International Journal of Women's Health

Dovepress
Taylor & Francis Group

Open Access Full Text Article

REVIEW

Innovative Drug Delivery Systems for Management of Menopausal Symptoms: A Systematic Review

Zahra Bostani Khalesi[1], Mahmood Abedinzade[2], Mostafa Golshekan[2,3]

[1]Department of Midwifery, Biomedicine Research Center, Trauma Institute, Guilan University of Medical Sciences, Rasht, Iran; [2]Department of Physiology, biomedicine research center, trauma institute, Guilan university of medical sciences, Rasht, Iran; [3]Department of Medicinal Chemistry, Biomedicine Research Center, Trauma Institute, Guilan University of Medical Sciences, Rasht, Iran

Correspondence: Mahmood Abedinzade, Department of Physiology, Biomedicine Research Center, Trauma Institute, Guilan University of Medical Sciences, Rasht, Iran, Fax +981333360669, Email mahmood.abedinzade@gmail.com

Abstract: Menopause characterized by estrogen deficiency and has various symptoms, including vasomotor, genitourinary, and psychological manifestations. Innovative drug delivery systems (IDDSs) offer targeted approaches that increase therapeutic efficacy, reduce side effects, and improve patient adherence. To update our knowledge about Drug Delivery Systems (DDS) for decrease menopausal symptoms and its benefits compare with conventional systems. This review systematically examines the application and clinical potential of IDDS for managing menopause-related symptoms, with a particular emphasis on improvements in efficacy, safety, and patient adherence. A comprehensive literature search across multiple databases (PubMed, Em-base, Cochran, Scopus; 2001–2024) yielded 23 studies, including RCTs and observational studies on trans dermal, intravaginal, and Nano-based DDS s (patches, vaginal rings, nano particles) and Neurokinin-3 (NK3) antagonists. Transdermal systems, such as estrogen patches, maintained stable hormone levels and reduced thromboembolism risk by 30% compared to oral hormone replacement therapy (HRT), by bypassing first-pass metabolism. Intravaginal DDS s, like estradiol rings, relieved genitourinary symptoms with less than 1% systemic absorption, thereby minimizing endometrial risks. Non-hormonal Neurokini3 antagonists like fezolinetant, decreased VMS by 60% and benefited high-risk patients. Emerging technologies, like hydro gels, showed preclinical potential but lack long-term safety data. Adherence to treatment was better with sustained-release formulations, such as pellet implants, compared to daily dosing regimens. DDSs offer personalized menopause management, balancing safety and efficacy. Future research should focus on pharmacogenomics, equity, and long-term safety of advanced DDSs, especially those using nanotechnology.

Keywords: Drug Delivery Systems, Menopause, Hormone Replacement Therapy, Nanoparticles

Introduction

Menopause, marking the permanent cessation of ovarian estrogen production, constitutes a significant life stage for women.[1] This demographic is substantial and growing; women over 50 currently represent approximately 26% of the global female population.[2] Coupled with increased life expectancy, many women now spend up to four decades in a state of relative estrogen deficiency, necessitating long-term management strategies for their health and well-being.[3]

The decline in estrogen levels precipitates a wide spectrum of symptoms that can severely impact quality of life. These include VMS, genitourinary syndrome of menopause (GSM) manifesting as vaginal dryness and dyspareunia, sleep disturbances, mood swings, anxiety, and an increased risk of osteoporosis.[4,5] The need to understand and address these physiological changes is paramount.[6] Epidemiological data underscore the pervasiveness of these issues and the widespread use of therapies for relief. A large 2024 study in the United States indicated that 2% to 7% of women aged 65 or older continue to use menopausal hormone therapy (MHT), reflecting a persistent need for symptom control.[7] This demand is driven by the high global prevalence of VMS, which affects 22%–63% of women in Asia and up to 74% in

Received: 2 August 2025
Accepted: 21 November 2025
Published: 13 December 2025

Europe.[8] While MHT can reduce VMS by 55%–90% and is considered the most effective pharmacological intervention, its use is nuanced.[9]

The goal of menopause treatment is to effectively relieve symptoms while minimizing risks. Treatment options are broadly categorized into hormonal and non-hormonal therapies.[3] MHT, previously termed hormone replacement therapy (HRT), is the "gold standard" for managing estrogen-deficiency symptoms, as it addresses the underlying pathophysiology.[9] It involves estrogen alone or in combination with a progestogen for women with a uterus to prevent endometrial hyperplasia.[10] However, long-term use of traditional, especially oral, formulations has been associated with concerns about an increased risk of venous thromboembolism, stroke, and certain cancers, which has spurred the search for safer alternatives.[11] A critical limitation of conventional therapies is their "one-size-fits-all" approach, which fails to account for individual differences in genetics, metabolism, comorbidities, and patient preference.[12]

This is where innovative IDDSs hold significant promise. Advanced DDSs, such as transdermal patches, gels, intravaginal rings, and nanoparticle-based formulations, aim to optimize pharmacokinetics and enhance targeted delivery.[13] By bypassing first-pass hepatic metabolism, transdermal and topical systems offer more stable serum hormone levels and a lower risk of thromboembolism compared to oral regimens.[14] Furthermore, sophisticated platforms like bioadhesive hydrogels, microneedle arrays, and sustained-release implants can prolong drug residence time, reduce dosing frequency, and improve patient compliance.[15,16] For non-hormonal agents, novel delivery systems can enhance bioavailability and targeting, expanding the therapeutic arsenal.[17]

While numerous studies have investigated individual DDSs, a comprehensive synthesis of the entire landscape of IDDSs —encompassing both hormonal and non-hormonal agents—is lacking.[18]

This review therefore aims to systematically identify, evaluate, and synthesize the current evidence on the application and clinical potential of these advanced DDSs for managing menopausal symptoms. Specifically, it will seek to: Compare the efficacy, safety, and adherence profiles of novel DDSs (eg, transdermal, intravaginal, nanoparticle-based) against conventional oral and topical formulations. Critically appraise the evidence for emerging non-hormonal therapies delivered via novel systems. Identify and articulate the specific research gaps and limitations in the current body of literature, particularly concerning long-term safety and comparative effectiveness. Provide a forward-looking perspective on how these innovations can facilitate truly individualized treatment plans in clinical practice.

By addressing these objectives, this review seeks to provide clinicians and researchers with a clear, evidence-based overview of the future directions in menopausal symptom management.

Methods

Study Design

The protocol created, executed, and reported following established standards for quality in systematic reviews encompassing identification, screening, evaluation of eligibility, and the inclusion of studies.

Data Sources and Research Methodology

A methodical search of numerous databases, including Excerpta Medica Database, Medical Literature Analysis and Retrieval System Online, PubMed/MEDLINE, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, and Scopus, enabled the identification of suitable studies. The search approach combined Medical Subject Headings (MeSH) with free-text terms related to menopause and novel drug-delivery systems.

