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SYSTEMATIC REVIEW

Genitourinary Syndrome of Menopause

In Partnership with



Genitourinary Syndrome of Menopause: A Systematic Review

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None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of healthcare in the United States. The Patient-Centered Outcomes Research Institute (PCORI®) requested this report from the EPC Program at AHRQ. AHRQ assigned this report to the Minnesota Evidence-based Practice Center (Contract No. 75Q80120D00008).

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Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, go to <https://effectivehealthcare.ahrq.gov/about/epc/evidence-synthesis>.

AHRQ expects that the EPC evidence reports and technology assessments, when appropriate, will inform individual health plans, providers, and purchasers as well as the healthcare system as a whole by providing important information to help improve healthcare quality. Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the website (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an email list to learn about new program products and opportunities for input.

If you have comments on this evidence report, they may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20857, or by email to epc@ahrq.hhs.gov.

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In designing the study questions, the EPC consulted several Key Informants who represent the end-users of research. The EPC sought the Key Informant input on the priority areas for research and synthesis. Key Informants are not involved in the analysis of the evidence or the writing of the report. Therefore, in the end, study questions, design, methodological approaches, and/or conclusions do not necessarily represent the views of individual Key Informants.

Key Informants must disclose any financial conflicts of interest greater than \$5,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any conflicts of interest.

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Genitourinary Syndrome of Menopause: A Systematic Review

Structured Abstract

Objectives. To conduct a systematic review of evidence regarding genitourinary syndrome of menopause (GSM) screening, treatment, and surveillance.

Data sources. Ovid/Medline®, Embase®, and EBSCOhost/CINAHL® from database inception through December 11, 2023.

Review methods. We employed methods consistent with the Agency for Healthcare Research and Quality Evidence-based Practice Center Program Methods Guidance to identify studies and synthesize findings for Key Questions related to screening for GSM, effectiveness and harms of U.S.-available interventions for GSM, appropriate followup intervals for patients using GSM treatments, and endometrial surveillance for patients using hormonal GSM treatments. For vaginal estrogen and vaginal or systemic non-estrogen hormonal interventions, energy-based interventions, and vaginal moisturizers, we first assessed study quality and then, for moderate or high-quality studies, reviewed outcomes related to GSM symptoms, treatment satisfaction, and adverse effects. For low-quality studies, we described limited study characteristics only. For studies of other non-hormonal interventions, we created an evidence map describing study characteristics without assessing study quality.

Results. After assessing 107 publications for risk of bias (RoB), we extracted and synthesized effectiveness and/or harms outcomes from 68 publications describing trials or prospective, controlled observational studies that were rated low, some concerns, or moderate RoB (24 estrogen publications, 35 non-estrogen, 11 energy-based, and 4 moisturizers). Of 39 high, serious, or critical RoB publications, we extracted long-term harms from only 15 uncontrolled studies of energy-based interventions (all serious or critical RoB due to confounding). An additional 66 publications evaluating 46 non-hormonal interventions, including natural products, mind/body practices, and educational interventions, were described in an evidence map. Across all 172 publications, studies differed in GSM definitions, diagnosis, enrollment criteria, and outcomes assessed. Few studies enrolled women with a history of breast or gynecologic cancers. Overall, we found that vaginal estrogen, vaginal dehydroepiandrosterone (DHEA), vaginal moisturizers, and oral ospemifene may all improve at least some GSM symptoms, while evidence does not demonstrate the efficacy of energy-based therapies, vaginal or systemic testosterone, vaginal oxytocin, or oral raloxifene or bazedoxifene for any GSM symptoms. Harms reporting was limited, in part, by studies not being sufficiently powered to evaluate infrequent but serious harms, though most studies did not report frequent serious harms. Common non-serious adverse effects varied by treatment and dose. No studies evaluated GSM screening or directly addressed appropriate followup intervals or the effectiveness and harms of endometrial surveillance among women with a uterus receiving hormonal therapy for GSM. The longest followup period for active endometrial surveillance in an included trial was 12 weeks (vaginal estrogen) or 1 year (non-estrogen hormonal interventions).

Conclusions. This systematic review provides comprehensive, up-to-date information to guide patients, clinicians, and policymakers regarding GSM. Despite the breadth of included studies, findings were limited by several factors, including heterogeneity in intervention-comparator-outcome combinations. Future studies would be strengthened by a standard definition and uniform diagnostic criteria for GSM, a common set of validated outcome measures and reporting standards, and attention to clinically relevant populations and intervention comparisons. Lack of

long-term data assessing efficacy, tolerability, and safety of GSM treatments leaves postmenopausal women and clinicians without evidence to guide treatment longer than 1 year.

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Executive Summary

Main Points

- One hundred seven publications of hormonal, non-hormonal moisturizers, and energy-based interventions for genitourinary syndrome of menopause (GSM) were assessed for study quality and further synthesis; 66 additional studies of non-hormonal interventions were described in an evidence map without quality assessments.
- Vaginal estrogen, dehydroepiandrosterone (DHEA), and moisturizers as well as oral ospemifene may improve at least some GSM symptoms, primarily vulvovaginal dryness and, to a lesser extent, dyspareunia. Evidence does not demonstrate the efficacy of vaginal or systemic testosterone, vaginal oxytocin, oral raloxifene or bazedoxifene, or energy-based therapies. No treatment significantly improved vaginal discomfort/irritation or dysuria. Placebo effect was high, particularly in studies using a lubricating vaginal gel or cream placebo.
- A broad array of non-hormonal interventions other than moisturizers, including natural products, mind/body practices, and educational interventions, have been tested for various GSM symptoms (particularly sexual function outcomes) in mostly small non-U.S. trials.
- Studies differed in GSM definitions and diagnosis, enrollment criteria, and outcomes assessed for a broad range of vulvovaginal, sexual, and urinary symptoms using heterogeneous and poorly validated patient-reported measurement tools.
- Harms reporting was limited by sample sizes and short followup duration though most studies did not find frequent serious harms. Most studies of hormonal interventions followed participants for 12 weeks, the longest followup period for any intervention was 12 months.
- Few studies enrolled women with a history of breast or gynecologic cancers.
- No studies evaluated the benefits or harms of screening for GSM, the timing of evaluation for response to treatment, or the benefits or harms of endometrial surveillance for patients using hormonal therapies for GSM.

Background and Purpose

Genitourinary syndrome of menopause describes the physical genitourinary tract changes, and vulvovaginal, urinary, and sexual symptoms associated with menopause. Clinically, diagnosis and treatment response evaluation are typically based on ad-hoc patient symptom reporting and clinical judgment. Many prior trials did not target patient-centered outcomes. Given the range of symptoms associated with GSM, the lack of definitive diagnostic criteria, impact of symptoms, and increasing number and range of treatments, evidence-based clinical guidelines addressing available treatments and focusing on patient-centered outcomes are needed.

This systematic review (SR) examined the evidence for Key Questions related to GSM screening (KQ1), treatment effectiveness and harms (KQ2, KQ3, and KQ4), and surveillance (KQ5) to assist patients, clinicians, and other stakeholders in making informed decisions. The report is intended, in part, to inform the work of the American Urological Association (AUA) in

their development of a clinical practice guideline and was funded by the Patient-Centered Outcomes Research Institute (PCORI®).

Methods

We used methods consistent with the Agency for Healthcare Research and Quality Evidence-based Practice Center Program [methods guidance](#), as described in the [full report](#). Our searches covered publication dates from database inception through December 11, 2023. To improve applicability of findings to U.S. patients and clinicians, we included only U.S.-available interventions. Where evidence was sufficient without an unacceptable amount of clinical heterogeneity, we conducted pairwise meta-analyses. For studies that evaluated non-hormonal interventions (other than vaginal moisturizers), we created an evidence map describing study characteristics. For hormonal and energy-based interventions, and vaginal moisturizers, we synthesized low and moderate risk of bias studies and provided Grading of Recommendations Assessment, Development and Evaluation (GRADE) certainty of evidence (COE) ratings for 8 patient-centered outcomes identified by the Core Outcomes in Menopause (COMMA) review¹ as most important to patients and clinicians, including: (1) pain with sex, (2) vulvovaginal dryness, (3) vulvovaginal discomfort/irritation, (4) dysuria, (5) change in Most Bothersome Symptom (MBS), (6) distress, bother, or interference of genitourinary symptoms, (7) satisfaction with treatment, and (8) treatment side effects. We derived COE from statistical rather than clinical significance or effect magnitude, in part because validated measures of clinically meaningful differences do not exist for most outcomes.

Results

After assessing 107 publications for risk of bias (RoB), we extracted effectiveness and/or harms outcomes from 68 publications describing trials or prospective, controlled observational studies that were rated low, some concerns, or moderate RoB (24 estrogen publications, 35 non-estrogen, 11 energy-based, and 4 moisturizers). Of 39 high, serious, or critical RoB publications, we only extracted long-term harms from 15 uncontrolled studies of energy-based interventions (all serious or critical RoB due to confounding). Among 19 high RoB randomized controlled trials, the most common source of bias was missing outcome data. An additional 66 publications evaluating 46 non-hormonal interventions are described in an evidence map. Most non-hormonal interventions in the evidence map were focused on natural products (i.e., herbal or botanical supplements and vitamins) and were small in sample size. Five trials²⁻⁶ (9 publications) compared active interventions from more than one category with placebo and are counted more than once in the description above. The relevant arms of each trial are described in their respective sections.

No studies evaluated Key Questions related to GSM screening (KQ1) or directly addressed appropriate followup intervals (KQ4) or the effectiveness and harms of endometrial surveillance (KQ5).

