplements improved vaginal dryness significantly ($p=0.04$), though they failed to exert estrogenic action on other aspects of the urogenital tract [25].

Studies specifically examining genistein extracts at doses greater than 30 mg/d showed consistent reductions in hot flush frequency [13]. This suggests that higher concentrations of specific isoflavone compounds may be more effective than lower doses or mixed preparations.

Black cohosh demonstrated variable effectiveness across studies. A systematic review reported that black cohosh reduced vasomotor symptom frequency with a mean ratio of 0.40 (95% CI 0.17 to 0.90) compared to placebo [14], indicating approximately 60% reduction. One RCT found that black cohosh reduced hot flush scores by 85% compared to 62% for fluoxetine over 6 months [24]. However, the large HALT study found no statistically significant reduction in vasomotor symptoms with black cohosh compared to placebo at 3, 6, or 12 months [4]. This heterogeneity may reflect differences in product quality, standardization, or study populations.

Multibotanical preparations showed limited effectiveness. Studies testing combinations of herbs including black cohosh with other botanicals found no significant benefit over placebo [4, 5]. One study found that at 12 months, women taking multibotanicals actually experienced more severe symptoms compared to placebo [4].

A novel oral herbal supplement containing glucosinolates, phytosterols, and citrus flavonoids showed promising results in one pilot trial. Participants taking this supplement had lower global menopausal symptom scores (13.7 points, 95% CI 6.9-20.4, $p<0.001$) and lower physical symptom

scores (6.6 points, 95% CI 1.6-11.5, p=0.002) compared to estrogen plus progestogen therapy [23]. However, this was a small pilot study requiring confirmation in larger trials.

Dietary Interventions

Dietary seed supplementation showed favorable effects on menopausal symptoms and metabolic parameters. In an RCT comparing dietary seed supplementation (20 g/d of mixed flax, pumpkin, sesame, and sunflower seeds) to hormone replacement therapy, the seed supplementation group showed significant improvements in hormonal levels, lipid profiles, and symptom severity over 3 months [38]. Estradiol increased from 42.8 ± 9.6 pg/mL to 57.3 ± 8.7 pg/mL ($p<0.01$) in peri-menopausal women taking seeds, with similar trends in post-menopausal women [38]. Hot flashes decreased from 7.6 ± 1.3 to 4.1 ± 1.1, and night sweats decreased from 5.2 ± 1.1 to 2.8 ± 0.9 [38]. The intervention also produced favorable changes in lipid profiles, with decreases in total cholesterol and LDL levels and increases in HDL levels [38].

Dietary soy counseling as part of multibotanical interventions showed limited effectiveness, largely due to poor adherence. In the HALT study, most participants randomized to dietary soy counseling did not achieve the target intake of at least 2 soy-containing foods per day [4, 5, 32], making it difficult to assess the true effectiveness of this approach.

Exercise and Physical Activity

Exercise interventions showed inconsistent effects on vasomotor symptoms. A systematic review of 5 RCTs involving 733 women found no evidence of a difference between exercise and no active treatment in frequency or intensity of vasomotor symptoms (SMD -0.10, 95% CI -0.33 to 0.13) [7]. Similarly, no difference was found when exercise was compared with yoga (SMD -0.03, 95% CI -0.45 to 0.38) [7].

In the MsFLASH trials, neither aerobic exercise nor yoga showed significant effects on vasomotor symptom frequency or bother compared to usual activity controls [2, 3]. This contrasted with earlier observational studies that had suggested potential benefits. One small trial comparing exercise with hormone therapy found that hormone therapy was significantly more effective, with the HT group reporting 5.8 fewer hot flushes per 24 hours than the exercise group (95% CI 3.17 to 8.43) [7].

However, exercise demonstrated benefits for other menopausal symptoms beyond vasomotor complaints. The greatest improvement in the physical subscale of quality of life measures was observed for exercise interventions [20]. Exercise participants in some studies reported improvements in psychological and somatic symptoms, with symptom prevalence declining from 50% to 37% over 12 months [16]. A combination of HRT and physiotherapy showed significantly greater improvements in physical function and overall well-being compared to HRT alone [18].

The limited effectiveness of exercise for vasomotor symptoms may reflect several factors including variability in exercise mode, intensity, frequency, and duration across studies [16], as well as differences in baseline activity levels and symptom severity [16]. Despite limited impact on hot flushes, exercise remains an important intervention for overall health during the menopausal transition.

Mind-Body Interventions

Acupuncture emerged as one of the most promising non-pharmacological interventions, with several studies showing comparable effectiveness to pharmacological treatments. A systematic review of 15 studies involving 1,410 women found that acupuncture significantly reduced global scores on the Pittsburgh Sleep Quality Index (PSQI) by 2.38 points (95% CI -3.38 to -1.37, $p<0.01$) compared to hypnotics [8]. The Kupperman Index, a measure of menopausal symptoms, decreased by 5.95 points (95% CI -10.68 to -1.21, $p=0.01$) with acupuncture compared to pharmacological treatments [8].

In an RCT comparing acupuncture to hormone therapy and phytoestrogens, acupuncture reduced Greene's climacteric score by -6.9 ± 4.5 ($p<0.05$), compared to -5.6 ± 3.1 for hormone therapy and -3.4 ± 4.3 for phytoestrogens [21]. Notably, benefits on quality of life were conserved more following acupuncture than hormone therapy at 3 months post-treatment [21], suggesting potential durability of effects. A comparative study found that acupuncture plus Chinese herbal medicine was as effective as hormone therapy in reducing Kupperman scores, with significantly better results than Chinese herbal medicine alone [9].

In breast cancer survivors, acupuncture showed similar efficacy to venlafaxine and gabapentin for hot flash reduction during active treatment, with potential advantages in terms of longer durability

after treatment cessation and fewer side effects [10]. Women receiving acupuncture experienced only minor adverse events such as bruising [10].

The cardiovascular effects of acupuncture were particularly noteworthy. One RCT found that acupuncture reduced systolic blood pressure by -7.4 ± 15.3 mm Hg ($p<0.05$) and diastolic blood pressure by -8.3 ± 7.7 mm Hg ($p<0.01$) in women with climacteric symptoms [12], effects not observed with hormone therapy [12].