Eligibility Criteria

The review included peer-reviewed research articles written in Persian and English from August 2001 to December 2024. ClinicalTrials.gov and the reference lists of included studies and relevant review articles obtained from other research papers were included in the review. The search strategy combined MeSH and free-text terms using Boolean operators as follows: ("post menopause" OR "menopause" OR "menopausal") AND ("drug delivery systems" OR "nanoparticles" OR "transdermal patches" OR "intravaginal rings" OR "microneedles" OR "bio adhesive gels" OR "implants" OR "hydrogels" OR "in situ gelling systems" OR "micelles" OR "Nano emulsions") AND ("vasomotor symptoms" OR "hot

flashes" OR "genitourinary syndrome of menopause" OR "vaginal atrophy" OR "sleep disturbances" OR "mood" OR "sexual dysfunction").

The review used the following eligibility terms from the PICO Framework:

- Population (P): Post-menopausal women (≥12 month's amenorrhea), experiencing VMS, GSM, or other menopause-related symptoms.
- Intervention (I): IDDSs (eg nanoparticles, transdermal patches, intravaginal rings, new non-hormonal agents).
- Comparator (C): Traditional hormone therapy, non-hormonal therapies (eg, Selective serotonin reuptake inhibitor (SSRIs), gabapentin), placebo.
- Outcomes (O): Symptom relief (validated scales), pharmacokinetics/pharmacodynamics, adverse effects, treatment adherence, patient satisfaction; secondary outcomes include biomarker changes and systemic absorption/exposure."

To be eligible for this systematic review, articles should report primary research results with the following characteristics: a population of postmenopausal women (experiencing >12 months of amenorrhea caused by ovarian failure and VMS or GSM). The study utilized state-of-the-art DDSs, such as nanoparticles (lipid and polymeric), transdermal patches, vaginal gels, and NK3 receptor antagonists, like fezolinetant. It also utilized microneedles, intravaginal rings, and other nanoformulations like liposomes, micelles, and nanoemulsions, controlled-release implants, and bioresponsive delivery platforms. Even though the included studies may contain other variables, DDSs must form an essential component. Control: Traditional hormone therapy (HT), non-hormonal treatments (eg, SSRIs, gabapentin), and placebo. Primary outcomes included symptom relief (measured through validated scales), pharmacokinetic/pharmacodynamic effects, adverse effects, treatment adherence, and patient satisfaction. Secondary outcomes included biomarker modulation, systemic exposure, and the efficacy of targeted delivery. Randomized controlled trials and observational studies were eligible for this research.

Exclusion criteria included pilot studies, non-randomized studies, review articles, conference abstracts, case reports, articles with incomplete data, animal models, laboratory-based research, studies without postmenopausal women, studies with a combination of postmenopausal and other life cycles, and studies including other genders (men), unless data were separated.

Study Selection

The titles and abstracts of all identified articles screened by two independent reviewers. Full-text versions then assessed for eligibility. Disagreements were resolved through discussion or by a third reviewer. The selection process documented using the PRISMA 2020 flow diagram.[19]

Data Extraction and Management

A standardize data extraction form was piloted. Extracted data included Study details (author, year, country, design, and sample size), population characteristics (age, menopausal status, and symptom profile), intervention description (type of delivery system, drug(s) used, dosage, and duration), comparator information, outcomes measured and key findings, adverse events, and safety data.

Quality Assessment

Two reviewers independently assessed the methodological quality and risk of bias using the Cochrane Risk of Bias 2. 2.0 tool for RCTs. Each study rated as having a "low", "moderate", or "high" risk of bias. Consensus or adjudication by a third reviewer resolved any disagreements. Incomplete or incompatible data addressed using methods recommended in the Cochrane Handbook.

Results

Literature Search and Study Selection

We searched 381 articles according to our inclusion and exclusion criteria. After removing duplicates and non-human original research, 197 articles screened by title and abstract. Fifty-seven articles selected for full text review; 33 excluded

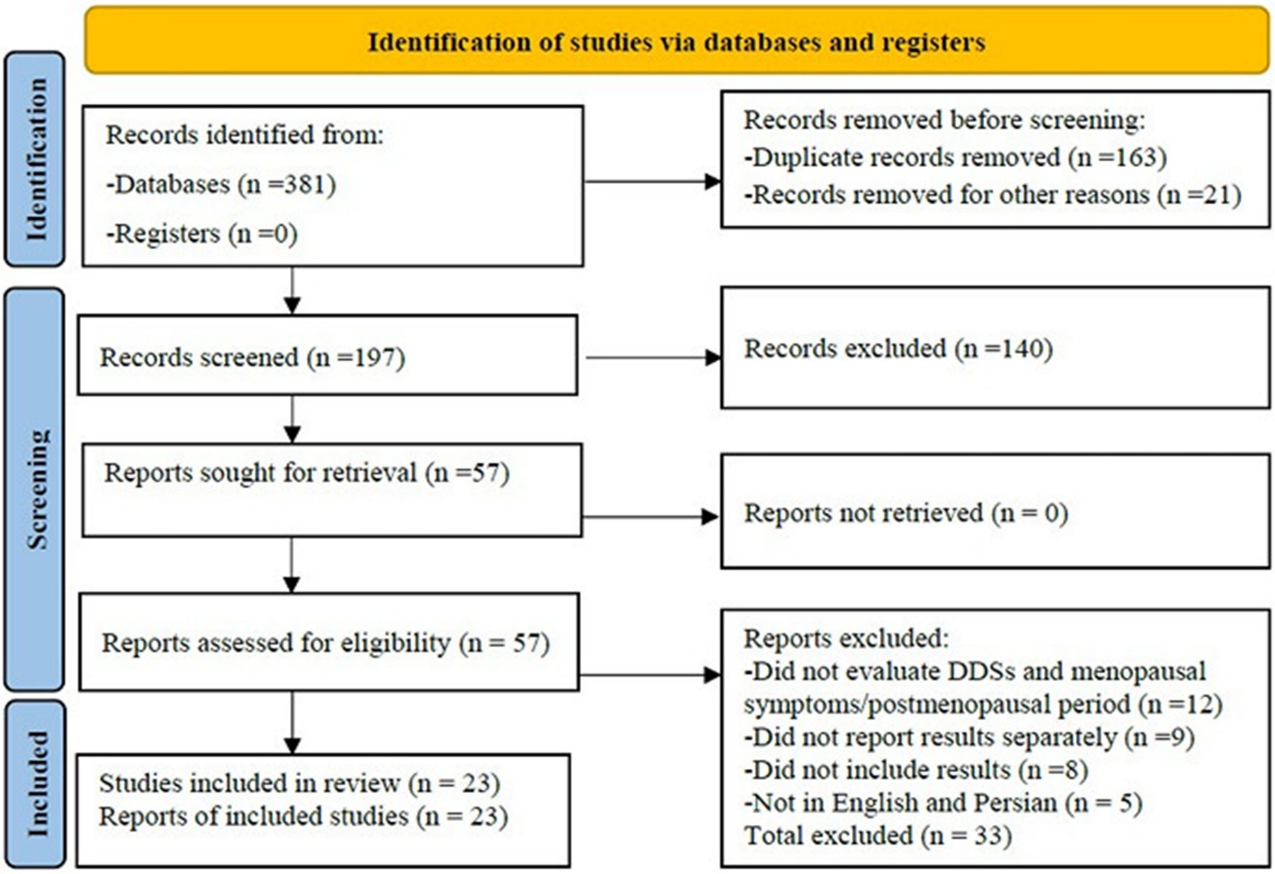

Figure 1 PRISMA Flow Diagram of the Study Selection Process.