For efficacy/effectiveness (KQ2) and harms (KQ3), the certainty of evidence for most intervention-comparison-outcome combinations was low or very low; COE was moderate or high for only a few comparisons (see Table A). Overall, for KQ2 we concluded that vaginal estrogen, vaginal DHEA, vaginal moisturizers, and oral ospemifene, may all improve *at least some* GSM symptoms, primarily vulvovaginal dryness and, to a lesser extent, dyspareunia. No treatment significantly improved vaginal discomfort/irritation or dysuria. Placebo effect was high, particularly in studies using a lubricating vaginal gel or cream placebo. Evidence does not

demonstrate the efficacy of energy-based therapies (carbon dioxide [CO₂] or Erbium-doped yttrium aluminum garnet [Er:YAG] laser), vaginal or systemic testosterone, vaginal oxytocin, oral raloxifene, or bazedoxifene for *any* GSM symptoms.

Compared with placebo, vaginal estrogen may improve vulvovaginal dryness, MBS, and treatment satisfaction (low COE), but probably results in little to no difference in quality of life (QoL) (moderate COE), and may result in little to no difference in dyspareunia or dysuria (low COE). Compared with no treatment, vaginal estrogen may improve vulvovaginal dryness and dyspareunia, and may result in little to no difference in vulvovaginal discomfort/irritation or dysuria (low COE).

Among non-estrogen hormonal interventions, vaginal DHEA compared with placebo may improve vulvovaginal dryness, dyspareunia, and quality of life (QoL) (low COE), but may result in more adverse effects (AEs) (low COE). Oxytocin compared with placebo probably results in little to no difference in MBS (moderate COE) and may result in little to no difference in serious adverse effects (SAEs) (low COE). Ospemifene compared with placebo may improve vulvovaginal dryness and dyspareunia (low COE) and results in higher treatment satisfaction (high COE), but results in little to no difference in vulvovaginal discomfort/irritation (high COE) and may result in little to no difference in SAEs (low COE). Raloxifene added to vaginal estrogen or moisturizer compared with vaginal estrogen or moisturizer plus placebo may result in little to no difference in vulvovaginal dryness, discomfort/irritation, dysuria, and dyspareunia (low COE). Bazedoxifene may improve QoL less than placebo (low COE). Oral bazedoxifene or raloxifene compared with placebo may result in higher treatment satisfaction (low COE). Systemic estrogen plus systemic testosterone compared with systemic estrogen alone may result in little to no difference in vulvovaginal dryness and dyspareunia (low COE).

Vaginal moisturizers compared with placebo may improve vulvovaginal dryness (low COE) but may result in little to no difference in MBS (low COE). Vaginal moisturizers compared with placebo probably result in little to no difference in AEs (moderate COE).

Among energy-based interventions, CO₂ laser (compared with sham laser) may result in little to no difference in MBS, dysuria, QoL, or SAEs (low COE). Compared with vaginal estrogen cream, CO₂ laser may result in little to no difference in vulvovaginal dryness, dyspareunia, discomfort/irritation, dysuria, QoL, or SAEs (low COE). Er:YAG laser compared with sham laser may result in little to no difference in QoL (low COE).

For the eight COMMA outcomes defined above, the evidence was very uncertain (very low COE) for all other studied intervention-comparator-outcome combinations. The full report contains results for additional effectiveness outcomes, including recurrent urinary infections, sexual function, urinary incontinence, physical signs of vulvovaginal atrophy, common adverse effects, and warnings reported by the Food and Drug Administration (FDA).

Harms reporting (KQ3) was limited, in part, by studies not being sufficiently powered to evaluate infrequent but serious harms, though most studies did not find evidence of frequent serious harms. Infrequent adverse effects varied by treatment. For example, vaginal estrogen was associated with vaginal bleeding, discharge, and breast tenderness; vaginal DHEA was associated with increased facial hair, voice changes, and headaches; oral ospemifene was associated with hot flushes and vaginal candidiasis; and CO₂ laser was associated with vaginal bleeding, pain, and discharge. For KQ4, limited evidence within studies of effective treatments, suggests that symptoms begin improving within 1-2 months and continue to improve through 12 weeks (average length of study followup). For endometrial outcomes (KQ5), among hormonal interventions, ospemifene was associated with thickened endometrial lining, proliferative

endometrial histology, and one case of endometrial hyperplasia. In 6 of 10 studies that evaluated endometrial stimulation up to 36 weeks, vaginal estrogen was associated with cases of vaginal bleeding, a nominal increase in endometrial thickness, proliferative endometrium, and one case of endometrial hyperplasia in a polyp. Limited evidence suggests that vaginal DHEA, vaginal oxytocin, oral bazedoxifene and raloxifene, and vaginal testosterone are not associated with clinically relevant endometrial stimulation as measured by transvaginal ultrasound or endometrial biopsy in primarily short-term studies and 3 year-long studies.

Table A. Overview of certainty of evidence statements for COMMA outcomes

Intervention Vs. Comparator	Dryness	Discomfort/Irritation	Dysuria	Dyspareunia	Change in MBS	Quality of Life	Treatment Satisfaction	Adverse Events
Vaginal estrogen vs. placebo	Low ^{a,b} ⊕⊕○○ Improves	Very low ^{a,b,c} ⊕○○○ Uncertain	Low ^{a,c} ⊕⊕○○ No difference	Low ^{a,b} ⊕⊕○○ No difference	Low ^{a,c} ⊕⊕○○ Improves	Moderate ^d ⊕⊕⊕○ No Difference	Low ^{a,d} ⊕⊕○○ Higher	Low ^{a,c} ⊕⊕○○ No difference
Vaginal estrogen vs. no treatment	Low ^{a,d} ⊕⊕○○ Improves	Low ^{a,d} ⊕⊕○○ No difference	Low ^{a,d} ⊕⊕○○ No difference	Low ^{a,d} ⊕⊕○○ Improves	NR	NR	NR	N/A
Vaginal estrogen ring vs. vaginal estrogen cream	Low ^{a,d} ⊕⊕○○ No difference	Very low ^{a,c,d} ⊕○○○ Uncertain	Low ^{a,d} ⊕⊕○○ No difference	Low ^{a,d} ⊕⊕○○ No difference	NR	NR	Moderate ^a ⊕⊕⊕○ Higher	N/A
Vaginal DHEA vs. placebo	Low ^{a,e} ⊕⊕○○ Improves	Very low ^{a,f} ⊕○○○ Uncertain	NR	Low ^{a,e} ⊕⊕○○ Improves	Very low ^{a,b,e} ⊕○○○ Uncertain	Low ^{a,d} ⊕⊕○○ Improves	NR	Low ^{a,c} ⊕⊕○○ More
Oral DHEA vs. placebo	NR	NR	NR	NR	NR	Very low ^{e,f} ⊕○○○ Uncertain	NR	Very low ^{c,f} ⊕○○○ Uncertain
Vaginal oxytocin vs. placebo	Very low ^{a,b,d} ⊕○○○ Uncertain	Very low ^{a,f} ⊕○○○ Uncertain	NR	Very low ^{a,b,d} ⊕○○○ Uncertain	Moderate ^d ⊕⊕⊕○ No Difference	NR	NR	Low ^{c,d} ⊕⊕○○ No difference
Oral ospemifene vs. placebo	Low ^{a,b} ⊕⊕○○ Improves	High ⊕⊕⊕⊕ No difference	NR	Low ^{a,b} ⊕⊕○○ Improves	NR	NR	High ⊕⊕⊕⊕ Higher	Low ^{a,c} ⊕⊕○○ No difference
Oral raloxifene and/or BZA vs. placebo	Low ^{a,d} ⊕⊕○○ No difference	Low ^{a,d} ⊕⊕○○ No difference	Low ^{a,d} ⊕⊕○○ No difference	Low ^{a,d} ⊕⊕○○ No difference	NR	Low ^{a,d} ⊕⊕○○ Improves less	Very low ^{a,c,f} ⊕○○○ Uncertain	N/A
Vaginal testosterone vs. placebo	Very low ^{d,f} ⊕○○○ Uncertain	NR	NR	Very low ^{d,f} ⊕○○○ Uncertain	NR	NR	NR	Very low ^{c,f} ⊕○○○ Uncertain

Intervention Vs. Comparator	Dryness	Discomfort/Irritation	Dysuria	Dyspareunia	Change in MBS	Quality of Life	Treatment Satisfaction	Adverse Events
Systemic testosterone + systemic estrogen vs. systemic estrogen alone	Low ^{c,d} ⊕⊕○○ No difference	NR	NR	Low ^f ⊕⊕○○ No difference	NR	NR	NR	Very low ^{a,c,d} ⊕○○○ Uncertain
Vaginal moisturizer vs. placebo	Low ^{a,c} ⊕⊕○○ Improves	NR	NR	Very low ^{a,b,c} ⊕○○○ Uncertain	Low ^{a,d} ⊕⊕○○ No difference	NR	Very low ^{a,c,d} ⊕○○○ Uncertain	Moderate ^a ⊕⊕⊕○ No difference
CO₂ laser vs. sham laser	Very low ^{a,b,d} ⊕○○○ Uncertain	Very low ^{a,b,d} ⊕○○○ Uncertain	Low ^{a,d} ⊕⊕○○ No difference	Very low ^{a,b,d} ⊕○○○ Uncertain	Low ^{a,d} ⊕⊕○○ No difference	Low ^{a,d} ⊕⊕○○ No difference	Very low ^{a,c,d} ⊕○○○ Uncertain	Very low ^{a,d,g} ⊕○○○ Uncertain
CO₂ laser vs. vaginal conjugated estrogens cream	Low ^{c,d} ⊕⊕○○ No difference	Low ^f ⊕⊕○○ No difference	Low ^f ⊕⊕○○ No difference	Low ^{c,d} ⊕⊕○○ No difference	NR	Low ^f ⊕⊕○○ No difference	Very low ^{c,f} ⊕○○○ Uncertain	Very low ^{f,g} ⊕○○○ Uncertain
CO₂ laser vs. CO₂ laser plus HA gel	Very low ^{a,f} ⊕○○○ Uncertain	Very low ^{a,f} ⊕○○○ Uncertain	Very low ^{a,f} ⊕○○○ Uncertain	Very low ^{a,f} ⊕○○○ Uncertain	NR	Very low ^{a,c,f} ⊕○○○ Uncertain	NR	Very low ^{a,f,g} ⊕○○○
CO₂ laser vs. radio-frequency, placebo	NR	NR	NR	NR	NR	Very low ^{a,c,d} ⊕○○○ Uncertain	NR	N/A
Er:YAG laser vs. sham laser	NR	NR	NR	NR	NR	Low ^f ⊕⊕○○ No difference	NR	Very low ^{f,g} ⊕○○○ Uncertain
Er:YAG laser vs. HA suppositories	Very low ^{a,c,f} ⊕○○○ Uncertain	NR	NR	Very low ^{a,c,f} ⊕○○○ Uncertain	NR	Very low ^{a,c,f} ⊕○○○ Uncertain	Very low ^{a,c,f} ⊕○○○ Uncertain	Very low ^{a,f,g} ⊕○○○ Uncertain
Er:YAG laser vs. Er:YAG hyperstack	NR	NR	NR	Very low ^{a,f} ⊕○○○ Uncertain	NR	NR	NR	N/A

Abbreviations: AE=adverse event; BZA=bazedoxifene; CO₂=carbon dioxide; COMMA=Core Outcomes in Menopause; DHEA=dehydroepiandrosterone; Er:YAG=Erbium-doped yttrium aluminum garnet laser; HA=hyaluronic acid; MBS=most bothersome symptom; NR=not reported; N/A=not assessed; OIS = optimal information size.