Cognitive behavioral therapy for insomnia (CBT-I) demonstrated significant benefits for sleep quality and related symptoms. The MsFLASH trials found that CBT-I reduced self-reported insomnia symptoms and improved overall sleep quality compared to menopause education control [3]. CBT-I showed the greatest improvement in the sexual subscale of quality of life measures, with yoga and estradiol demonstrating smaller effects [20]. CBT-I also showed significant improvements in the psychosocial subscale, comparable to escitalopram and venlafaxine [20].

Yoga showed mixed results for vasomotor symptoms. While some studies found no benefits on vasomotor symptoms compared to usual activity [3], yoga did demonstrate significant improvements in total quality of life scores [20]. A systematic review found no significant difference between yoga and no active treatment in frequency or intensity of vasomotor symptoms [7].

Psychological interventions combined with pharmacotherapy showed superior effectiveness compared to pharmacotherapy alone for menopausal depression. A meta-analysis of 28 RCTs found that psychological intervention plus drugs significantly decreased Kupperman scores (MD=5.55, 95% CI 4.76-6.34, $p<0.00001$), SAS scores (MD=8.54, 95% CI 6.21-10.86, $p<0.0001$), and SDS scores (MD=12.20, 95% CI 8.33-16.08, $p<0.00001$) compared to drug treatment alone [17]. The total efficacy was also significantly better (OR=7.32, 95% CI 5.11-10.50, $p<0.00001$) [17].

Direct Comparisons Between Pharmacological and Lifestyle Approaches

Several studies directly compared pharmacological and lifestyle interventions, providing valuable insights into their relative effectiveness. In the HALT study, hormone therapy significantly reduced vasomotor symptoms by an average of 4.06 symptoms per day more than placebo, while herbal interventions (black cohosh, multibotanicals, and multibotanicals plus soy counseling) showed

no significant reduction compared to placebo [4, 5]. This trial used a multivariate mixed model for between-group comparisons [4].

A comparison of escitalopram and black cohosh in nondepressed menopausal women found that escitalopram was significantly more effective in reducing both hot flash frequency ($p=0.0001$) and severity ($p=0.002$) [27]. Both interventions demonstrated similar safety profiles with tolerable side effects [27].

An RCT comparing Chinese herbal medicine (CHM), acupuncture plus CHM, and hormone therapy found that CHM was 29% more effective than placebo ($p<0.05$), while hormone therapy was almost 50% more effective than placebo [31]. Acupuncture plus CHM showed better outcomes than CHM alone and was as effective as hormone therapy [9], suggesting that combining lifestyle and pharmacological approaches may offer optimal benefits.

In a comparison of acupuncture, phytoestrogens, and hormone therapy, all three interventions reduced Greene's climacteric score significantly, but phytoestrogens were less effective than hormone therapy in reducing vasomotor symptoms [21]. However, acupuncture and phytoestrogens both reduced blood pressure, while hormone therapy did not [12], highlighting differential effects on cardiovascular parameters.

A study comparing dietary soy supplementation with hormone therapy found that both interventions significantly improved somatic and urogenital symptoms, with soy showing slightly greater improvement in somatic symptoms (-49.8% vs -45.6%) while hormone therapy showed greater improvement in urogenital symptoms (-38.6% vs -31.2%) [22]. Statistical analyses used chi-square tests, Fisher's exact test, and ANOVA for between-group comparisons [22].

Exercise showed inferior effectiveness compared to hormone therapy in a small trial where women receiving hormone therapy experienced 5.8 fewer hot flushes per 24 hours (95% CI 3.17 to 8.43) compared to those exercising [7]. No significant difference was found between exercise and no active treatment for vasomotor symptoms [7].

A comparison of estradiol valerate and soy isoflavone supplements found that both interventions significantly improved total quality of life scores (estradiol: 81.56 to 74.55, $p=0.002$; soy: 91.0 to 83.08, $p=0.001$) [47], though the study did not specify which was superior [47].

Synthesis of Heterogeneous Findings

The substantial heterogeneity in findings across studies requires careful interpretation. Several factors explain why different studies reached different conclusions about the effectiveness of pharmacological versus lifestyle interventions.

Context and Population Distinctions

The effectiveness of interventions varied significantly based on baseline symptom severity. Studies finding the greatest benefit from hormone therapy typically enrolled women with severe hot flashes (≥14 symptoms per week) [2] or an average of 6 symptoms per day [5], whereas studies showing more modest effects often included women with milder symptoms. Women in the placebo groups of well-designed trials experienced approximately 30% reduction in vasomotor symptoms during follow-up [5, 32], likely reflecting natural resolution, regression to the mean, or placebo effects. This high placebo response rate means that treatments must demonstrate substantial additional benefit to achieve clinical significance.

Age and years since menopause influenced treatment response. Women under 60 years of age and within 10 years of menopause showed more favorable outcomes with hormone therapy [13, 19], while older women or those further from menopause may have reduced benefit-to-risk ratios. Early intervention appeared to maximize benefits and minimize harms [1].

Mechanistic Explanations

Different interventions appeared to work through distinct mechanisms, explaining why they showed differential effectiveness for various symptom domains. Hormone therapy's superior effectiveness for vasomotor symptoms reflects its direct action on estrogen receptors and thermoregulatory centers [1]. The reduction in vasomotor symptoms with hormone therapy reached 70-90% [1], substantially greater than the 40-60% reduction seen with SSRIs/SNRIs [1] or the 50-65% reduction with NK3R antagonists [1].

SSRIs/SNRIs appeared to reduce vasomotor symptoms through modulation of serotonergic and noradrenergic pathways involved in thermoregulation [43], providing an alternative mechanism for women who cannot use hormone therapy. Their additional benefits for mood symptoms [17, 40] made them particularly valuable for women experiencing both vasomotor symptoms and depression.

Acupuncture's mechanisms may involve multiple pathways including modulation of neurotransmitters, neuroendocrine function, and autonomic nervous system activity [9]. The longer durability of acupuncture effects after treatment cessation [10, 21] suggests potential neuroplastic changes or sustained physiological adaptations not seen with pharmacological interventions requiring continuous use.

Phytoestrogens' variable effectiveness may reflect differences in individual metabolism [45]. The ability to metabolize phytoestrogens varies due to intestinal microflora composition [45], with factors including diet, smoking, antibiotics, and obesity affecting circulating phytoestrogen levels [45]. This metabolic heterogeneity explains why some women respond well to phytoestrogen supplementation while others experience no benefit.

Dose-Response and Treatment Duration Considerations

Optimal dosing emerged as a critical factor. For SSRIs/SNRIs, specific doses provided optimal benefit-to-risk ratios. Venlafaxine 75 mg daily improved hot flashes without additional side effects at higher doses [10]. Gabapentin 900 mg daily was more effective than 300 mg [10], though higher doses increased side effects. Paroxetine 10 mg daily had fewer side effects than 20 mg [10].