because they did not evaluate DDSs and menopausal symptoms or postmenopausal period, did not report results separately, were not in English, or did not include results. Twenty-three articles met the eligibility criteria and included in this review (Figure 1).

Study Characteristics

The sample sizes in the study reviewed varied between 22 and 900 participants. Most of the research was randomized controlled trials and took place in the United States (USA) (11), while two studies based in the United Kingdom (UK), and two others were multinational. In Finland, Germany, Brazil, South Africa, and Hungary carried out one study. The eligible articles reported innovative DDSs for menopausal symptoms in women (Table 1).

Due to the significant heterogeneity in interventions, outcomes, and reporting methods among the included studies, a meta-analysis was not feasible.

Novel DDSs for Menopausal Symptom Management

The evaluated DDSs are categorized into hormonal and non-hormonal therapies, with their key characteristics, advantages, and limitations summarized below.

Hormonal Therapies (Table 2)

Hormonal DDSs offer targeted delivery to mitigate the systemic risks associated with conventional hormone therapy. They are primarily divided into transdermal/topical and intravaginal systems.

Table 1 Characteristics and Data Extracted of Included Studies About

Author	Article Type	Year	Study Duration	Sample Size	Route of HT Administration	Main Outcome
Varila E et al[20]	Prospective Cohort Study	2001	5 years	29 completed the 5-year follow-up	Oral estradiol valerate or transdermal patch, Intrauterine levonorgestrel-releasing system	The LNG-IUS produced a strong suppression of endometrial proliferation. Approximately 90% of participants experienced amenorrhea throughout the treatment, and spotting occurred in fewer than 10% of women, resolving rapidly after IUS replacement.
Archer DF et al[21]	Randomized Controlled Trial	2003	Not reported	Not reported	Percutaneous 17β-estradiol gel	The study demonstrated a significant reduction of 70–80% in the frequency and severity of hot flashes compared with placebo. Over 85% of participants reported overall symptom improvement, and the treatment was well tolerated **with** minimal local skin irritation (<5%)
Buckler et al[22]	Randomized Controlled Trial	2003	24 week	Not reported	Vaginal ring releasing estradiol	The treatment led to a reduction of 65–75% in the frequency of hot flushes and night sweats, and over 80% of participants reported significant improvement in overall climacteric symptoms. The vaginal ring was well tolerated, with only mild local discomfort in <5% of users.
Rufford J et al[23]	Randomized Controlled Trial	2003	6 months	40	Subcutaneous implant of 25 mg 17β-estradiol	Although the estradiol group showed some improvement in urge incontinence there were no statistically significant differences between the estradiol and placebo groups in either subjective symptom scores or objective urodynamic measures. The treatment was generally well tolerated, with no major adverse effects reported.
Shulman and Harari[24]	Open-label Observational Study	2004	12 months	22	Transdermal estradiol patch	The results showed a reduction of approximately 70% in VMS, with over 80% of participants reporting marked improvement in hot flashes and night sweats. The treatment was well tolerated, and no serious adverse events were observed during the study period.
Simon JA et al[25]	Randomized Controlled Trial	2007	Not reported	Not reported	Transdermal (micellar nanoparticles)	The results showed the emulsion significantly reduced the mean daily frequency of hot flashes by 11.1 episodes ($P < 0.001$) compared to placebo. A significant decrease in symptom severity was observed from weeks 4 to 12 ($P < 0.001$). At the study's endpoint, mean serum estradiol levels were 63 pg/mL in the treatment group. The treatment was well-tolerated, with mild local skin reactions occurring in 4% of participants.
Simon JA et al[26]	Clinical Study	2007	Not reported	Not reported	The topical emulsion of estradiol	A topical estradiol emulsion reduced hot flash frequency by 85%, demonstrating high efficacy in managing vasomotor symptoms
Bachmann GA et al[27]	Randomized Controlled Trial	2007	12 week	425	Transdermal (17β-estradiol)	The results showed 41.3% of participants experienced a 75% or greater reduction in hot flush frequency. Both low-dose E2/levonorgestrel and micro-dose E2 groups showed significant improvements compared to placebo ($P < 0.001$).
Buster et al[28]	Randomized, double-blind, placebo-controlled, multicenter trial	2008	12 week	454	Transdermal estradiol (E2) spray	The results showed significantly reduced hot flash frequency by 60–70% and severity, compared with placebo, demonstrating effective relief of vasomotor symptoms
Bachmann GA et al[29]	Randomized Controlled Trial	2009	12 week	121	Transdermal (micro dose estrogen)	Microdose transdermal estradiol significantly improved vulvovaginal health, lowering vaginal pH, increasing the vaginal maturation index, and reducing the proportion of women with moderate-to-severe symptoms.

(*Continued*)

Table 1 (Continued).