Certainty of evidence (COE):

High certainty (⊕⊕⊕⊕): We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty (⊕⊕⊕○): We are moderately confident in the effect estimate; the true effect is likely to be close to the effect estimate, but there is a possibility that it is substantially different.

Low certainty (⊕⊕○○): Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

Very low certainty (⊕○○○): We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

Explanations for downgrading:

^aDowngraded one level for study limitations (one or more trials assessed as “some concerns” risk of bias)

^bDowngraded one level for inconsistency (effect varied across trials)

^cDowngraded one level for study limitations (one or more trials did not provide adequate statistical reporting)

^dDowngraded one level for imprecision (total sample size less than OIS of 400)

^eDowngraded one level for imprecision (SD crosses no-effect threshold)

^fDowngraded two levels for imprecision (total sample size much less than OIS of 400)

^gDowngraded one level for imprecision (no or few events)

Limitations

Despite the breadth of studies, findings were limited by heterogeneity in intervention-comparator-outcome combinations. Studies of specific interventions or direct comparisons were few, small, short, and often lacked methodologic rigor in outcome reporting and analyses. Limiting inclusion to U.S.-available interventions improved applicability but excluded a substantial literature base, especially for vaginal estrogen therapies that are not FDA-approved for any indication such as estriol. Higher certainty of evidence does not imply a clinically important effect. Few validated scales or thresholds for clinical importance exist which makes it difficult to translate statistical effects into net clinical benefits. Considerable placebo effects were present and absolute differences versus comparators were generally modest. Given wide-ranging symptoms associated with GSM, we focused COE on eight outcomes previously identified by the COMMA review; other outcomes that may be clinically relevant, such as recurrent urinary infections, are not rated. Populations and symptom severity in these studies may not fully reflect patients seen in many clinical settings especially in primary care.

Implications and Conclusions

This SR provides comprehensive, up-to-date information to guide patients, clinicians, and policymakers regarding GSM. Overall, vaginal estrogen, vaginal DHEA, oral ospemifene, and vaginal moisturizers may improve at least some GSM symptoms in the populations studied. Evidence does not demonstrate efficacy of vaginal or systemic testosterone, vaginal oxytocin, oral raloxifene or bazedoxifene, or energy-based therapies. Harms were inconsistently reported but there was not a strong signal for frequent serious adverse effects in short-term, relatively small studies. Clinicians may choose to tailor treatment based on specific outcomes of concern, intervention side effects, personal risk factors (e.g., cancer history), insurance coverage or cost, patient preference for route or type of therapy, and treatment availability. Future studies would be strengthened by a standard definition and uniform diagnostic criteria for GSM, a common set of validated outcome measures and reporting standards, and attention to clinically relevant populations and intervention comparisons. Long-term followup for efficacy, tolerability, and safety represents a critical gap needed to guide treatment longer than 1 year.

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1. Introduction

1.1 Background

The term genitourinary syndrome of menopause (GSM) describes the spectrum of symptoms and physical changes resulting from declining estrogen and androgen concentrations in the female genitourinary tract during and after menopause.^{1,2} Menopause is defined as 12 months without a menstrual period, and is a natural function of physiologic changes in ovarian function around age 51 (or after surgical or medical interventions).³ For some women, menopause is associated with vasomotor symptoms (i.e., hot flashes/flushes and/or night sweats) and/or genitourinary symptoms, with wide variability in prevalence, duration, and severity.⁴

Since the introduction of the term GSM in 2014,^{1,2} no consensus has been reached about the number or type of symptoms (vulvovaginal, urinary, or sexual) needed to diagnose GSM, nor a requirement for identifying concurrent physical signs.^{5,6} Vulvovaginal symptoms associated with menopause include dryness, burning, and irritation.⁷ Urinary symptoms include urgency, frequency, dysuria, and recurrent urinary infections.⁸ The vulvovaginal and urinary effects of menopause are often considered the cause of sexual symptoms of GSM, including dyspareunia and bleeding during intercourse, as well as broader impacts on sexual function, such as reduced libido, arousal, and orgasm.⁸⁻¹⁰ Physical changes associated with GSM include labial atrophy, reduced moisture, introital stenosis, and clitoral atrophy.^{1,2} The vaginal surface may be friable and hypopigmented, with petechiae, ulcerations, and tears; urethral findings may include caruncles, prolapse, or polyps.¹¹ However, presence and severity of physical exam findings do not directly correlate with self-reported GSM symptoms.¹¹⁻¹³

Clinicians generally diagnose GSM based on symptoms in a postmenopausal woman, with or without related physical findings, and after ruling out other etiologies or co-occurring pathologies (e.g., infectious vaginitis, vulvar lichen sclerosis, dermatitis, lichen planus, or an active urinary infection).^{8,14,15} Objective measures of postmenopausal vaginal changes include the Vaginal Maturation Index (VMI)¹⁶ and vaginal pH.¹⁷ The VMI demonstrates a shift from superficial cells to parabasal cells as the vaginal epithelium thins, and vaginal pH then rises as fewer superficial epithelial cells exfoliate and break down to release glycogen and glucose, which would typically be broken down into lactic acid by lactobacilli in an estrogenized vagina.⁷ Trials sometimes limit inclusion to women with at least moderate to severe GSM symptoms, 5% or fewer superficial cells on VMI, and vaginal pH greater than 5, but these measures are neither required nor commonly used for clinical diagnosis and treatment of GSM.¹⁸

GSM prevalence estimates in postmenopausal women vary widely from 13 to 87 percent.¹⁹ This inconsistency stems from many factors including variation in the symptoms and/or signs assessed and evaluated, the symptom assessment tools used, and the demographics and settings of study populations.¹⁹ Unlike vasomotor symptoms of menopause (i.e., hot flashes and/or night sweats), the prevalence and intensity of some genitourinary symptoms, such as vulvovaginal dryness, increase with advancing age.^{20,21} GSM may be associated with reduced quality of life and sexual functioning, and a higher likelihood of urinary complaints, all of which may interfere with interpersonal relationships.²²⁻²⁷ Despite the potentially disruptive nature of GSM, only about half of women with GSM symptoms report discussing their symptoms with their clinicians, and of those who did, most said the clinician did not initiate the conversation.^{28,29}

Several organizations recommend identifying GSM through a case-finding approach, by screening women for symptoms with routine questions.³⁰⁻³² However, few tools have been validated for GSM assessment and existing tools are limited to vulvovaginal symptoms.^{33,34} The

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urinary symptoms associated with GSM are also associated with other common urinary conditions in older women, such as reduced bladder capacity, idiopathic overactive bladder, and detrusor muscle overactivity, making identification, evaluation, and treatment of these and other symptoms complex.¹¹ A causal relationship between reduced hormone levels and urinary symptoms remains controversial.³⁵⁻³⁷ Some have even questioned whether GSM meets the definition of a disease syndrome.³⁸ These questions create uncertainty around the optimal approach to screening, identification, evaluation, and management of GSM.

Nonetheless, the range of GSM treatments has increased substantially in recent years.^{39, 40} Traditional therapies include vaginal estrogen, moisturizers, and lubricants. Estrogen binds to receptors in the vagina, vulva, urethra, bladder, and pelvic floor, shifts the vaginal cytology toward superficial cells, away from parabasal cells, and reduces the vaginal pH. Vaginal moisturizers increase the fluid content in the endothelium and reduce the vaginal pH. Personal lubricants can be water, silicone, or oil-based and are primarily used to provide short-term lubrication during sexual activity; lubricants are often used as a placebo or control treatment in clinical trials. Newer hormonal approaches include vaginal or systemic dehydroepiandrosterone (DHEA), vaginal oxytocin, selective estrogen receptor modulators (SERMs), and testosterone. DHEA is a precursor to both androgens and estrogens that is transformed into estradiol and testosterone, for example, within vaginal mucosal cells. Oxytocin is a pituitary hormone primarily implicated in uterine labor contractions and lactation, but vaginal oxytocin gel has also been shown to reduce vaginal pH and increase the proportion of superficial cells in small studies. SERMs have varied estrogen agonist/antagonist effects throughout the body; among SERMs, ospemifene has unique estrogen receptor agonist activity in vaginal tissue. Testosterone may improve libido and is aromatized to estradiol.⁴¹ Complementary therapies, including oral and vaginal natural products (herbal supplements, phytoestrogens, vitamins, probiotics), mind-body practices, and educational interventions, offer various mechanisms of action while appealing to women who wish to avoid hormonal treatments. Finally, energy-based treatments such as laser and radiofrequency devices claim to stimulate collagen formation, angiogenesis, and epithelial thickening by causing microtrauma or heating superficial tissue layers.