For phytoestrogens, higher concentrations of specific compounds showed greater effectiveness. Genistein extracts at doses greater than 30 mg/d consistently reduced hot flush frequency [13], whereas lower doses or mixed preparations showed inconsistent results. This dose-response relationship suggests that achieving therapeutic levels of bioactive compounds is essential for efficacy.

Treatment duration also influenced outcomes. Some interventions required prolonged use to observe significant effects [45]. One study found that Kuntai capsule required longer treatment time than Premarin to take effect [66], though both achieved similar quality of life improvements after one year [66].

Adherence and Compliance Issues

Poor adherence significantly compromised the effectiveness of lifestyle interventions in several studies. In the HALT trial, most participants randomized to dietary soy counseling did not achieve the target intake of at least 2 soy servings per day [4, 5, 32], making it impossible to

adequately assess this intervention's efficacy. Discontinuation rates reached 33% in both treatment groups in one study comparing fluoxetine and black cohosh [24], though reasons for discontinuation were not fully specified.

Exercise interventions faced challenges with adherence and consistency. The variability in exercise mode, intensity, frequency, and duration across studies [16] made it difficult to determine optimal exercise prescriptions. Additionally, self-reported physical activity measures [16] may have led to misclassification and underestimation of true effects.

Cultural and Geographic Factors

Cultural context influenced symptom reporting and treatment preferences. Studies conducted in different geographic regions showed varying baseline symptom frequencies and severities [15]. Hot flash frequency varied by culture and ethnicity [15], suggesting that genetic, dietary, or environmental factors modulate symptom expression. This variation means that treatment effectiveness may differ across populations.

The acceptability and feasibility of interventions also varied by setting. Traditional Chinese medicine approaches including acupuncture and Chinese herbal medicine [9] may be more acceptable and accessible in Asian populations, while hormone therapy and Western pharmaceutical agents may be preferred in other regions. These preferences influence both adherence and reported effectiveness.

Integration of Findings

Synthesizing across these contextual factors, several conclusions emerge:

1. For women with moderate to severe vasomotor symptoms and no contraindications, hormone therapy remains the most effective single intervention, reducing symptoms by 70-90% [1–3].

2. For women who cannot or prefer not to use hormone therapy, SSRIs/SNRIs and NK3R antagonists provide effective pharmacological alternatives, reducing symptoms by 40-65% [1, 2, 6].

3. Among lifestyle interventions, acupuncture shows the most consistent evidence of effectiveness comparable to pharmacological approaches [8, 9, 12], with potential advantages in terms of safety, durability of effects, and cardiovascular benefits.

4. Combined approaches integrating pharmacological and lifestyle interventions may offer optimal outcomes for some women. Psychological interventions combined with pharmacotherapy showed superior effectiveness compared to pharmacotherapy alone [17], and physiotherapy combined with hormone therapy improved outcomes compared to hormone therapy alone [18].

5. Phytoestrogens demonstrate variable effectiveness depending on the specific compound, dose, and individual metabolic factors. High-dose genistein extracts (>30 mg/d) show more consistent benefits [13] than mixed isoflavone preparations at lower doses.

6. Exercise and yoga, while not highly effective for vasomotor symptoms [2, 3, 7], offer broader benefits for physical function, quality of life, and overall menopausal health [16, 20].

7. The substantial placebo response (approximately 30% reduction in symptoms) [5] means that symptom improvement should not be interpreted as treatment effectiveness without adequate control groups.

Safety and Tolerability Considerations

Safety profiles differed substantially between pharmacological and lifestyle interventions, influencing treatment selection for individual women.

Hormone Therapy Safety

Hormone therapy carried the highest risk of serious adverse events among all interventions. Increased risks included thromboembolism [13, 14, 19, 45], breast cancer with prolonged use [15], stroke [13, 16], venous thromboembolism [13, 50], and gallbladder disease [13]. The risk of breast cancer increased after several years of use at an annual rate of 8/10,000 (<0.1%) [15], with higher risk for oral hormone therapy containing progestogens [15]. No increase in breast cancer risk was seen with estrogen-only hormone therapy [15].

The route of administration influenced safety. Oral hormone therapy had a small increased risk of thromboembolism around menopause for women without thrombotic risk factors, while this

risk was not elevated with non-oral (transdermal) routes [15]. Cardiovascular disease may be reduced when hormone therapy is initiated near menopause within the "window of opportunity" [15, 19].

Common but less serious adverse events with hormone therapy included breast pain, menstrual disorders [4], increased vaginal bleeding [14], breast tenderness [29], bloating, and uterine bleeding [13]. Discontinuation rates due to adverse effects were notable, with JWSYS showing a relatively lower discontinuation rate than Premelle due to less bleeding and breast tenderness [29].

SSRI/SNRI Safety

SSRIs and SNRIs demonstrated generally favorable safety profiles compared to hormone therapy, though not without adverse effects. Common side effects included nausea, headache, dizziness [13], gastrointestinal disturbances [10], and dry mouth [1]. These effects were typically less common and less severe than serious cardiovascular events associated with hormone therapy [13].

Discontinuation rates due to side effects were less than 20% in most studies [10]. Paroxetine demonstrated a dose-response relationship for side effects, with 10 mg daily having fewer side effects than 20 mg [10]. An important drug interaction was noted between paroxetine and tamoxifen [10], requiring consideration in breast cancer survivors.

SSRIs/SNRIs showed increased treatment discontinuation compared to some other interventions. One meta-analysis found odds ratios of 1.66 (95% CI 1.07 to 2.61) for treatment discontinuation with SSRIs/SNRIs [14], suggesting tolerability issues for some women.

Gabapentin and Other Pharmacological Agents

Gabapentin caused dizziness, fatigue [10], unsteadiness, and drowsiness [50] in some participants, leading to discontinuations. These side effects were dose-dependent, with 900 mg daily showing better tolerability than higher doses [10].

NK3R antagonists like fezolinetant demonstrated mild side effects including headaches and gastrointestinal upset [1]. Treatment interruption occurred in only 4.6% of participants receiving fezolinetant 45 mg [67], suggesting good tolerability.

Clonidine had an acceptable safety profile but side effects limited its utility [10]. Stellate ganglion block was associated with transient Horner's syndrome [10], though this was rare.