Author	Article Type	Year	Study Duration	Sample Size	Route of HT Administration	Main Outcome
Hedrick RE et al[30]	Randomized, Double-Blind, Placebo-Controlled, Multicenter Trial	2009	12 weeks	488	Transdermal estradiol gel 0.1%	Significant reduction in frequency and severity of moderate to severe VMS compared to placebo as early as Week 2
Nelken *RS* et al[31]	Randomized Controlled Trial	2011	12 weeks	59	Vaginal estradiol ring (ultralow-dose)	Both the estradiol ring and oxybutynin groups showed a reduction in daily voids. However, the difference between the two treatments was not statistically significant.
Griesser H et al[32]	Randomized Controlled Trial	2012	12 weeks	436	Pessaries estradiol	The efficacy of estriol containing pessaries compared to placebo in the treatment of vaginal atrophy
Ruiz AD et al[33]	Prospective observational cohort study	2014	Outcomes assessed at 1–3 months and 3–6 months	40	Sublingual preparations contained estrogen combinations and progesterone	Significant reduction in moderate/ (VMS) at 1–3 months, hot flashes, night sweats, sleep disturbances improvements sustained at 3–6 months
Botelho MA et al[34]	Confocal Raman Study	2014	Not reported	Not reported	Transdermal (nanostructured)	The results indicated 92.5% of participants reported improvement in climacteric symptoms after 60 months of treatment. Serum estradiol and follicle-stimulating hormone levels decreased from 82.04±4.9 to 57.12±4.1 IU/mL. No adverse health-related events were attributed to this hormone replacement therapy protocol. Bilateral mammography assessments revealed normal results in all women, with no cases of increased endometrial thickness or vaginal bleeding.
Simon JA et al[35]	Review of Phase 1–3 Clinical Trials	2017	12 weeks	Phase 3 REJOICE trial included 764 and pharmacokinetic sub study involved 72 participants	Vaginal soft gel capsule containing 17β-estradiol at doses	The results indicated significant improvements in vaginal cytology (increase in superficial cells, decrease in paranasal cells), reduction in vaginal pH, and alleviation of symptoms such as dyspareunia, vaginal dryness, and vulvar/vaginal irritation or itching
Mitchell CM et al[36]	Randomized Clinical Trial	2018	12 weeks	302	Vaginal estradiol tablet and vaginal moisturizer	Reductions in most bothersome symptom severity estradiol; moisturizer; and placebo Group. No significant differences were seen between estradiol and moisturizer compared with placebo.
Bhupathiraju et al[37]	Prospective Cohort Study	2018	18 years	900	Vaginal estrogen	The findings support the safety of vaginal estrogen use for treating GSM.
Leibaschoff GH et al[38]	Randomized, Double-blind, Placebo-controlled	2021	Two treatment cycles of 10 days each	20	Transdermal Gel (CO2 delivery)	The results indicated significant improvements in both the Female Sexual Function Index (FSFI) and the Day-to-Day Impact of Vaginal Aging (DIVA) questionnaire scores. Histological analysis of vulvovaginal biopsies revealed regenerative effects on the tissues.
Dixit A et al[39]	Service Evaluation Study	2022	Retrospective	119	Subcutaneous implants estradiol	The study reported high satisfaction rates and good symptom control among participants.
Thurman A et al[40]	Phase 1/2 Open-Label Study	2023	12 weeks	20	Intravaginal ring releasing estradiol and progesterone	Both DARE-HRT1 intravaginal rings safely released estradiol at levels within the low, normal premenopausal range, with progesterone concentrations suggesting adequate endometrial protection.
Takacs P et al[41]	Preclinical Study	2024	Not reported	Not applicable (laboratory-based study)	Vaginal hydrogel containing estriol-hydroxypropyl-β-cyclodextrin complex	A new vaginal gel containing estriol with hydroxyethyl cellulose and hydroxypropyl-β-cyclodextrin showed effective drug release and good tissue absorption in lab tests, indicating promise for treating GSM.
Abdelgader A et al[42]	preclinical/ experimental	2024	In vitro release assessed over 4 weeks	Not applicable (laboratory-based study)	Intrauterine device delivering norethindrone acetate	The intrauterine device sustained norethindrone acetate release, with release kinetics following the Peppas–Sahlin model.

Table 2 Comparison of Hormonal DDSs for Menopause Management

Delivery System	Key Examples	Primary Indication	Key Advantages	Key Disadvantages & Risks	Evidence Strength & Key Findings
Transdermal Patch	Various matrix/ reservoir patches	VMS	- Bypasses first-pass metabolism[43]- Stable serum levels- ~30% lower VTE risk vs oral[44]	- Skin irritation/allergy[45]- Variable adhesion- Altered absorption with heat	RCTs, Meta-analyses- 73% VMS relief; 11% complete resolution[44]- Improved sexual function (KEEPS)[46]
Topical Gel/Spray	EstroGel®, Lenzetto®	VMS	- Bypasses first-pass metabolism- Dosing flexibility- No adhesive issues	- Risk of interpersonal transfer[47]- Variable inter-patient absorption	RCTs- Significant reduction in hot flash frequency/ severity[48,49]
Vaginal Ring	Estring®, Femring®, DARE-HRT1[17]	GSM	- Continuous release; low maintenance- High patient satisfaction- Very low systemic absorption	- Patient discomfort with insertion/ removal- Foreign body sensation	RCTs- Effective relief of vaginal dryness/ dyspareunia[50,51]
Vaginal Tablet	Vagifem®, Yuvafem®	GSM	- Low systemic absorption- Less messy than creams	- Requires applicator (can affect compliance)- Frequent dosing initially	RCTs- Significant improvement in vaginal health indexes[51]
Vaginal Cream	Premarin®, Estrace®	GSM	- Highly effective for GSM- Soothes dry mucosa	- Messy; poor patient acceptance- Higher systemic absorption potential	Long-term use- Confirmed efficacy for GSM symptoms[52]
Subcutaneous Implant	Estradiol pellets	VMS	- Long-term (3–6 month) sustained release- High satisfaction for severe symptoms[53]	- Minor surgical procedure required- Potential for erratic absorption	Cohort Studies- Good symptom control and high satisfaction reported[39–53]

https://doi.org/10.2147/IJWH.S557866

Transdermal and Topical Systems

These systems bypass first-pass hepatic metabolism, leading to more stable serum hormone levels and a reduced risk of venous thromboembolism (VTE) compared to oral formulations.

- Transdermal Patches: Patches deliver estradiol through the skin (eg, abdomen, buttocks, and thigh) via controlled release over several days.
  - Advantages: Stable serum estrogen levels, reduced VTE risk, and improved adherence due to less frequent dosing.
  - Disadvantages: Potential for local skin irritation, allergic reactions to adhesives, and altered absorption upon heat exposure.

Topical Gels, Creams, and Sprays: These formulations are applied to areas such as the arms or thighs.

Advantages: Avoid first-pass liver metabolism and offer flexible dosing.
Disadvantages: Risk of transfer through skin contact and inconsistent absorption across patients.

Intravaginal Systems for GSM

Intravaginal DDSs provide localized estrogen delivery, minimizing systemic absorption while effectively treating GSM symptoms.

Vaginal Tablets (Eg, Vagifem®, Yuvafem®)

Advantages: Low systemic absorption and better user acceptance compared to creams.
Disadvantages: Require insertion devices, which may affect compliance.

Vaginal Creams (Eg, Premarin®, Estrace®)

Advantages: Effective for GSM symptoms.

- Disadvantages: Messiness, higher potential for systemic absorption compared to other localized forms, and risk of endometrial stimulation.

Vaginal Rings (Eg, Estring®, Femring®, DARE-HRT1)

Advantages: Continuous hormone release, no daily dosing, and high patient satisfaction.
Disadvantages: Insertion and removal may be less acceptable to some patients.