Some of these treatments aim to improve a broad range of GSM symptoms, while others target a specific bothersome symptom. Randomized trials are typically short term, and lack long-term intervention efficacy, adherence, or harms data. Consequently, guidance for longer-term followup and surveillance as well as treatment in special populations, such as women with a history of breast cancer, has relied on expert consensus in the absence of robust evidence.^{30, 31, 42}

1.2 Purpose of Review

The Agency for Healthcare Research and Quality conducted a systematic evidence review on the topic of GSM that was funded by the Patient Centered Outcome Research Institute (PCORI®) and will serve as the basis for development of American Urological Association (AUA) clinical practice guidelines. The intended audience includes guideline developers, health system administrators, clinicians, patients, and others interested in making informed decisions about GSM screening, evaluation, and treatment.

2. Methods

2.1 Review Approach

For all Key Questions (KQs), the systematic review (SR) followed Evidence-based Practice Center (EPC) program methodology, as laid out in the EPC Methods Guide. We registered the protocol for this SR in PROSPERO (registration number CRD42023400684).

2.2 Key Questions

After discussion with Key Informants and our team's content and methods experts, we chose to interpret the term "screening" in KQ1 as identifying underreported, symptom-based conditions (similar to screening for anxiety and depression), rather than "screening" for an asymptomatic condition. Based on input from public commenters, Key Informants, and members of a Technical Expert Panel, we drafted the following KQs.

KQ1. What are the effectiveness and harms of screening strategies to identify genitourinary syndrome of menopause (GSM) in postmenopausal women? Does screening impact patient reported symptoms or improve quality of life (QoL)?

KQ2. What are the effectiveness and comparative effectiveness of hormonal, non-hormonal, and energy-based interventions when used alone or in combination for treatment of GSM symptoms? Which treatments show improvement for which symptoms?

KQ3. What are the harms (and comparative harms) of hormonal, non-hormonal, and energy-based interventions for GSM symptoms?

KQ4. What is the appropriate followup interval to assess improvement, sustained improvement, or regression of symptoms of GSM in women treated with hormonal, non-hormonal, and energy-based interventions?

KQ5. What are the effectiveness, comparative effectiveness, and harms of endometrial surveillance among women who have a uterus and are using hormonal therapy for GSM?

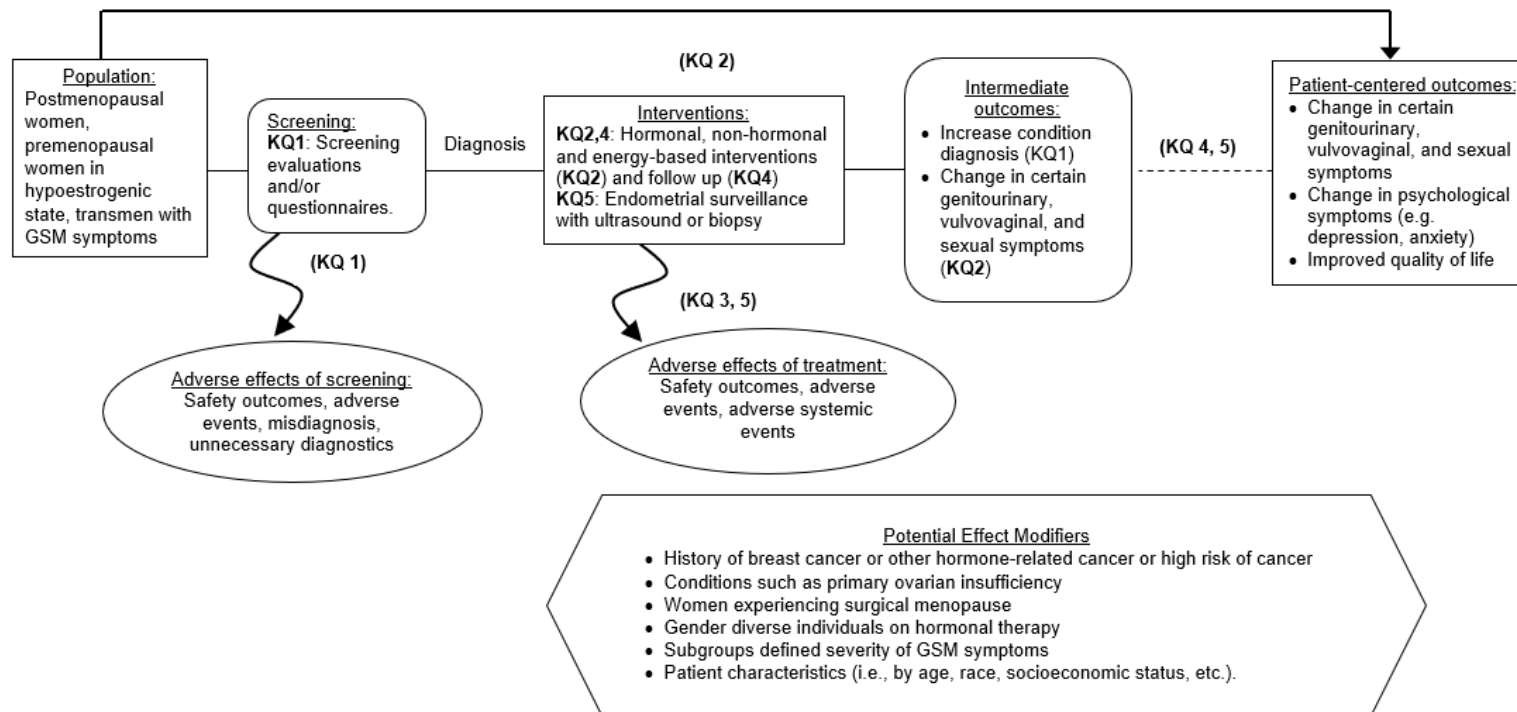
For all KQs, how do the findings vary for women with a history of breast cancer or other hormone-related cancers, a high risk of cancer, or conditions such as primary ovarian insufficiency, women experiencing surgical menopause, gender diverse individuals, and within subgroups defined by severity of GSM symptoms, and patient characteristics (i.e., by age, race, socioeconomic status, etc.)?

2. Methods

2.3 Analytic Framework

Based on discussions with Key Informants and Technical Expert Panel members, we developed an analytic framework for the KQs (Figure 1).

Figure 1. Analytic framework for genitourinary syndrome of menopause



Abbreviations: GSM=Genitourinary Syndrome of Menopause; KQ=Key Question

This figure depicts the Key Questions within the context of the PICOTS (Population, Intervention, Comparator, Outcomes, Timing, and Study design/setting) described above. In general, the figure illustrates how screening or case-finding may identify patients with GSM, who may then be treated with hormonal, non-hormonal, or energy-based interventions. These interventions may result in intermediate outcomes such as change in genitourinary, vulvovaginal, or sexual symptoms and/or patient-centered outcomes such as change in psychological symptoms or QoL. Also, adverse effects (AEs) may occur at any point after patients are screened.

2. Methods

2.4 Study Selection

We searched for published studies for all KQs in MEDLINE[®], Embase[®], and CINAHL[®] from database inception through December 11, 2023 (Appendix A). We included vocabulary and natural language terms, along with free-text words, relevant to the KQ. We supplemented our bibliographic database searches with citation searching of relevant systematic reviews and original research. All searches were independently peer reviewed.

After we removed duplicates, we uploaded citations into DistillerSR, a programmable online citation and article screening tool for SRs.⁴³ Using prespecified inclusion and exclusion criteria (Table 1), titles and abstracts were initially screened by two independent reviewers for potential relevance to the Key Questions. Articles included by either reviewer underwent full-text screening. We screened abstracts with the assistance of DistillerSR's Artificial Intelligence System (DAISY) until the DAISY-predicted score for likelihood of inclusion was less than 0.1 percent and the inclusion rate had fallen to less than 5 percent. The remaining abstracts (~2000) with an inclusion score less than 0.1 percent were not screened by a second reviewer, but a word search of the titles and abstracts was completed to ensure that any relevant articles were not missed. At the full-text screening stage, two independent reviewers agreed on the final inclusion or exclusion decision. Articles that met eligibility criteria were included for risk of bias (RoB) assessment. See Appendix B for references excluded at the full-text screening stage.

After initial study selection, citations were grouped by type of intervention: hormonal, non-hormonal, or energy-based, based on the primary intervention studied (trials of combined interventions were assigned to a single category for organizational purposes but described separately). Non-hormonal interventions were heterogeneous and we created an evidence map with limited data extraction. Because of the potential for long-term effects of energy-based treatments and the shorter duration of clinical experience with these relatively new interventions, we included uncontrolled observational studies of energy-based interventions that reported long-term harms (See Section 2.7, Data Synthesis).

Study selection criteria for each KQ are listed in Table 1 below. Minimum followup duration of 8 weeks was selected to allow time for outcomes to change. Study size criteria was set at 20 participants per study group based on expert consensus that it is difficult to achieve balance from randomization with smaller trials.