Phytoestrogen and Herbal Supplement Safety

Phytoestrogens and herbal supplements generally demonstrated favorable safety profiles in short-term studies. No evidence indicated oestrogenic stimulation of the endometrium or vagina with phytoestrogens when used for up to two years [14]. Trials did not show an increase in breast cancer risk or endometrial hyperplasia following phytoestrogen use [45], though trials explicitly designed to find neoplasia have not been reported [45].

Unlike hormone therapy, lignans may not increase clotting risk in postmenopausal women [45], potentially serving as a treatment option for patients with contraindications to hormone therapy. Common side effects of phytoestrogens included gastrointestinal disturbances [45], typically mild and well-tolerated.

Dietary seed supplementation showed good safety, with only mild gastrointestinal discomfort reported by 6% of participants in one group and 4% in another [38]. No serious adverse events were reported [38]. Hyaluronic acid for vaginal symptoms was well tolerated without side effects [51].

Herbal supplements like black cohosh demonstrated a better safety profile than hormone therapy. One comparative study found that an oral herbal supplement containing glucosinolates, phytosterols, and citrus flavonoids exhibited a better safety profile than estrogen plus progestogen therapy [23]. However, potential liver toxicity with some alternative therapies has been noted [50], requiring monitoring.

Danggui Liuhuang (DLH) decoctions showed similar adverse events to conventional drug therapies, including breast pain, gastrointestinal reactions, stomach ache, and vaginal bleeding [35]. Safety profiles were comparable between traditional Chinese medicine and conventional treatments [35].

Lifestyle Intervention Safety

Lifestyle interventions generally showed the most favorable safety profiles. Exercise had few known side effects [16] and offered broader health benefits beyond symptom management. No serious adverse events were associated with exercise interventions in the reviewed studies.

Acupuncture demonstrated minimal adverse effects, with the most common being minor bruising at needle sites [10]. No side effects were reported in one comparative study of acupuncture versus Livial

[11]. The low risk profile of acupuncture made it particularly attractive for women with medical contraindications to pharmacological approaches.

Yoga was described as "safe and effective" [68] with no significant adverse events reported. Mind-body interventions like cognitive behavioral therapy had no reported safety concerns [39], making them appropriate for all women regardless of medical history.

Psychological interventions had fewer side effects compared to pharmacological interventions [17], an important consideration for women concerned about medication risks. Combined psychological and pharmacological approaches showed lower incidence of adverse events than pharmacotherapy alone (RR = 0.25; 95% CI = 0.16, 0.38) [40].

Long-Term Safety Considerations

Long-term safety data remained limited for many interventions. Phytoestrogens lacked comprehensive long-term trials explicitly evaluating cancer risk [45], though available evidence through 2 years showed no concerning signals [14]. Hormone therapy's long-term risks of breast cancer and cardiovascular events with prolonged use [13] necessitated careful risk-benefit assessment for extended therapy.

For sedative hypnotics used for sleep disturbances, long-term use may lead to dependence [60], limiting their utility for chronic management. Non-hormonal therapies lacked data beyond 2 years [1], creating uncertainty about very long-term safety.

The safety profiles strongly influenced treatment selection. For women with existing cardiovascular disease or recent breast cancer, hormone therapy was contraindicated [3, 68], making non-hormonal pharmacological and lifestyle approaches essential alternatives. Similarly, women with history of estrogen-dependent cancers [61, 67] required non-hormonal management strategies.

Treatment Selection Considerations

The choice between pharmacological and lifestyle approaches should be individualized based on multiple factors including symptom severity, medical history, patient preferences, and available resources.

For women with severe vasomotor symptoms (≥14 per week) and no contraindications, hormone therapy offered the greatest symptom reduction of 70-90% [1, 2]. However, the "window of

opportunity" concept suggested that initiating hormone therapy before age 60 and within 10 years of menopause maximized benefits while minimizing cardiovascular risks [14, 15, 19].

For women with contraindications to hormone therapy or moderate symptoms, SSRIs/SNRIs provided effective alternatives with 40-60% symptom reduction [1, 2]. These agents offered the additional benefit of treating comorbid mood symptoms, making them particularly valuable for women experiencing both vasomotor symptoms and depression [17, 40].

Acupuncture represented a promising lifestyle-based option with effectiveness comparable to pharmacological approaches [8, 9] and favorable safety profile [10, 11]. Its additional cardiovascular benefits [12] and longer durability of effects [10, 21] made it an attractive choice for appropriate candidates.

Combined approaches integrating multiple modalities showed particular promise. Psychological interventions combined with pharmacotherapy demonstrated superior effectiveness compared to pharmacotherapy alone for depression [17]. Physiotherapy combined with hormone therapy improved outcomes beyond hormone therapy alone [18]. Acupuncture combined with Chinese herbal medicine was as effective as hormone therapy and more effective than herbal medicine alone [9].

For women prioritizing non-hormonal approaches, several options existed. High-dose genistein extracts (>30 mg/d) showed more consistent effectiveness than mixed isoflavone preparations [13]. Dietary seed supplementation demonstrated favorable effects on hormonal balance, lipid profiles, and symptoms with good safety [38, 38]. NK3R antagonists like fezolinetant offered effective symptom reduction without cardiovascular concerns [1].

The substantial placebo response rate of approximately 30% [5, 32] suggested that watchful waiting with supportive care might be appropriate for women with mild symptoms, given natural symptom resolution over time [5]. Lifestyle modifications including cessation of smoking, exercise, reduction of alcohol, diet modification, and stress reduction showed reasonable effects on some symptoms [15, 15], providing a foundation for comprehensive symptom management regardless of pharmacological choices.

DISCUSSION

Summary of Principal Findings

This systematic review of 80 studies comparing pharmacological and lifestyle-based interventions for menopausal symptoms yields several principal findings. First, hormone therapy demonstrates superior efficacy for vasomotor symptoms, achieving 70-90% reduction compared to approximately 30% with placebo (1-3). Second, non-hormonal pharmacological alternatives including SSRIs/SNRIs and gabapentin provide effective options with 40-60% symptom reduction, particularly valuable for women with contraindications to HT (2,6,10). Third, among lifestyle interventions, acupuncture shows the most consistent evidence of effectiveness comparable to pharmacological approaches, with additional benefits including cardiovascular effects and durable post-treatment responses (8,9,12). Fourth, phytoestrogens demonstrate variable effectiveness dependent on specific compound, dose, and individual metabolic factors, with high-dose genistein extracts (>30 mg/d) showing more consistent benefits than mixed preparations (13,14). Fifth, exercise and yoga, while not highly effective for vasomotor symptoms, offer broader benefits for physical function, quality of life, and overall menopausal health (7,16,20). Sixth, combined approaches integrating pharmacological and lifestyle interventions demonstrate superior outcomes compared to either approach alone (17,18). Seventh, safety profiles differ substantially, with lifestyle interventions uniformly demonstrating favorable safety compared to pharmacological alternatives (13,14,23). These findings collectively support an individualized, shared decision-making approach to menopausal symptom management.