Soft Gel Capsules (Eg, Imvexxy®)

Advantages: Applicator-free, ultra-low systemic absorption, and appropriate for breast cancer survivors.
Limitations: Still requires vaginal insertion.

- Emerging Intravaginal Delivery Systems: This category includes hydrogels, nanoparticles, and hormone-releasing intrauterine devices.

Advantages: Enhanced mucosal absorption, prolonged drug residence time, and reduced dosing frequency.
Research Gap: Limited long-term efficacy and safety data exist.

Non-Hormonal Therapies (Table 3)

For patients who cannot or prefer not to use hormones, non-hormonal DDSs offer alternative mechanisms of action.

Table 3 Comparison of Non-Hormonal and Emerging DDSs

Delivery System / Drug Class	Key Examples	Mechanism of Action	Key Advantages	Key Disadvantages & Risks	Evidence Strength & Key Findings
NK3 Receptor Antagonists	Fezolinetant	Blocks NK3 receptors in thermoregulatory center	- Non-hormonal; no endometrial/breast risk- Specific for VMS	- Transient liver enzyme elevations (1–6%)- Headache, nausea[54]	Phase 3 RCTs- ~60% reduction in VMS frequency[55]
Dual NK1/NK3 Antagonists	Elinzanetant	Blocks NK1 & NK3 receptors	- May improve sleep and mood disturbances[56]- Non-hormonal	- Similar side effect profile to NK3 antagonists- Awaiting phase 3 results	Phase 2b RCTs- Significant reduction in VMS vs placebo[57]
SERMs	Ospemifene	Tissue-selective ER agonist/antagonist	- Treats dyspareunia without endometrial proliferation[58]	- Contraindicated in hormone-sensitive cancers- Hot flashes as a side effect	RCTs- Effective for moderate-to-severe dyspareunia[58]
Nanoparticle Systems	Micellar emulsions	Enhances skin penetration and solubility	- Improved bioavailability and tolerability vs patches[59]- Sustained release potential	- Limited long-term safety data[60]- Complex manufacturing and cost	Emerging (Preclinical & Early Clinical)- 85% reduction in hot flashes in a 12-wk study[59]
Vaginal Hydrogels	Estriol gel[61]	Bioadhesive platform for sustained release	- Enhanced mucosal contact and residence time- Improved patient comfort	- Early stage of development- Long-term efficacy data lacking	Preclinical (In Vitro/Animal Studies)- Promising drug release and absorption profile[52]

https://doi.org/10.2147/IJWH.S557866

Table 4 Synthesis of Key Considerations for Clinical Practice

Consideration	Clinical Implications	Examples
Safety Profile	- Transdermal routes are preferred for women at increased VTE risk[45,56] - Vaginal routes are safest for GSM-only symptoms due to minimal systemic exposure[40,49]	A woman with a history of DVT should be offered a transdermal patch or gel over oral HT.
Adherence & Preference	- Long-acting systems (rings, implants) improve adherence[42] - Messiness (creams) and skin issues (patches) can reduce adherence[48]	A patient averse to daily routines may benefit more from a 3-month vaginal ring than from daily tablets.
Symptom Specificity	- VMS: Systemic (oral, transdermal) or NK3 antagonists are first-line[9,45] - GSM: Local vaginal therapies are first-line and highly effective[37,39]	A woman with only vaginal dryness should start with a vaginal estrogen tablet, not systemic therapy.
Research Gaps	- Long-term data (>1-2 years) is sparse for newer systems (nanoparticles, hydrogels)[46] - Head-to-head comparisons between novel DDSs are limited.	The 5-year safety profile of a novel nanoparticle gel cannot be fully ascertained from current literature.

NK3 Receptor Antagonists

This class of drugs inhibits hypothalamic thermoregulatory pathways, reducing vasomotor VMS without hormonal modulation. They have no estrogenic activity and are generally well tolerated, with mild side effects such as headache and nausea. A notable consideration is the potential for transient liver enzyme elevations (1–6%).

Fezolinetant: **A** selective NK3 receptor antagonist approved for the treatment of moderate-to-severe VMS.

Elinzanetant (Dual NK1/NK3 Antagonist)

Evidence: Phase 3 OASIS trials demonstrate significant improvements in VMS and sleep quality.

- Advantages: Dual activity on NK1 and NK3 receptors may provide additional benefits for anxiety and mood disturbances.

Selective Estrogen Receptor Modulators (SERMs)

SERMs act as estrogen agonists in specific tissues (eg, vaginal epithelium) and antagonists in others (eg, breast, endometrium).

Examples: Ospemifene and Bazedoxifene (the latter in combination with conjugated estrogens).

Advantages: Effective in improving GSM symptoms without increasing breast cancer or endometrial risks.

Limitations: Generally contraindicated in patients with a history of hormone-sensitive malignancies.

The clinical implementation of innovative drug delivery systems for menopause management necessitates a patient-centric framework that integrates key considerations of safety, adherence, and symptom profile. This paradigm prioritizes transdermal routes for systemic vasomotor symptoms in high-thrombotic-risk patients and localized vaginal systems for genitourinary syndrome to minimize systemic exposure, while acknowledging that long-acting formulations enhance therapeutic adherence (Table 4).

Discussion

This systematic review synthesizes the current landscape of IDDSs for managing menopausal symptoms, underscoring a paradigm shift towards targeted therapies that optimize the risk-benefit profile of treatment. The collective evidence indicates that transdermal, intravaginal, and emerging nanoparticle-based systems offer viable alternatives to conventional oral hormone therapy, primarily by enhancing bioavailability, minimizing systemic exposure, and improving patient adherence.[62]

The findings corroborate that transdermal estradiol formulations effectively bypass first-pass hepatic metabolism, a key advantage that translates to more stable serum hormone levels and a significantly lower risk of VTE compared to oral administration.[63] This pharmacological benefit is clinically relevant, as demonstrated by studies where a substantial majority of women experienced relief from VMS, with additional benefits for sexual function observed in trials like KEEPS.[46] Furthermore, large-scale reviews have associated transdermal therapy with a reduced risk of stroke without increasing cardiovascular mortality, reinforcing its safety profile for many patients.[11] The recent advent of nanoparticle-enhanced systems, such as micellar emulsions, promises to further advance this field by improving skin absorption and tolerability, as evidenced study reporting reduction in hot flashes.[59] However, the promising efficacy of these novel platforms is tempered by a lack of long-term safety data, highlighting a critical research gap.