Table 1. Study eligibility criteria

PICOTS	KQ	Inclusion	Exclusion
Population	KQ1:	Postmenopausal women	--
	KQ2-4:	Postmenopausal women, premenopausal women in hypoestrogenic state, or gender diverse individuals on hormonal therapy, with one or more symptom of GSM	Individuals with genitourinary symptoms for reasons other than GSM
	KQ5:	Postmenopausal women or premenopausal women in hypoestrogenic state, with a uterus using hormonal therapy primarily for GSM symptoms	Women using hormonal therapy for reasons other than GSM
Interventions	KQ1:	Screening evaluations and/or questionnaires	Physical exam
	KQ2-4:	Hormonal Interventions: vaginal estrogen therapy (including vaginal cream, tablets, inserts or ring), SERMs, DHEA, oxytocin vaginal gel, testosterone, Energy-based interventions: CO ₂ laser, Erbium:YAG laser, radiofrequency	Systemic estrogen as the intervention of interest (included if comparator or co-treatment)

2. Methods

PICOTS	KQ	Inclusion	Exclusion
		<p>Non-hormonal interventions: Over-the-counter non-hormone vaginal lubricants and moisturizers, hyaluronic acid, herbal therapies/supplemental alternatives, phytoestrogens, vitamin D, vitamin E, probiotics, pelvic floor physical therapy to treat vaginal or sexual symptoms of GSM.</p> <p>For KQ4. Assess different durations of followup</p>	<p>Menopausal hormone therapy only for reasons other than GSM</p> <p>Laser therapy for anatomic areas other than the vagina</p> <p>Pelvic floor physical therapy for urinary incontinence</p> <p>Any intervention not available in the United States (e.g., estriol)</p> <p>Any obsolete intervention (e.g., 25 mcg estradiol tablets)</p>
	KQ5:	Endometrial surveillance with ultrasound or biopsy	--
Comparison	KQ1:	Usual care	--
	KQ2-4:	<p>Efficacy: Placebo, inactive control, sham</p> <p>Comparative Effectiveness: Another hormonal, non-hormonal, or energy-based intervention</p> <p>For KQ3: long-term (> 12 months) laser harms did not require comparison</p> <p>For KQ4. Assess different durations of follow up</p>	--
	KQ5:	Usual care, or different type or level of surveillance	--
Outcomes	KQ1:	<p>Diagnosis of GSM, potential harms: misdiagnosis as another condition with similar presentation such as inflammatory dermatologic conditions, malignancy, infections, or presence of symptoms prior to menopause</p> <p>Progressing to unnecessary diagnostics for the index patient such as vaginal or endometrial biopsy</p>	--
	KQ 1-2&4:	<p>Change in symptoms or clinical conditions:</p> <ul style="list-style-type: none"> Vulvovaginal: vaginal/vulvar irritation, vaginal soreness, vaginal pain[†], vulvovaginal dryness/lubrication[†] Urinary: dysuria[†], recurrent urinary tract infections, urinary frequency, urinary urgency, nocturia, urinary urge incontinence,* overactive bladder* Sexual: dyspareunia[†], orgasmic dysfunction, low libido, decreased arousal, sexual desire, sexual function, bleeding associated with sexual activity Psychological symptoms: QoL (i.e., distress, bother or interference of GSM symptoms[†]), depression, anxiety, and partner satisfaction Genital or vulvovaginal signs: urethral caruncle, urethral prolapse, vaginal atrophy or atrophic vaginitis Most Bothersome Symptom (MBS)[†]: (clinical symptom identified by the patient as most bothersome) <p>Treatment satisfaction[†]</p>	<p>Serum hormone concentration</p> <p>Stress incontinence</p>

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PICOTS	KQ	Inclusion	Exclusion
	KQ3&5:	<p>Safety outcomes: breast cancer, breast cancer recurrence or progression, breast tenderness, cardiovascular risk, endometrial cancer (KQ5), post-menopausal bleeding (KQ5), endometrial hyperplasia (KQ5), endometrial thickness (KQ5)</p> <p>AEs[†]: worsening or onset of urinary, genital, or sexual symptoms: vaginal burning, vaginal bleeding, vaginal discharge, vaginal scarring, vaginal stenosis; pelvic pain; dyspareunia; urethral strictures; meatal stricture/stenosis</p> <p>Systemic AEs: chronic pain, stroke, VTE (DVT or PE), death, hot flashes, headache, breast pain, cramps, bloating, nausea, vomiting</p>	--
Timing	All KQ	<p>Intervention: any treatment duration</p> <p>Outcomes:</p> <ul style="list-style-type: none"> For RCTs and prospective observational studies: 8 weeks minimum followup from treatment initiation For “other” study designs (i.e., studies reporting EBT harms): 1-year minimum followup from treatment initiation 	--
Setting	All KQ	Any	--
Study design	KQ1	RCTs and prospective observational studies with concurrent comparison group and analytic techniques to control for sample selection bias	--
	KQ2	RCTs	--
	KQ3	<p>RCTs and prospective observational studies with concurrent comparison group and analytic techniques to control for sample selection bias</p> <p>For energy-based therapy harms with followup ≥ 1 year, any study design.</p>	--
	KQ4	RCTs	--
	KQ5	RCTs and prospective observational studies with concurrent comparison group and analytic techniques to control for sample selection bias	--
Language	All KQ	English only	--
Geographic Location	All KQ	Any	--
Study size	All KQ	<p>N=20 or more participants randomized per study arm for RCTs</p> <p>N=20 for any observational study of energy-based therapy harms with followup ≥ 1 year</p>	--
Publication date	All KQ	Any	--

Abbreviations: AE=adverse effect; CO₂=carbon dioxide; DHEA=dehydroepiandrosterone; COMMA=Core Outcomes in Menopause; DVT=deep vein thrombosis; EBT=energy-based treatment; Erbium:YAG laser=erbium-doped yttrium aluminum garnet laser; GSM=genitourinary syndrome of menopause; KQ=Key Question; mcg=microgram; PE=pulmonary embolism; PICOTS=Population, Intervention, Comparator, Outcomes, Timing, and Study design/setting; QoL=quality of life; RCT=randomized controlled trial; SERM=selective estrogen receptor modulator; VTE=venous thromboembolism

*Incontinence and overactive bladder outcomes evaluated only for interventions other than pelvic floor muscle training

[†]Prioritized outcome identified by COMMA review group⁴⁴

2. Methods

2.5 Assessment of Risk of Bias

We did not assess RoB for studies included in the non-hormonal interventions evidence map. For remaining studies, we evaluated each study for RoB using the Cochrane Risk of Bias Tool 2.0 (RoB-2)⁴⁵ for randomized controlled trials (RCTs) and the Risk of Bias in non-Randomized Studies - of Interventions (ROBINS-I) for observational studies.⁴⁶ Components of the RoB-2 include participant group assignment (random sequence generation, allocation concealment), blinding (performance and detection bias), completeness of followup (attrition bias), analyses and outcome reporting consistent with predefined protocols (selective reporting bias), and other issues (such as appropriateness of analytic approach). RCT RoB was assessed for each domain above, and assigned a summary RoB rating for each study as low, some concerns, or high.

Components of the ROBINS-I include assessing bias due to confounding, classification of interventions, selection of participants (into the study, or into the analysis), deviations from intended interventions, missing data, measurement of the outcome and selection of the reported results. Observational studies RoB was assessed for each domain above, and assigned a summary RoB rating for each study as low, moderate, serious, or critical.

One investigator assessed RoB and a second reviewed; discrepancies were reconciled via consensus.

2.6 Data Extraction and Data Management

We extracted data into DistillerSR⁴³ and present detailed evidence tables in Appendix C. For trials that were rated low or some concerns RoB with the RoB-2 tool, or observational studies rated low or moderate RoB using the ROBINS-I tool, data elements extracted included author, year, trial registration number, study funding, setting, subject inclusion and exclusion criteria, intervention and control characteristics, sample size, followup duration, participant baseline age, race, and results of primary outcomes and adverse effects. Data were extracted by one reviewer and verified for accuracy by a second reviewer. When data were only presented in figures, point estimates were visually estimated from the figure to be entered into the meta-analysis. Instances where the point estimate needed to conduct the meta-analysis was not reported were calculated with the use of available point estimates following Cochrane guidance.⁴⁷ We followed guidance to calculate mean differences as well as standard deviations. In studies that provided insufficient data to calculate a standard deviation, imputation was employed, again following Cochrane guidance.

For trials that were rated high RoB with the RoB-2 tool, or observational studies rated serious or critical with the ROBINS-I tool, we extracted limited study characteristics data, including author, year, trial registration number, study funding, setting, subject inclusion and exclusion criteria, intervention and control characteristics, sample size, followup duration and outcomes reported. Consistent with standard practice for systematic reviews, we did not extract detailed results data for these studies, except for harms reported in long-term energy-based therapy studies. No synthesis or sensitivity analysis was performed using high RoB studies.

For studies included in the non-hormonal evidence map, we extracted limited study characteristics data, including author, year, trial registration number, study funding, setting, intervention and control characteristics, sample size, followup duration and outcomes reported. We did not extract detailed results data for these studies.

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2.7 Data Synthesis

After initial study selection, citations were grouped by type of intervention (hormonal, non-hormonal, or energy based), then organized by specific treatment-outcome comparisons. Each class of intervention required a different synthesis strategy as detailed below.

2.7.1 Hormonal Interventions

Hormonal interventions included vaginal estrogen therapy (including vaginal cream, tablets, inserts, or ring), vaginal or systemic dehydroepiandrosterone (DHEA), oxytocin vaginal gel, selective estrogen receptor modulators (SERMs), and vaginal or systemic testosterone. In comparisons of vaginal estrogen to placebo, all formulations and doses were grouped together.⁴⁸ Vaginal estrogen formulations and doses were evaluated separately in trials designed for those comparisons. Systemic estrogen therapy was not included as an intervention of interest. For SERMs, we evaluated ospemifene separately from raloxifene and bazedoxifene because of its unique estrogen receptor agonist activity in vaginal tissue. For DHEA and testosterone, we included both vaginal and systemic formulations, but evaluated efficacy and safety separately for vaginal and systemic formulations.

For studies with low or some concerns RoB, we synthesized evidence for each unique comparison with meta-analysis, when possible and appropriate. In cases where we found too few studies to calculate a pooled estimate (i.e., at least 3 studies of the same intervention/comparison with the same outcome measure/assessment), we provide a narrative summary.⁴⁹ We assessed the clinical and methodological heterogeneity and variation in treatment effect size to determine the appropriateness of pooling data.⁴⁹ If pooling was possible, we planned to synthesize data using the *metacont* function using a random effects model in R (a language and environment for statistical computing, <https://www.R-project.org/>). We used the Knapp-Hartung adjustment, Hedges' *g*, and the restricted maximum likelihood estimator for τ^2 when calculating the standardized mean differences (SMDs).⁵⁰ We planned to calculate SMDs with the corresponding 95 percent confidence intervals (CIs) for continuous outcomes when combining similar outcomes measured with different instruments.