Comparative Effectiveness of Pharmacological Interventions

Hormone Therapy: The Gold Standard Reaffirmed

The consistent superiority of hormone therapy for vasomotor symptom management across multiple high-quality studies reaffirms its position as the most effective intervention for appropriate candidates. Pooled analysis from the MsFLASH trials demonstrated that low-dose oral estradiol reduced vasomotor symptom frequency by 2.4 symptoms per day compared to placebo, significantly exceeding reductions achieved by any lifestyle intervention (2). The magnitude of effect, with 70-

90% symptom reduction (1), substantially exceeds the 30% placebo response observed in well-designed trials (5,32), confirming true therapeutic benefit beyond nonspecific effects.

The differential efficacy of various HT formulations warrants consideration. Non-oral estrogen plus progestogen demonstrated superior efficacy with a mean ratio of 0.23 compared to placebo (77% reduction), while oral formulations showed somewhat lower efficacy with mean ratio 0.52 (48% reduction) (14). This finding suggests that transdermal routes may offer enhanced bioavailability or more consistent therapeutic levels, though direct comparative trials are limited. The MsFLASH trials confirmed that low-dose estradiol, escitalopram, and venlafaxine all achieved approximately 50% symptom reduction compared to 30% with placebo, establishing a hierarchy where HT and specific SSRIs demonstrate comparable efficacy within the pharmacological domain (3).

The 12-month HALT study findings are particularly instructive, demonstrating that HT reduced vasomotor symptoms by an average of 4.06 symptoms per day more than placebo, while herbal interventions including black cohosh, multibotanicals, and soy counseling showed no significant benefit over placebo (4,5). This direct comparison provides compelling evidence for HT superiority when directly contrasted with popular herbal alternatives under rigorous trial conditions. Importantly, the sustained benefit through 12 months follow-up indicates durable effectiveness without tachyphylaxis (4).

However, HT effectiveness must be contextualized within the "window of opportunity" concept. Women under 60 years and within 10 years of menopause demonstrate optimal benefit-to-risk ratios, with cardiovascular risk reduction potentially observed when initiated during this window (14,15,19). Older women or those further from menopause may experience attenuated benefits and enhanced risks, supporting the current clinical paradigm of early intervention for appropriate candidates.

Beyond vasomotor symptoms, HT demonstrated significant improvements in quality of life outcomes. Pooled analysis of four RCTs showed estradiol produced the largest improvement in vasomotor subscale scores (-1.2 points), with significant improvements in total quality of life measures (20). The differential domain-specific effects—with CBT-I and exercise showing greatest

physical subscale improvements—highlight that optimal management may require targeting specific symptom clusters with different interventions (20).

SSRIs/SNRIs: Valuable Non-Hormonal Alternatives

The evidence strongly supports SSRIs/SNRIs as effective non-hormonal pharmacological alternatives. Meta-analysis demonstrating reduction of 1.13 daily hot flashes compared to placebo (6) establishes clinically meaningful efficacy, though somewhat less than HT. The comparative effectiveness of individual agents reveals important distinctions.

Escitalopram 10-20 mg daily reduced vasomotor symptom frequency by 1.4 symptoms per day over 8 weeks (2). The direct comparison with black cohosh is particularly informative: escitalopram demonstrated significantly greater reduction in both hot flash frequency ($p=0.0001$) and severity ($p=0.002$) (27), establishing superiority over this popular herbal alternative. The comparable efficacy to low-dose estradiol and venlafaxine in pooled analyses (2) positions escitalopram as a first-line non-hormonal pharmacological option.

Venlafaxine 75 mg daily reduced symptoms by 1.8 per day compared to placebo (2). The comparative data from breast cancer survivors is clinically valuable: venlafaxine alleviated symptoms faster than clonidine, and participants expressed preference over gabapentin (10). The identification of 75 mg as the optimal dose balancing efficacy and tolerability (10) provides practical prescribing guidance. The absence of additional benefit at higher doses supports conservative dose titration.

The differential value of SSRIs/SNRIs for women with contraindications to HT cannot be overstated. For breast cancer survivors, women with thromboembolic risk factors, or those preferring non-hormonal options, these agents provide effective symptom relief with acceptable safety profiles (10,53,58). The additional benefit for mood symptoms (17,40) makes them particularly valuable for women experiencing both vasomotor symptoms and depression—a common comorbidity during menopause transition.

Emerging Pharmacological Agents: NK3 Receptor Antagonists

The emergence of neurokinin-3 receptor (NK3R) antagonists represents a significant therapeutic advance. Fezolinetant 45 mg daily achieving 50-65% symptom reduction without cardiovascular effects (1) addresses a critical gap for women seeking non-hormonal options with

novel mechanisms of action. The favorable tolerability profile with only mild gastrointestinal effects and 4.6% treatment interruption (67) suggests these agents may offer advantages over SSRIs/SNRIs for some women. However, the absence of long-term safety data beyond 2 years (1) necessitates continued pharmacovigilance.

Comparative Effectiveness of Lifestyle-Based Interventions

Acupuncture: The Most Promising Lifestyle Approach

Among lifestyle interventions, acupuncture demonstrates the most consistent evidence of effectiveness comparable to pharmacological approaches. The systematic review of 15 studies demonstrating significant reductions in PSQI scores (2.38 points) and Kupperman Index scores (5.95 points) compared to hypnotics (8) establishes clinically meaningful benefits for both sleep and global menopausal symptoms.

The direct comparative trials are particularly compelling. The RCT comparing acupuncture, phytoestrogens, and HT found acupuncture reduced Greene's climacteric score by -6.9 ± 4.5 ($p<0.05$), comparable to HT (-5.6 ± 3.1) and superior to phytoestrogens (-3.4 ± 4.3) (21). The conserved benefits on quality of life at 3 months post-treatment (21) suggests acupuncture may induce sustained physiological adaptations not observed with pharmacological interventions requiring continuous use—a clinically significant advantage.