For GSM, intravaginal DDSs remain the cornerstone of localized treatment. The extensive body of evidence, encompassing over 50 studies, confirms their efficacy in alleviating symptoms like vaginal dryness and dyspareunia. Innovations such as bioadhesive hydrogels and the next-generation DARE-HRT1 ring are designed to enhance drug residence time and mucosal absorption, thereby improving efficacy and patient comfort.[40] The concomitant use of levonorgestrel-releasing intrauterine systems provides a strategic solution for endometrial protection during estrogen therapy, representing a synergistic approach to MHT.[10]

The expansion of non-hormonal options addresses a crucial need for women with contraindications or a preference to avoid hormones. The approval of NK3 receptor antagonists like fezolinetant provides a mechanism-based, effective treatment for VMS, with dual NK1/NK3 antagonists such as elinzanetant showing additional potential for improving sleep and mood disturbances.[54–57] Similarly, ospemifene and other selective estrogen receptor modulators (SERMs) offer a tissue-selective approach to managing GSM without proliferative effects on the endometrium, expanding the arsenal for individualized care.[48]

Despite these advancements, challenges persist. Topical therapies, while advantageous, can suffer from variable inter-patient absorption and risk of accidental transfer.[14] The integration of digital health technologies, including wearables and AI for symptom tracking, presents new opportunities for personalized management but also raises important ethical considerations regarding data privacy and algorithmic bias.[64] Ultimately, the selection of a DDS must be a shared decision-making process, tailored to individual symptom profiles, comorbidities, and patient preferences to maximize adherence and therapeutic outcomes.[65]

Limitation

A significant limitation, over half of the entries for "Main side effects" in the extracted data were listed as "Not reported."

The assessment of several promising innovative DDSs, such as nanoparticle-based systems, hydrogels, and micro-needle arrays, was constrained by a scarcity of robust clinical data. The evidence for these platforms often derives from a small number of preclinical studies, early-phase clinical trials, or short-term investigations, resulting in a critical lack of long-term efficacy, safety, and comparative effectiveness data.

Conclusion

This systematic review synthesizes evidence on IDDSs, clarifying their role in personalizing menopausal symptom management. The "most effective" DDS is not a single entity but is contingent upon the patient's specific symptom profile, risk factors, and preferences.

For the management of VMS, transdermal estrogen systems (patches, gels) establish themselves as a superior first-line hormonal option for many women, particularly those at increased risk of venous thromboembolism. Their ability to bypass first-pass metabolism results in a more favorable safety profile regarding thrombotic risk compared to oral therapy, without compromising efficacy. For women who cannot or prefer not to use hormones, non-hormonal NK3 receptor antagonists represent a breakthrough, offering targeted, effective relief for moderate-to-severe VMS.

For the treatment of GSM, localized intravaginal DDSs are unequivocally the most effective and safest option. Among these, vaginal tablets and softgel capsules offer excellent efficacy with minimal systemic absorption and high patient acceptability, while vaginal rings provide a compelling advantage for those desiring less frequent dosing through sustained drug delivery.

In general transdermal estradiol gels or patches are the recommended DDS of choice isfor women with VMS and high thrombotic Risk. Also, Low-dose vaginal estradiol tablets or estradiol softgel capsules are recommended for their ease of use and minimal systemic exposure for women with GSM. Innovations like the DARE-HRT1 ring, which combines estradiol and progesterone, should be advanced to offer a convenient, long-acting option for women with an intact uterus.

NK3 receptor antagonists are the recommended innovative pharmacologic class are suitable for women seeking non-hormonal VMS therapy. Future efforts should be directed toward developing novel DDSs for these agents to potentially improve their pharmacokinetic profile and convenience.

Future research must prioritize nanoparticle-based systems and bioadhesive hydrogels designed for both transdermal and intravaginal routes. These platforms hold the promise of unparalleled controlled release and tissue targeting, which could minimize side effects and maximize efficacy. Furthermore, integrating pharmacogenomic data and digital health tools (FemTech) into DDS selection will be crucial for moving beyond a one-size-fits-all approach to truly individualized menopause care.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Soules MR, Sherman S, Parrott E, et al. Executive summary: stages of Reproductive Aging Workshop (STRAW). *Fertil Steril*. 2001;76(5):874–878. doi:10.1016/S0015-0282(01)02909-0
2. United Nations. Department of economic and social affairs. *World Population Prospects*. 2022.
3. Manson JE, et al. Menopause and health in older women. *N Engl J Med*. 2015;372(4):255–265. doi:10.1056/NEJMra1404616
4. Davis SR, Davies M, Lumsden MA, et al. Menopause: diagnosis and management. *BMJ*. 2015;351:h5746. doi:10.1136/bmj.h5746
5. Nappi RE, Palacios S. Impact of vulvovaginal atrophy on sexual health. *Climacteric*. 2014;17(1):3–9. doi:10.3109/13697137.2013.864269
6. Sood R, et al. Advances in menopause management. *Mayo Clin Proc*. 2014;89(5):556–566. doi:10.1016/j.mayocp.2014.03.002
7. Baik SH, Baye F, McDonald CJ. Use of menopausal hormone therapy beyond age 65 years and its effects on women's health outcomes by types, routes, and doses. *Menopause*. 2024;31(5):363–371. doi:10.1097/GME.0000000000002335
8. Palacios S, Henderson VW, Siseles N, Tan D, Villaseca P. Age of menopause and impact of climacteric symptoms by geographical region. *Climacteric*. 2010;13(5):419–428. doi:10.3109/13697137.2010.507886
9. Górecka K, Krzyżanowska M. Prevalence of menopausal hormone therapy and alternative methods, health benefits experienced by peri- and postmenopausal Polish women. *Prz Menopauzalny*. 2022;21(1):27–36. doi:10.5114/pm.2022.113731
10. Harper-Harrison G, Carlson K, Shanahan MM.Hormone replacement therapy. [updated 2024 oct 6]. in: statpearls [internet]. treasure island.(FL). StatPearls Publishing;2025.https://www.ncbi.nlm.nih.gov/books/NBK493191/. Accessed November 26, 2025.
11. Canonico M. Hormone therapy and risk of venous thromboembolism among postmenopausal women. *Maturitas*. 2015;82(3):304–307. doi:10.1016/j.maturitas.2015.06.040
12. Talaulikar V. Menopause transition: physiology and symptoms. *Best Pract amp; Res Clin Obstet amp Gynaecol*. 2022;81:3–7. doi:10.1016/j.bpobgyn.2022.03.003
13. Simon JA, et al. Innovations in hormone therapy delivery systems. *Drugs Aging*. 2018;35(4):325–334. doi:10.1007/s40266-018-0535-5
14. Kopper NW, Gudeman J, Thompson DJ. Transdermal hormone therapy in postmenopausal women: a review of metabolic effects and drug delivery technologies. *Drug Des Devel Ther*. 2009;2:193–202. doi:10.2147/dddt.s4146
15. Valenzuela P, Simon JA. Nanoparticle delivery for transdermal HRT. *Maturitas*. 2012;73(1):74–80. doi:10.1016/j.maturitas.2011.12.019
16. Jain KK. An Overview of Drug Delivery Systems. *Methods Mol Biol*. 2020;2059:1–54. doi:10.1007/978-1-4939-9798-5_1
17. Sangavi R, Khute S, Subash P. Advances in novel drug delivery systems: a focus on nanoparticles and mucoadhesive technologies. *Drug Dev Ind Pharm*. 2025;51:1673–1688. doi:10.1080/03639045.2025.2564364
18. Depypere H, Timmerman D, Donders G, et al. Treatment of menopausal vasomotor symptoms with fezolinetant, a neurokinin 3 receptor antagonist: a phase 2a trial. *J Clin Endocrinol Metab*. 2019;104(12):5893–5905. doi:10.1210/jc.2019-00677
19. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021:372:n71. doi:10.1136/bmj.n71.
20. Varila E, Wahlström T, Rauramo I. A 5-year follow-up study on the use of a levonorgestrel intrauterine system in women receiving hormone replacement therapy. *Fertil Steril*. 2001;76(5):969–973. doi:10.1016/S0015-0282(01)02846-1
21. Archer DF, Group ES. Percutaneous 17beta-estradiol gel for the treatment of vasomotor symptoms in postmenopausal women. *Menopause*. 2003;10(6):516–521. doi:10.1097/01.GME.0000070526.74726.8A
22. Buckler H, Al-Azzawi F. for the UK VR Multicentre Trial Group. The effect of a novel vaginal ring delivering oestradiol acetate on climacteric symptoms in postmenopausal women. *BJOG*. 2003;110(8):753–759. doi:10.1046/j.1471-0528.2003.02294.x
23. Rufford J, Hextall A, Cardozo L, Khullar V. A double-blind placebo-controlled trial on the effects of 25 mg estradiol implants on the urge syndrome in postmenopausal women. *Int Urogynecol J Pelvic Floor Dysfunct*. 2003;14(2):78–83. doi:10.1007/s00192-003-1054-3
24. Shulman LP, Harari D. Low-dose transdermal estradiol for symptomatic perimenopause. *Menopause*. 2004;11(1):34–39. doi:10.1097/01.GME.0000074705.98544.16