We identified heterogeneity (inconsistency) of treatment effects on outcomes through visual inspection of the forest plots to assess the amount of overlap of CIs, 95% prediction intervals, T^2 , and the I^2 statistic to assess the impact of heterogeneity on the meta-analysis.⁵¹ The I^2 statistic as interpreted as follows:⁵²

- 0% to 40%: heterogeneity across studies may not be important
- 30% to 60%: may indicate moderate heterogeneity
- 50% to 90%: may indicate substantial heterogeneity
- 75% to 100%: considerable heterogeneity

When heterogeneity was identified, we examined individual study and subgroup characteristics to better understand the possible contributing sources. When heterogeneity exceeded 75 percent, we did not calculate a pooled estimate.

2.7.2 Non-Hormonal Interventions

Non-hormonal interventions included over-the-counter non-hormonal vaginal lubricants and moisturizers, hyaluronic acid, herbal therapies/supplemental alternatives, phytoestrogens, vitamin D, vitamin E, probiotics, mind and body practices, educational interventions, non-hormonal pharmaceuticals, and pelvic floor physical therapy to treat vaginal or sexual symptoms

2. Methods

of GSM. Phytoestrogens have variable agonist and antagonist activity on hormone receptors⁵³ and were grouped with non-hormonal interventions to be consistent with prior literature.^{54, 55}

Vaginal moisturizers are considered a first-line therapy for GSM, so were included for full RoB assessment and data extraction. We distinguished between vaginal lubricants and moisturizers based on intended use: lubricants are primarily used for short-term relief during sexual activity, whereas moisturizers are applied regularly and are intended to mimic the natural secretions in an estrogenized vagina.⁵⁶ Many studies used a water-based lubricant as a placebo or control treatment, often applied regularly to match the treatment schedule for the active intervention; lubricants were not evaluated as an independent intervention. For comparisons of moisturizers to placebo, all moisturizers, including hyaluronic acid-based moisturizers, were grouped together.

We took an evidence map approach to synthesizing the remaining non-hormonal intervention studies.^{57, 58} We organized studies by the type of intervention, according to the National Center for Complementary and Integrative Health (NCCIH) framework,⁵⁹ with narrative summaries of the body of evidence provided, including population and study characteristics, intervention(s), and outcomes reported.

2.7.3 Energy-Based Interventions

Energy-based interventions included carbon dioxide (CO₂) laser, erbium-doped yttrium aluminum garnet (Er:YAG) laser, and radiofrequency. The most commonly used lasers for GSM include the fractional microablative CO₂ laser and the nonablative Er:YAG laser.⁶⁰ We included any treatment protocol and grouped findings by laser type and comparison. For prospective studies of low or some concerns RoB, we synthesized evidence for each unique treatment-outcome comparison with meta-analysis, when possible and appropriate (i.e., at least three studies of the same intervention/comparator with similar outcome assessment) using the methods described above for hormonal interventions. We narratively summarized outcomes not suitable for meta-analysis. For studies without a comparison group, we narratively summarized AEs reported at a minimum of 1-year post-intervention.

2.8 Grading the Strength of Evidence

The American Urological Association (AUA) intends to use this evidence report to develop guidelines on the topic of GSM. Because this organization uses Grading of Recommendations Assessment, Development and Evaluation (GRADE)⁶¹ for rating evidence certainty, we used the GRADE framework to assess the overall certainty of evidence (COE).

We present the overall certainty of the evidence for the eight outcomes identified in the Core Outcomes in Menopause (COMMA) review (these include (1) pain with sex, (2) vulvovaginal dryness, (3) vulvovaginal discomfort/irritation, (4) dysuria, (5) change in MBS, (6) distress, bother, or interference of genitourinary symptoms (i.e., QoL), (7) satisfaction with treatment, and (8) side effects of treatment).⁴⁴ Remaining outcomes from Table 1 are described in the text without a summary COE statement.

We considered measures of vulvovaginal lubrication together with measures of vulvovaginal dryness. For “change in MBS,” we included studies in which most bothersome symptom (MBS) was used as a global scale. In a global MBS assessment, patients review a list of several GSM symptoms, often including vulvovaginal dryness, dyspareunia, and irritation or itching, and rate the severity of each symptom on a 4-point scale (none, mild, moderate, severe). Patients are asked to select which symptom is most bothersome at baseline and then followed for change in

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severity of that symptom after treatment. However, some studies used the MBS 4-point severity scale in different ways: either to restrict the study population to only those patients for whom dryness or dyspareunia was the MBS, for example, or to measure the change in severity of a single symptom for all patients in the study, regardless of whether that symptom was the patient's MBS. In these instances, we used the change in severity outcomes to describe the specific symptoms being reported, not as a global measure of "change in MBS." We interpreted "distress, bother, or interference of genitourinary symptoms" to mean the impact that GSM symptoms had on QoL. For side effects of treatment, we described serious, any, and common adverse effects, discontinuation due to adverse effects, as well as endometrial safety, and provide GRADE statements for the most serious effects reported.

The GRADE approach assesses five criteria which measure either internal validity (RoB, inconsistency, imprecision, publication bias) or external validity (directness of results).⁶¹ Briefly, for each prioritized outcome, we evaluated characteristics of the evidence across 5 domains: study limitations (RoB), imprecision (number of events, sample size, and precision of effect estimates reported by included studies),⁶² inconsistency (whether the direction and magnitude of effects are similar [or different] across the included studies), indirectness (how applicable the results were to our Key Questions), and publication bias (preferential reporting of positive results). The overall COE takes into consideration individual ratings in each of these 5 domains, but domains may not be weighted equally in determining the overall rating. If a study reported multiple measures for a single outcome, we described all results, but selected the highest quality or most commonly used measure for GRADE assessment (e.g., we selected a validated scale over a single-item measure)

For each treatment-outcome comparison, one reviewer rated the collective COE as high, moderate, low, or very low using GRADEpro GDT (www.gradepro.org). We then discussed those ratings as a team and came to a team consensus on overall COE ratings.

For each intervention, we present a summary of the evidence for the main outcomes in a summary of findings table, which provides key information about the direction of effect reported by included studies for each relevant comparison of alternative management strategies; numbers of participants and studies addressing each important outcome; and the rating of the overall confidence in summary statements for each outcome.⁶³

We derived COE based on statistical rather than clinical significance (non-contextualized approach) in part because validated measures of clinical significance were not available. We assessed magnitude of effect by reporting differences between intervention and control.

3. Results

3.1 Overview

From 11,993 unique search results, we identified 172 eligible articles (Figure 2), consisting of 147 unique studies. Most eligible studies were of hormonal interventions and addressed vulvovaginal atrophy symptoms or sexual function. We identified zero studies addressing Key Question (KQ) 1, 131 addressing KQ2, and 112 addressing KQ3. Zero studies directly addressed KQ4 and KQ5, so indirect evidence for those questions was reviewed in the KQ2 and KQ3 studies, respectively.

We identified 46 trials of hormonal interventions, including vaginal estrogen, vaginal and systemic dehydroepiandrosterone (DHEA), vaginal oxytocin, oral ospemifene, bazedoxifene, and raloxifene, and vaginal and systemic testosterone. Of these, 11 trials were rated high risk of bias (RoB), with the remaining 35 rated low or some concerns RoB. Three studies included 1 year of followup, the remainder were shorter than 1 year, most commonly 12 weeks duration. About 90 percent of hormonal studies enrolled women with a mean or median age in their 50s. Over 40 percent of studies did not report racial or ethnic demographics; of those that did report, more than half included 90 percent or greater white women. About 40 percent of hormonal studies included U.S. trial sites.

We identified 17 trials of energy-based therapies, of which 6 were rated high RoB and the remaining 11 rated low or of some concerns (for randomized controlled trials [RCTs]) or moderate (for non-RCTs) RoB. One study included 1 year of followup, while most were 3 to 4 months duration. About 70 percent of energy-based studies enrolled women with a mean or median age in their 50s, the remainder had a mean or median of 60-62 years. Only 2 energy-based studies reported racial/ethnic demographics; both were >90 percent white. Only one energy-based study was conducted in the US. An additional 15 uncontrolled observational studies of energy-based therapies were rated critical or serious RoB and were included for assessment of long-term harms only (see Section 3.3.3.5).