The finding that acupuncture plus Chinese herbal medicine was as effective as HT and superior to herbal medicine alone (9) supports integrated approaches combining multiple lifestyle modalities. The comparable efficacy to venlafaxine and gabapentin in breast cancer survivors, with advantages in durability and fewer side effects (10), positions acupuncture as a particularly valuable option for this challenging population.

The cardiovascular effects of acupuncture deserve special mention. The reduction in systolic blood pressure (-7.4 ± 15.3 mm Hg) and diastolic blood pressure (-8.3 ± 7.7 mm Hg) (12) represents clinically meaningful cardiovascular risk reduction not observed with HT (12). For women with hypertension or cardiovascular risk factors, this additional benefit enhances the value proposition of acupuncture beyond symptom management alone.

The mechanisms underlying acupuncture's effects likely involve multiple pathways including modulation of neurotransmitters (serotonin, endorphins), neuroendocrine function (hypothalamic-pituitary-ovarian axis), and autonomic nervous system activity (9). The longer durability of effects suggests potential neuroplastic changes or sustained physiological adaptations—mechanistic considerations warranting further investigation.

Phytoestrogens and Herbal Supplements: Variable and Context-Dependent

The heterogeneous findings regarding phytoestrogen effectiveness require nuanced interpretation. The systematic review finding no conclusive evidence for phytoestrogen supplements in reducing hot flush frequency (13) contrasts with evidence that isoflavones reduced symptoms with mean ratio 0.62 (38% effectiveness) compared to placebo (14). This apparent contradiction resolves when considering specific compound, dose, and individual metabolic factors.

Genistein extracts at doses >30 mg/d consistently reduced hot flush frequency (13), suggesting that achieving therapeutic levels of specific bioactive compounds is essential. The dose-response relationship implies that many studies using lower doses or mixed preparations may have failed to achieve therapeutic thresholds, producing false-negative results. This has important implications for clinical practice: recommending specific high-dose genistein preparations may be more effective than general advice to consume soy products.

The dietary soy supplementation trial demonstrating significant improvements in somatic symptoms (-49.8%) and urogenital symptoms (-31.2%), with effectiveness comparable to HT for somatic symptoms (22), supports the potential of whole-food approaches when adequate intake is achieved. The improvement in vaginal dryness at 16 weeks ($p=0.04$) (25) suggests specific urogenital benefits, though the failure to demonstrate estrogenic effects on other urogenital parameters indicates selective tissue effects requiring further study.

The HALT study findings of no significant benefit with black cohosh at 3, 6, or 12 months (4) contrast with the systematic review reporting mean ratio 0.40 (60% reduction) compared to placebo (14) and the RCT showing 85% reduction with black cohosh versus 62% with fluoxetine (24). This heterogeneity likely reflects differences in product quality, standardization, and study populations. The finding that multibotanical preparations showed no benefit, with women

experiencing more severe symptoms at 12 months compared to placebo (4), raises concerns about herb-herb interactions or antagonistic effects.

The novel herbal supplement containing glucosinolates, phytosterols, and citrus flavonoids showing promising results (lower global menopausal symptom scores and physical symptom scores compared to HT) (23) represents an interesting development requiring confirmation in larger trials. The superior safety profile compared to HT (23) aligns with the generally favorable safety of herbal approaches, though the small pilot study design limits definitive conclusions.

Dietary Interventions: Beyond Symptom Management

The dietary seed supplementation trial demonstrating significant improvements in hormonal levels, lipid profiles, and symptom severity (38) represents an important contribution. The increase in estradiol from 42.8 ± 9.6 pg/mL to 57.3 ± 8.7 pg/mL ($p<0.01$) in peri-menopausal women, with similar trends in post-menopausal women (38), suggests dietary interventions may modestly influence hormonal parameters. The reduction in hot flashes from 7.6 ± 1.3 to 4.1 ± 1.1 and night sweats from 5.2 ± 1.1 to 2.8 ± 0.9 (38) represents clinically meaningful symptom improvement.

The favorable lipid profile changes (decreased total cholesterol and LDL, increased HDL) (38) demonstrate that dietary interventions offer cardiovascular benefits beyond symptom management. This broader health impact is particularly valuable given the increased cardiovascular risk associated with menopause transition. The excellent safety profile with only mild gastrointestinal discomfort in 4-6% of participants (38) supports dietary approaches as first-line interventions for women with mild symptoms or those seeking non-pharmacological options.

However, the HALT study experience with dietary soy counseling—most participants failing to achieve target intake (4,5,32)—highlights the critical challenge of adherence with dietary interventions. The gap between efficacy (effect under ideal conditions) and effectiveness (effect in real-world practice) may be particularly wide for dietary approaches, necessitating intensive support and behavioral interventions to achieve therapeutic goals.

Exercise and Physical Activity: Limited Vasomotor Effects but Broad Benefits

The systematic review finding no evidence of difference between exercise and no active treatment for vasomotor symptoms (SMD -0.10) (7) challenges earlier observational studies

suggesting benefits. The null findings from the MsFLASH trials, where neither aerobic exercise nor yoga showed significant effects compared to usual activity controls (2,3), provide high-quality evidence that exercise should not be recommended primarily for vasomotor symptom relief.

The direct comparison with HT is particularly instructive: the HT group reported 5.8 fewer hot flushes per 24 hours than the exercise group (95% CI 3.17 to 8.43) (7), establishing clear superiority of pharmacological intervention for this specific outcome. This finding should inform patient expectations—women seeking primarily vasomotor relief should understand that exercise alone is unlikely to provide adequate symptom control.

However, the broader benefits of exercise for menopausal health warrant emphasis. The greatest improvement in physical subscale of quality of life measures observed for exercise interventions (20) supports recommendations for overall well-being. The decline in psychological and somatic symptoms from 50% to 37% over 12 months (16) suggests modest but meaningful benefits for non-vasomotor symptoms. The superior outcomes with combined HRT and physiotherapy compared to HRT alone (18) support integrated approaches addressing both hormonal and physical function domains.

The variability in exercise effects across studies (16) likely reflects differences in exercise mode, intensity, frequency, and duration, as well as baseline activity levels and symptom severity. This heterogeneity complicates efforts to define optimal exercise prescriptions, though the absence of harm supports general recommendations for physical activity as part of comprehensive menopause management.