25. Simon JA. Estradiol topical emulsion for the treatment of moderate-to-severe vasomotor symptoms associated with menopause. *Women's Health*. 2007;3(1):29–37. doi:10.2217/17455057.3.1.29
26. Simon JA, Bouchard C, Waldbaum A, Utian W, Zborowski J, Snabes MC. Low dose of transdermal estradiol gel for treatment of symptomatic postmenopausal women: a randomized controlled trial. *Obstet Gynecol*. 2007;109(3):588–596. doi:10.1097/01.AOG.0000254160.62588.41
27. Bachmann GA, Schaefers M, Uddin A, Utian WH. Lowest effective transdermal 17beta-estradiol dose for relief of hot flushes in postmenopausal women: a randomized controlled trial. *Obstet Gynecol*. 2007;110(4):771–779. doi:10.1097/01.AOG.0000284450.51264.31
28. Buster JE, Koltun WD, Pascual MLG, Day WW, Peterson C. Low-dose estradiol spray to treat vasomotor symptoms: a randomized controlled trial. *Obstet Gynecol*. 2008;111(6):1343–1351. doi:10.1097/AOG.0b013e318175d162
29. Bachmann GA, Schaefers M, Uddin A, Utian WH. Microdose transdermal estrogen therapy for relief of vulvovaginal symptoms in postmenopausal women. *Menopause*. 2009;16(5):877–882. doi:10.1097/gme.0b013e3181a15606
30. Hedrick RE, Ackerman RT, Koltun WD, Halvorsen MB, Lambrecht LJ. Transdermal estradiol gel 0.1% for the treatment of vasomotor symptoms in postmenopausal women. *Menopause*. 2009;16(1):132–140. doi:10.1097/GME.0b013e31817d5372
31. Nelken RS, Ozel BZ, Leegant AR, Felix JC, DR M Jr. Randomized trial of estradiol vaginal ring versus oral oxybutynin for the treatment of overactive bladder. *Menopause*. 2011;18(9):962–966. doi:10.1097/gme.0b013e3182104977
32. Griesser H, Skonietzki S, Fischer T, Fielder K, Kirchner B, Goepel C. Low-dose estriol pessaries for the treatment of vaginal atrophy: a double-blind placebo-controlled trial investigating the efficacy of pessaries containing estriol and lactobacilli in postmenopausal women. *Climacteric*. 2012;15(6):571–579. doi:10.3109/13697137.2012.658110
33. Ruiz AD, Daniels KR, Barner JC, Carson JJ, Frei CR. The effectiveness of sublingual and topical compounded bioidentical hormone replacement therapy in postmenopausal women: an observational cohort study. *Int J Pharm Compd*. 2014;18(1):70–77.
34. Botelho MA, Queiroz DB, Barros G, et al. Nanostructured transdermal hormone replacement therapy for relieving menopausal symptoms: a confocal Raman spectroscopy study. *Clinics*. 2014;69(2):75–82. doi:10.6061/clinics/2014(02)01
35. Simon JA, Archer DF, Constantine GD, et al. A vaginal estradiol softgel capsule, TX-004HR, has negligible to very low systemic absorption of estradiol: efficacy and pharmacokinetic data review. *Maturitas*. 2017;99:51–58. doi:10.1016/j.maturitas.2017.02.008
36. Mitchell CM, Reed SD, Diem S, et al. Efficacy of vaginal estradiol or vaginal moisturizer vs placebo for treating postmenopausal vulvovaginal symptoms: a randomized clinical trial. *JAMA Intern Med*. 2018;178(5):681–690. doi:10.1001/jamainternmed.2018.0116
37. Bhupathiraju SN, Grodstein F, Stampfer MJ, et al. Vaginal estrogen use and chronic disease risk in the Nurses' Health Study. *Menopause*. 2018;26 (6):603–610. doi:10.1097/GME.0000000000001284
38. Leibaschoff GH, Arrieta CTN, Reyes CLG, Melamed JL. A pilot randomized, double-blind, placebo-controlled clinical trial on the efficacy and safety of a transdermal gel that delivers co2 in the treatment of vulvovaginal atrophy. *Surg Technol Int*. 2021;38:234–239. doi:10.52198/21.STI.38.GY1350
39. Dixit A, Carden N, Stephens E, Chadwick M, Tamblyn J, Robinson L. Hormone replacement therapy subcutaneous implants for refractory menopause symptoms; the patient's perspective. *Post Reprod Health*. 2022;28(2):79–91. doi:10.1177/20533691221097042
40. Thurman A, Hull ML, Stuckey B, et al. A phase 1/2, open-label, parallel group study to evaluate the preliminary efficacy and usability of DARE-HRT1 (80 µg estradiol/4 mg progesterone and 160 µg estradiol/8 mg progesterone intravaginal RinGSM) over 12 weeks in healthy postmenopausal women. *Menopause*. 2023;30(9):940–946. doi:10.1097/GME.0000000000002230
41. Takacs P, Kozma B, Rátonyi D, et al. Development and bioavailability assessment of an estriol-containing vaginal hydrogel. *Gels*. 2024;10(12):823. doi:10.3390/gels10120823
42. Abdelgader A, Govender M, Kumar P, Choonara YE. A novel intrauterine device for the spatio-temporal release of norethindrone acetate as a counter-estrogenic intervention in the genitourinary syndrome of menopause. *Pharmaceutics*. 2024;16(5):587. doi:10.3390/pharmaceutics16050587
43. Mohammed K, Abu Dabrh A, Benkhadra K, et al. Oral vs transdermal estrogen therapy and vascular events: a systematic review and meta-analysis. *J Clin Endocrinol Metab*. 2015;100(11):4012–4020. doi:10.1210/jc.2015-2237
44. Vinogradova Y, Coupland C, Hippisley-Cox J. Use of hormone replacement therapy and risk of venous thromboembolism: nested case–control studies using primary care data. *BMJ*. 2019;364:k4810. doi:10.1136/bmj.k4810
45. de Palacios PI, Toole JF, Erianne JA, et al. Comparative study to evaluate skin irritation, adhesion and estradiol delivery of transdermal estradiol patches (matrix vs reservoir systems). *Maturitas*. 2002;41(2):125–134. doi:10.1016/S0378-5122(02)00189-5
46. Constantine GD, Simon JA, Kaunitz AM, et al. TX-001HR is associated with a clinically meaningful effect on severity of moderate to severe vasomotor symptoms in the REPLENISH trial. *Menopause*. 2020;27(11):1236–1241. doi:10.1097/GME.0000000000001602
47. Manson JE. The kronos early estrogen prevention study women's health. *Women's Health*. 2013;9(1):9–11. doi:10.2217/whe.12.69
48. Taylor MB, Gutierrez MJ, Maidana PN. Absorption, bioavailability and partner transfer of estradiol from a topical estradiol emulsion: a skin-to-skin contact study. *Climacteric*. 2008;11(6):509–516. doi:10.1080/13697130802407614
49. Derzko C, et al. Comparative efficacy and safety of estradiol transdermal gels (Divigel, EstroGel) for menopausal vasomotor symptoms: review of randomized trials. *Climacteric*. 2016;19(1):1–8. doi:10.3109/13697137.2015.1126758
50. Hadji P,chmeißer JO, Peters K, Göckeler-Leopold E. Use of an estradiol transdermal spray in women with menopausal symptoms: randomized trials and real-world satisfaction data. *Maturitas / Climacteric*. 2024;27:473–481. doi:10.1080/13697137.2024.2376185
51. Eriksen B, Kosha S, Noguchi S, et al. A randomized, open, parallel-group study on the efficacy and safety of the silicone vaginal ring (Estring) in postmenopausal urogenital symptoms. *Maturitas*. 1999;31(2):161–169. doi:10.1016/S0378-5122(98)00098-3
52. Chollet JA. Efficacy and safety of ultra-low-dose Vagifem (10 mcg). *Patient Prefer Adherence*. 2011;5:571–574. doi:10.2147/PPA.S22940
53. Archer DF, Kimble TD, Lin FDY, et al. Study to evaluate the safety and efficacy of estradiol vaginal cream 0.003% in postmenopausal women with vaginal dryness as the most bothersome symptom. *J Womens Health*. 2018;27(3):231–237. doi:10.1089/jwh.2017.6515
54. Wender MCO, Steiner ML, Fernandes CE, et al. Compounded hormonal pellets: a critical review of current evidence and risks. *Rev Assoc Med Bras*. 2025;71(7):e20250121. doi:10.1590/1806-9282.20250121
55. Lederman S, Ottery FD, Cano A, et al. Fezolinetant for treatment of moderate-to-severe vasomotor symptoms associated with menopause (SKYLIGHT 1): a phase 3 randomised controlled study. *Lancet*. 2023;401(10382):1091–1102. doi:10.1016/S0140-6736(23)00085-5
56. Johnson KA, Martin N, Nappi RE, et al. Efficacy and safety of fezolinetant in moderate to severe vasomotor symptoms associated with menopause: a phase 3 RCT. *J Clin Endocrinol Metab*. 2023;108(8):1981–1997. doi:10.1210/clinem/dgad058