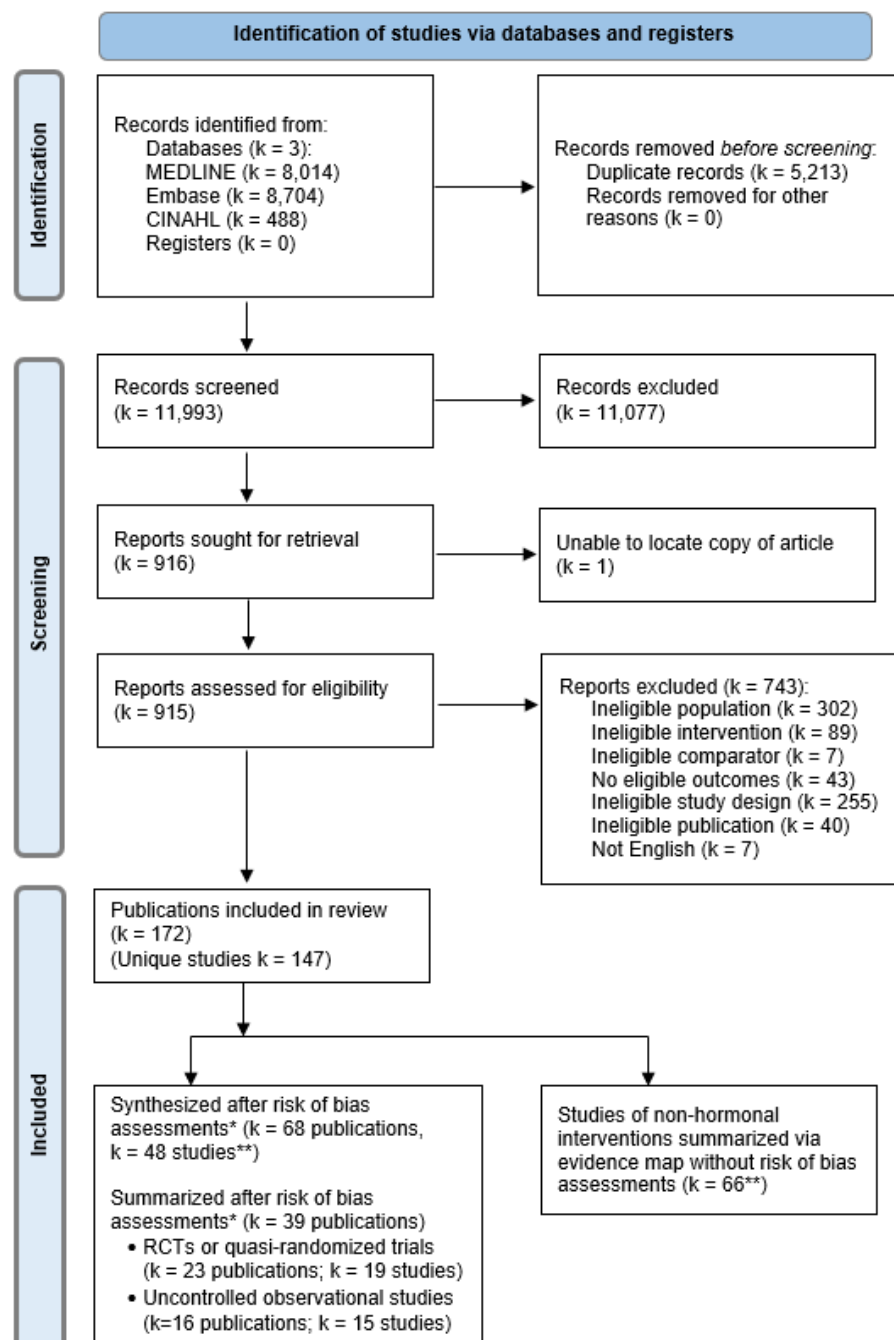
We identified 70 studies of non-hormonal interventions, of which 66 are described in an evidence map without RoB assessments. The remaining four are of moisturizers, which were discussed in more detail than other non-hormonal interventions. Two of the moisturizer trials were rated high RoB, and the remaining two were rated some concerns RoB. Moisturizer studies were 12 weeks or 3 months duration. Average age of participants ranged from 45 to 60 years; neither study reported racial or ethnic demographics or was conducted in the US. Two additional low- or moderate-RoB trials counted in the hormonal interventions included moisturizer arms and are also discussed with these studies.

Appendix Table C.3 summarizes the key findings and certainty of evidence (COE) statements for Core Outcomes in Menopause (COMMA) outcomes. Detailed RoB assessments, trial characteristics and outcomes data for studies rated low, some concerns or moderate RoB can be found in Appendix C. Trials rated high or critical RoB are not discussed in subsequent sections of this report, except for uncontrolled observational studies of energy-based interventions that reported long-term harms. Limited characteristics of the trials assessed as high RoB can be found in Table 2 and Appendix C. Limited characteristics of the uncontrolled observational studies of energy-based interventions that reported long-term harms can be found in Table 13 in Section 3.3.3.5 and Appendix C. Limited characteristics of studies that were included in the evidence map can be found in Appendix C. Appendix D provides Food and Drug Administration (FDA) reported indications, warnings, and contraindications of included

3. Results, Overview

therapies. Appendix E details the report's adherence to Patient-Centered Outcomes Research Institute (PCORI®) methodology standards, and Appendix F provides the references for all appendix materials.

Figure 2. Literature flow



Abbreviations: RCT=randomized controlled trial; RoB=risk of bias.

*Data extraction and synthesis completed for low/moderate/some concerns RoB RCTs and prospective observational studies with a concurrent comparison group. Study characteristics summarized for high RoB studies. Harms outcome data and study characteristics summarized for uncontrolled observational studies of energy-based treatments.

**One 3-arm RCT of estrogen, isoflavone, and placebo was assessed for RoB (estrogen vs. placebo) and included in the evidence map (isoflavone vs. placebo).

3. Results, Overview

Table 2. Overview of included trials rated high RoB*

Category	Characteristics	Estrogen (k=10) ⁶⁴⁻⁷³	Testosterone (k=1) ⁷⁴	Moisturizer (k=2) ^{75, 76}	Energy- Based (k=6) ⁷⁷⁻⁸²	Total (k=19)
Sample Size	≤60	3	1	1	2	7
	61-99	1	0	0	3	4
	100-199	4	0	1	1	6
	200-550	2	0	0	0	2
Special Populations	History of/high risk for breast cancer	0	0	1	2	3
Route of Administration†	Vaginal	10	0	2	6	18
	Systemic	0	1	0	0	1
Comparator	Placebo or sham	4	0	2	3	9
	Estrogen	3	1	0	1	5
	Other active comparator	3	0	0	2	5
Outcomes Reported‡	Genital or vulvovaginal symptoms	3	0	1	5	9
	Genital or vulvovaginal signs	6	0	0	5	11
	Urinary symptoms	4	0	0	1	5
	Sexual symptoms	4	1	2	3	10
	QoL	1	1	0	2	4
	Treatment satisfaction	3	1	1	0	5
	Adverse effects	5	0	2	6	13
Location	Asia	4	0	2	1	7
	Australia	0	0	0	1	1
	Europe	2	1	0	1	4
	North America	4	0	0	0	4
	South America	0	0	0	3	3
Funding Source	Industry	6	0	1	1	8
	Academia	3	0	1	1	5
	Government	0	0	0	1	1
	None	0	0	0	3	3
	NR	1	1	0	0	2

Abbreviations: QoL=quality of life; RoB=risk of bias; NR=not reported; COMMA=Core Outcomes in Menopause; AE=adverse effect; GSM=genitourinary syndrome of menopause.

*Excludes 15 uncontrolled observational studies of energy-based therapies that were only assessed for long-term harms

†Route of administration refers to intervention of interest.

‡Outcome categories (COMMA outcomes underlined): **Genital or vulvovaginal symptoms:** vaginal/vulvar irritation, vaginal soreness, vaginal pain, vulvovaginal dryness/lubrication; **Urinary symptoms:** dysuria, recurrent urinary tract infections, urinary frequency, urinary urgency, nocturia, urinary urge incontinence, overactive bladder; **Sexual symptoms:** dyspareunia, orgasmic dysfunction, low libido, decreased arousal, sexual desire, sexual function, bleeding associated with sexual activity; **Quality of life:** distress, bother or interference of GSM symptoms; **Adverse effects:** any reported AE or safety outcomes (breast cancer, breast cancer recurrence or progression, breast tenderness, cardiovascular risk

3.2 Findings for Key Question 1

What are the effectiveness and harms of screening strategies to identify genitourinary syndrome of menopause (GSM) in postmenopausal women? Does screening impact patient reported symptoms or improve quality of life (QoL)?

No studies were designed to directly evaluate the effectiveness and harms of screening strategies to identify GSM in postmenopausal women, or the impact of screening on symptoms or quality of life.

3. Results, Findings for Key Questions 2 and 3, Estrogen Hormonal Interventions

3.3 Findings for Key Questions 2 and 3

KQ2. What are the effectiveness and comparative effectiveness of hormonal, non-hormonal, and energy-based interventions when used alone or in combination for treatment of GSM symptoms? Which treatments show improvement for which symptoms?

KQ3. What are the harms (and comparative harms) of hormonal, non-hormonal, and energy-based interventions for GSM symptoms?

FDA Reported Indications, Warnings and Contraindications: We reviewed FDA websites for all FDA approved pharmacologic interventions to identify and report on indications, warnings, and contraindications of included therapies. The information is provided in Appendix D. Several of the reviewed treatments are not FDA approved for treatment of GSM and are not covered by specific FDA statements.

3.3.1 Estrogen Hormonal Interventions

3.3.1.1 Key Messages

- Compared with placebo, vaginal estrogen may improve vulvovaginal dryness, most bothersome symptom (MBS), and treatment satisfaction (low COE) but may result in little to no difference in dyspareunia or dysuria (low COE), and probably results in no difference in QoL (moderate COE). The evidence is very uncertain on the effect of vaginal estrogen versus placebo on vulvovaginal discomfort/irritation (very low COE).
- Compared with no treatment, vaginal estrogen may improve vaginal dryness and dyspareunia and may result in little to no difference in vulvovaginal discomfort/irritation and dysuria (low COE).
- Compared with vaginal estrogen cream, vaginal estrogen ring probably results in higher treatment satisfaction (moderate COE), but may result in little to no difference in vulvovaginal dryness, dysuria, and dyspareunia (low COE). The evidence is very uncertain on the effect of vaginal estrogen ring versus cream on vulvovaginal discomfort/irritation (very low COE).
- The evidence is very uncertain on the effect of vaginal estrogen on adverse effects (AEs) compared with placebo (very low COE).
- Authors did not report AEs in a consistent way across trials, although many report counts (%) of common AEs. Only four trials reported incidence of vaginal bleeding and only two reported on breast tenderness.
- Vaginal estrogen was associated with cases of vaginal bleeding and with endometrial proliferation and one case of hyperplasia in an endometrial polyp. There were no cases of endometrial malignancy in these short duration studies.

3. Results, Findings for Key Questions 2 and 3, Estrogen Hormonal Interventions

3.3.1.2 Overview

Thirty-seven publications reporting 26 randomized controlled trials (RCTs) of vaginal estrogen were included. Twenty-four publications (16 RCTs) were assessed as low (4 RCTs⁸³⁻⁸⁶) or some concerns RoB (12 RCTs⁸⁷⁻⁹⁸). The other thirteen publications^{64-73, 99-101} (10 RCTs) were assessed as high RoB and will not be discussed further. Table 3 presents an overview of the trials assessed as low or some concerns RoB, including key study, patient, symptom, and outcome reporting characteristics. Detailed RoB assessments can be found in Appendix Tables C.1 and C.2. Detailed trial characteristics are reported in Appendix Table C.4. Limited information about the high RoB trials is in Table 2 and Appendix Table C.8.