Mind-Body and Psychological Interventions

The cognitive behavioral therapy for insomnia (CBT-I) findings from MsFLASH trials—reduced self-reported insomnia symptoms and improved overall sleep quality (3)—establish CBT-I as an effective non-pharmacological approach for sleep disturbances. The greatest improvement in sexual subscale of quality of life measures with CBT-I, and significant improvements in psychosocial subscale comparable to escitalopram and venlafaxine (20), suggest broader benefits beyond sleep alone.

The meta-analysis demonstrating superior effectiveness of psychological intervention plus pharmacotherapy compared to pharmacotherapy alone for menopausal depression (decreased Kupperman scores, SAS scores, SDS scores, and significantly better total efficacy) (17) provides strong evidence for integrated approaches. The lower incidence of adverse events with combined treatment (RR = 0.25) (40) suggests psychological interventions may mitigate medication-related side effects or enable lower medication doses.

Yoga's mixed results—no benefits for vasomotor symptoms (3) but significant improvements in total quality of life scores (20)—parallel the exercise findings. The characterization of yoga as "safe and effective" (68) appropriately reflects its favorable risk profile and broader wellness benefits, even without specific vasomotor efficacy.

Direct Comparisons and Integrated Approaches

Head-to-Head Comparative Trials

The direct comparison trials provide the highest quality evidence for relative effectiveness. The HALT study's multivariate mixed model demonstrating HT superiority over herbal interventions (4,5) represents the most rigorous comparison of pharmacological versus lifestyle approaches for vasomotor symptoms. The absence of significant benefit with black cohosh, multibotanicals, or soy counseling compared to placebo (4,5) challenges widespread assumptions about herbal efficacy.

The escitalopram versus black cohosh comparison ($p=0.0001$ for frequency, $p=0.002$ for severity) (27) establishes clear superiority of this SSRI over the popular herbal alternative. The similar safety profiles (27) suggest that efficacy differences, not tolerability, drive the comparative advantage.

The Chinese herbal medicine (CHM) trials revealing CHM 29% more effective than placebo ($p<0.05$) and HT almost 50% more effective than placebo (31) establish a hierarchy where HT > acupuncture + CHM > CHM alone, with combined approaches matching HT efficacy (9). This gradient supports stepped-care approaches beginning with lifestyle interventions and progressing to combined or pharmacological approaches based on response.

The acupuncture, phytoestrogens, and HT comparison showing all three interventions significantly reduced Greene's score, with phytoestrogens less effective than HT for vasomotor

symptoms (21), aligns with the overall pattern of HT superiority for this domain. However, the differential cardiovascular effects—acupuncture and phytoestrogens reducing blood pressure while HT did not (12)—highlight that different interventions offer distinct benefit profiles, supporting individualized selection based on patient characteristics and priorities.

Combined Approaches: Synergy and Integration

The evidence for combined approaches is particularly compelling. Psychological interventions plus pharmacotherapy demonstrating superior effectiveness compared to pharmacotherapy alone (17) suggests additive or synergistic effects when addressing both biological and psychological dimensions. The lower adverse event incidence with combined treatment (40) may reflect improved coping, stress reduction, or true biological interactions warranting further study.

The HRT plus physiotherapy combination showing significantly greater improvements in physical function and overall well-being compared to HRT alone (18) supports multidisciplinary care addressing multiple symptom domains. This finding has practical implications: women receiving HT should not be considered "treated" for all menopausal symptoms but may benefit from additional interventions targeting physical function.

Acupuncture plus CHM demonstrating better outcomes than CHM alone and comparable effectiveness to HT (9) supports integration of multiple lifestyle modalities. This finding challenges the assumption that single interventions should be evaluated in isolation, suggesting that comprehensive lifestyle programs may achieve cumulative benefits.

Moderating Factors and Individualized Treatment

The influence of baseline symptom severity on treatment effectiveness is clinically critical. Studies finding greatest HT benefit enrolled women with ≥14 symptoms per week (2) or average 6 symptoms per day (5), while studies showing more modest effects included women with milder symptoms. This dose-response relationship—where greater baseline severity predicts greater absolute benefit—supports reserving HT for women with moderate to severe symptoms, consistent with clinical guidelines.

Age and years since menopause emerged as critical moderators. Women under 60 and within 10 years of menopause showed more favorable HT outcomes with better benefit-to-risk ratios

(13,15,19). This finding supports current recommendations for early intervention and reinforces the "window of opportunity" concept for optimizing HT benefit while minimizing cardiovascular risks.

The metabolic heterogeneity in phytoestrogen response—variation due to intestinal microflora composition, diet, smoking, antibiotics, and obesity affecting circulating levels (45)—explains individual variation in treatment response. This finding suggests that non-response to phytoestrogens should not be interpreted as class ineffectiveness but may reflect individual metabolic factors that could potentially be modified.

Cultural and geographic factors influenced both symptom reporting and treatment preferences. Variation in hot flash frequency by culture and ethnicity (15) suggests genetic, dietary, or environmental factors modulate symptom expression, with implications for generalizability of trial findings across populations. The greater acceptability and accessibility of traditional Chinese medicine approaches in Asian populations (9) highlights the importance of culturally-appropriate treatment recommendations.

Safety and Tolerability: The Lifestyle Advantage

The safety profile differences between pharmacological and lifestyle interventions fundamentally influence treatment selection. Hormone therapy's increased risks of thromboembolism (13,14,19,45), breast cancer with prolonged use (15), stroke (13,16), and gallbladder disease (13) necessitate careful risk-benefit assessment for each woman. The annual breast cancer risk increase of 8/10,000 (<0.1%) after several years (15), with higher risk for oral combined formulations, must be weighed against symptom burden and quality of life impact. The lower risk with estrogen-only therapy (15) and transdermal routes (15) provides risk-mitigation strategies for appropriate candidates.

The dose-response relationship for SSRI/SNRI side effects—paroxetine 10 mg having fewer side effects than 20 mg (10)—supports using minimum effective doses. The discontinuation rates <20% (10) indicate acceptable tolerability for most women, though the meta-analysis finding odds ratio 1.66 for treatment discontinuation (14) suggests tolerability challenges for some. The important tamoxifen interaction with paroxetine (10) requires careful consideration in breast cancer survivors.

Gabapentin's dose-dependent side effects (dizziness, fatigue, unsteadiness, drowsiness) (10,50) support using 900 mg daily as the optimal balance of efficacy and tolerability. NK3R antagonists' mild side effect profile with 4.6% treatment interruption (67) suggests these newer agents may offer tolerability advantages over older non-hormonal options.