57. Pinkerton JV, Simon JA, Joffe H, et al. Elinzanetant for the treatment of vasomotor symptoms associated with menopause: OASIS 1 and 2 randomized clinical trials. *JAMA*. 2024;332:1343–1354. doi:10.1001/jama.2024.14618
58. Cardoso F, Parke S, Brennan DJ, et al. Elinzanetant for vasomotor symptoms from endocrine therapy for breast cancer. *N Engl J Med*. 2025;393 (8):753–763. doi:10.1056/NEJMoa2415566
59. Portman DJ, Bachmann GA, Simon JA, Group OS. Ospemifene, a novel selective estrogen receptor modulator for treating dyspareunia associated with postmenopausal vulvar and vaginal atrophy. *Menopause*. 2013;20(6):623–630. doi:10.1097/gme.0b013e318279ba64
60. Simon JA, Group ESTRASORBS. Estradiol in micellar nanoparticles: the efficacy and safety of a novel transdermal drug-delivery technology in the management of moderate to severe vasomotor symptoms. *Menopause*. 2006;13(2):222–231. doi:10.1097/01.gme.0000174096.56652.4f
61. Vinogradova Y, Coupland C, Hippisley-Cox J. Use of hormone replacement therapy and risk of venous thromboembolism: nested case-control studies using the QResearch and CPRD databases. *BMJ*. 2019;364:k4810. doi:10.1136/bmj.k4810
62. Miller VM, Naftolin F, Asthana S, et al. The Kronos Early Estrogen Prevention Study (KEEPS): what have we learned? *Menopause*. 2019;26 (9):1071–1084. doi:10.1097/GME.0000000000001326
63. Archer DF, Sturdee DW, Baber R, et al. Menopausal hot flushes and night sweats: where are we now? *Climacteric*. 2019;22(6):611–617. doi:10.1080/13697137.2019.1640198
64. Harman SM, Black DM, Naftolin F, et al. Arterial imaging outcomes and cardiovascular risk factors in recently menopausal women: a randomized trial. *Ann Intern Med*. 2014;161(4):249–260. doi:10.7326/M14-0353
65. Garg R, Munshi A. Revolutionizing menopause management: harnessing the potential of artificial intelligence. *J Midlife Health*. 2024;15(2):53–54. doi:10.4103/jmh.jmh_104_24