The uniformly favorable safety profile of lifestyle interventions represents their greatest advantage. Exercise's few side effects (16) and broader health benefits support recommendation for all women regardless of symptom severity. Acupuncture's minimal adverse effects—minor bruising being most common (10)—and absence of side effects in some trials (11) make it appropriate even for women with medical contraindications to pharmacological approaches. Psychological interventions having no safety concerns (39) and fewer side effects compared to pharmacological interventions (17) support their use as first-line or adjunctive treatment.

The long-term safety data limitations for many interventions warrant acknowledgment. Phytoestrogens lack comprehensive long-term trials evaluating cancer risk (45), though available evidence through 2 years shows no concerning signals (14). Non-hormonal therapies lack data beyond 2 years (1), creating uncertainty about very long-term safety. For sedative hypnotics, long-term dependence risk (60) limits utility for chronic management.

Clinical Implications and Treatment Algorithms

Synthesizing the evidence, we propose an individualized treatment algorithm. For women with mild symptoms (mildly bothersome, minimal quality of life impact), initial management should include lifestyle modifications (cessation of smoking, exercise, alcohol reduction, diet modification, stress reduction) (15) with watchful waiting given 30% placebo response (5) and natural symptom resolution over time.

For women with moderate to severe vasomotor symptoms (≥14 per week) and no contraindications, hormone therapy offers greatest symptom reduction (70-90%) (1,2). Initiation before age 60 and within 10 years of menopause maximizes benefits and minimizes risks (14,15,19). Transdermal routes may offer enhanced efficacy and improved safety profile (14,15). Women with contraindications to HT should be offered SSRIs/SNRIs (40-60% reduction) (1,2) or NK3R antagonists (50-65% reduction) (1).

For women preferring non-pharmacological approaches or with contraindications to all pharmacological options, acupuncture represents the most evidence-based lifestyle intervention (8,9,12). High-dose genistein extracts (>30 mg/d) may benefit select women (13). Dietary seed supplementation offers hormonal and cardiovascular benefits (38). Combined approaches—acupuncture plus CHM (9), psychological interventions plus pharmacotherapy (17), physiotherapy plus HT (18)—may optimize outcomes.

For all women, lifestyle interventions including exercise, healthy diet, and stress reduction should be recommended for overall health regardless of symptom-specific efficacy (16,20). The favorable safety profile supports universal recommendation.

CONCLUSION

This systematic review of 80 studies provides comprehensive evidence regarding the comparative effectiveness of pharmacological versus lifestyle-based management strategies for menopausal symptoms in postmenopausal women. Hormone therapy remains the most effective intervention for vasomotor symptoms, achieving 70-90% reduction in appropriately selected candidates, particularly women under 60 years within 10 years of menopause without contraindications. Non-hormonal pharmacological alternatives including SSRIs/SNRIs and NK3 receptor antagonists provide effective options with 40-65% symptom reduction for women who cannot or prefer not to use hormone therapy.

Among lifestyle interventions, acupuncture demonstrates the most consistent evidence of effectiveness comparable to pharmacological approaches, with additional cardiovascular benefits and durable post-treatment effects. Phytoestrogens show variable effectiveness dependent on specific compound, dose, and individual metabolic factors, with high-dose genistein extracts demonstrating most consistent benefits. Exercise and yoga, while not highly effective for vasomotor symptoms, offer broader benefits for physical function, quality of life, and overall menopausal health. Combined approaches integrating pharmacological and lifestyle interventions demonstrate superior outcomes compared to either approach alone, supporting multidisciplinary, individualized care.

Safety profiles differ substantially, with lifestyle interventions uniformly demonstrating favorable safety compared to pharmacological alternatives. This safety advantage, combined with

broader health benefits, supports lifestyle interventions as foundational components of menopause management for all women, regardless of whether pharmacological treatment is also utilized.

Recommendations for Clinical Practice

1. **Individualized assessment**: Evaluate symptom severity, medical history, contraindications, and patient preferences before treatment selection.
2. **Shared decision-making**: Engage women in informed discussions about comparative effectiveness, safety profiles, and personal values to guide treatment choices.
3. **Hormone therapy**: Offer to women with moderate to severe vasomotor symptoms, aged <60 years or within 10 years of menopause, without contraindications. Use lowest effective dose, consider transdermal routes, and regularly reassess benefit-risk balance.
4. **Non-hormonal pharmacological options**: Offer SSRIs/SNRIs or NK3R antagonists to women with contraindications to HT, those preferring non-hormonal options, or those with comorbid mood symptoms.
5. **Acupuncture**: Recommend as first-line lifestyle intervention for women preferring non-pharmacological approaches or with contraindications to all pharmacological options.
6. **Dietary approaches**: Advise high-dose genistein extracts (>30 mg/d) for women selecting phytoestrogen therapy. Consider dietary seed supplementation for hormonal and cardiovascular benefits.
7. **Exercise and physical activity**: Recommend for all women regardless of symptom severity for broader health benefits, while managing expectations regarding limited vasomotor effects.
8. **Combined approaches**: Consider integrating multiple modalities (e.g., psychological interventions plus pharmacotherapy, acupuncture plus herbal medicine, physiotherapy plus HT) for enhanced outcomes.

9. **Monitoring and follow-up**: Regularly assess treatment response, tolerability, and evolving patient preferences, with willingness to modify treatment strategies over time.

Recommendations for Future Research

1. Conduct rigorous head-to-head comparative effectiveness trials directly comparing pharmacological and lifestyle interventions
2. Investigate moderating factors and develop prediction models for individualized treatment selection
3. Evaluate long-term safety of non-hormonal pharmacological agents beyond 2 years
4. Standardize outcome measures across trials to facilitate meta-analysis
5. Study combined and sequential treatment strategies to identify optimal treatment algorithms
6. Include diverse populations and cultural contexts to enhance generalizability
7. Conduct cost-effectiveness analyses to inform healthcare policy
8. Investigate mechanisms underlying differential treatment effects
9. Develop and validate patient decision aids to support shared decision-making
10. Evaluate implementation strategies to translate evidence into clinical practice

In conclusion, both pharmacological and lifestyle interventions have important roles in menopausal symptom management. The optimal approach integrates evidence-based selection based on individual patient characteristics, preferences, and values, with willingness to combine modalities and modify strategies over time. This personalized, shared decision-making approach offers the greatest potential to optimize outcomes and improve quality of life for postmenopausal women experiencing menopausal symptoms.

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