Among the trials that reported on the population race/ethnicity (k=9 of 16), white women made up approximately 80 percent of the population. One-third of the trials required Vaginal Maturation Index (VMI) and pH to verify vaginal atrophy for study inclusion; most trials excluded women with a history of cancer, and many excluded women with a history of cardiovascular or thromboembolic disease.

The 16 trials compared vaginal estrogen with placebo or lubricant gel (k=9),^{84-86, 91, 92, 94-96, 98} no treatment (k=1),⁸⁹ vaginal testosterone (k=1),⁹⁷ different vaginal estrogen doses or delivery methods (k=3),^{83, 87, 88} or vaginal estrogen versus or in addition to pharmaceuticals used for overactive bladder (k=2).^{90, 93} Of the three trials that compared vaginal estrogen doses or delivery methods, two trials^{83, 88} compared a vaginal estradiol ring with a vaginal conjugated estrogens cream and one trial⁸⁷ compared different doses of vaginal estrogen cream.

Four trials evaluated other active interventions, including vaginal testosterone (k=2),^{97, 98} moisturizer (k=1),⁸⁶ or both vaginal testosterone and moisturizer (k=1).⁸⁴ The results for the vaginal testosterone and moisturizer arms are reported in Section 3.3.2 and Section 3.3.4, respectively. Twelve additional publications (11 RCTs) used vaginal estrogen as a comparator and are described in other report sections, including eight publications^{94, 102-108} (7 RCTs) comparing various phytoestrogens with estrogens and two publications^{109, 110} (2 RCTs) of Vitamin E versus estrogen in Section 3.6, and two publications^{111, 112} (2 RCTs) comparing carbon dioxide (CO₂) laser versus vaginal estrogen in Section 3.3.3. Three additional publications¹¹³⁻¹¹⁵ (3 RCTs) in Section 3.3.2 evaluated the effect of adding systemic testosterone to systemic estrogen compared with systemic estrogen alone.

All 16 trials that investigated vaginal estrogen as an intervention of interest assessed at least one effectiveness outcome and 15 trials also reported harms outcomes. No trial captured all eight COMMA outcomes, though each effectiveness outcome was assessed by at least three trials. Measures and methods used for outcomes reporting varied widely. We were unable to perform a meta-analysis of results due to variability in populations, interventions, comparisons, outcomes, and reporting used including length of followup. COE ratings for priority outcomes are listed in Table 4. Complete outcomes data are presented in Appendix Tables C.12-13.

3. Results, Findings for Key Questions 2 and 3, Estrogen Hormonal Interventions

Table 3. Overview of included vaginal estrogen trials rated low or some concerns RoB

Category	Characteristics	Vaginal Estrogen Vs. Placebo or Lubricant (k=9)	Vaginal Estrogen Vs. No Treatment (k=1)	Vaginal Estrogen Dose or Delivery Comparisons (k=3)	Vaginal Estrogen Vs. OAB Pharmaceuticals (k=2)	Total (k=15*)
Sample Size	<100	4	0	1	2	7
	100-199	0	1	2	0	3
	200-499	3	0	0	0	3
	>500	2	0	0	0	2
Diagnosis of VVA/GSM symptoms	Clinical diagnosis	1	1	1	1	4
	Self-reported	6	0	1	1	8
	Study verified	3	0	0	0	3
Type of VVA/GSM symptom for inclusion	Vulvovaginal	7	0	2	0	9
	Urinary	0	1	1	2	4
	Sexual	4	0	1	0	5
	Urinary and Sexual	1	0	0	0	1
Baseline VVA/GSM symptom severity	Mild, moderate or severe	0	0	0	0	0
	Moderate to severe	6	0	1	0	7
	Not reported	3	1	2	2	8
Other eligibility criteria	Included women s/p hysterectomy	5	0	2	2	9
	Presence/hx of cancer or high-risk for cancer	0	0	0	0	0
	Treatment naïve/washout period	6	0	0	0	6
Length of followup	8 weeks	1	0	0	0	1
	12 weeks	8	0	2	2	12
	15 weeks	0	0	1	0	1
	36 weeks	0	1	0	0	1
COMMA Outcomes Reported	Vulvovaginal dryness	8	0	2	0	10
	Discomfort/irritation	4	1	1	0	6
	Dysuria	1	1	1	0	3
	Dyspareunia	8	1	3	0	12
	Change in MBS	4	0	0	0	4
	QoL	1	0	0	0	1
	Satisfaction with treatment	1	0	2	0	3
	Adverse effects	9	1	2	1	13

Abbreviations: COMMA=Core Outcomes in Menopause; GSM=genitourinary syndrome of menopause; hx=history; MBS=most bothersome symptom; OAB=overactive bladder; QoL=quality of life; RoB=risk of bias; s/p=status post; VVA=vulvovaginal atrophy

*Total count does not include Melisko (2017),⁹⁷ which evaluated vaginal estrogen and vaginal testosterone but did not report any comparison of the two arms.

3. Results, Findings for Key Questions 2 and 3, Estrogen Hormonal Interventions

3.3.1.3 COMMA Outcomes

Table 4. Summary of COMMA outcomes, findings, and certainty of evidence for vaginal estrogen

Outcome	Intervention Vs. Comparator Followup	Study Design: No. Trials (N) Direction of Effect	Findings	Certainty of Evidence	Summary Statement
Vulvovaginal dryness	Vaginal estrogen vs. placebo 8 or 12 weeks	RCT: 7 (2072*††) ^{84-86, 91, 92, 94, 95} ↑ 2 trials ↔ 1 trial ↑↔ 2 trials ? 2 trials	Seven trials found mixed effects of vaginal estrogen compared with placebo using two measurement tools. Three trials used the FSFI lubrication domain; one trial ⁸⁶ found no significant difference between groups, one trial ⁸⁵ observed a significant benefit of 10 mcg but not 4 mcg vaginal estrogen compared with placebo, while the third trial ⁸⁴ did not provide a statistical comparison of change over time between arms. Two trials ^{91, 95} found a significant benefit of vaginal estrogen versus placebo using a 4-point severity scale, while the other two trials either observed a significant benefit of daily but not twice weekly vaginal estrogen ⁹² compared with placebo or did not provide a statistical comparison of the groups. ⁹⁴	Low ⊕⊕○○ ^{a,b}	Vaginal estrogen may improve vulvovaginal dryness compared with placebo.
	Vaginal estrogen vs. no treatment 36 weeks	RCT: 1 (108) ⁸⁹ ↑ 1 trial	One trial found significantly more patients (%) with symptom resolution from baseline to treatment termination in the vaginal estrogen versus no treatment group.	Low ⊕⊕○○ ^{a,d}	Vaginal estrogen may improve vulvovaginal dryness compared with no treatment.
	Vaginal estrogen ring vs. vaginal estrogen cream 12 or 15 weeks	RCT: 2 (390) ^{83, 88} ↔ 2 trials	Two trials reported equivalence between groups in terms of symptom improvement or resolution. One trial ⁸³ used a 4-point severity scale to measure symptoms, while it was unclear what measurement tool the other trial used. ⁸⁸	Low ⊕⊕○○ ^{a,d}	A vaginal estrogen ring may result in little to no difference in vulvovaginal dryness compared with a vaginal estrogen cream.
Vulvovaginal discomfort/irritation	Vaginal estrogen vs. placebo 12 weeks	RCT: 4 (1777) ^{85, 91, 92, 95} ↑ 1 trial ↔ 1 trial ↑↔ 1 trial ↓↔ 1 trial	Four trials found mixed effects of vaginal estrogen compared with placebo using a 4-point severity scale. One trial ⁹¹ found significantly more vaginal estrogen participants reported symptom improvement than placebo participants, while another ⁹⁵ found no significant difference between arms. The third trial ⁸⁵ found a significant benefit in a 10 mcg vaginal estrogen arm, but not a 4 mcg vaginal estrogen arm, versus placebo. The fourth trial ⁹² assessed both irritation and burning and found mostly non-significant differences between two schedules of vaginal estrogen versus placebo, though also found one significant effect favoring daily placebo over daily estrogen.	Very low ⊕○○○ ^{a,b,c}	The evidence is very uncertain on the effect of vaginal estrogen on vulvovaginal discomfort/irritation compared with placebo.

3. Results, Findings for Key Questions 2 and 3, Estrogen Hormonal Interventions

Outcome	Intervention Vs. Comparator Followup	Study Design: No. Trials (N) Direction of Effect	Findings	Certainty of Evidence	Summary Statement
	Vaginal estrogen vs. no treatment 36 weeks	RCT: 1 (108) ⁸⁹ ↔ 1 trial	One trial found more patients (%) with symptom resolution from baseline to treatment termination in the vaginal estrogen versus no treatment group, though the difference was not statistically significant.	Low ⊕⊕○○ ^{a,d}	Vaginal estrogen may result in little to no difference in vulvovaginal discomfort/irritation compared with no treatment.
	Vaginal estrogen ring vs. vaginal estrogen cream 15 weeks	RCT: 1 (196) ⁸⁸ ↔ 1 trial	One trial reported equivalence in improvement in vaginal burning between vaginal estrogen ring and estrogen cream groups but did not report the data.	Very low ⊕○○○ ^{a,c,d}	The evidence is very uncertain on the effect of a vaginal estrogen ring on vulvovaginal discomfort/irritation compared with a vaginal estrogen cream.
Dysuria	Vaginal estrogen vs. placebo 12 weeks	RCT: 1 (488) ⁹⁵ ↔ 1 trial	One trial stated that improvements in dysuria severity were similar between groups at all time points but did not report the data.	Low ⊕⊕○○ ^{a,c}	Vaginal estrogen may result in little to no difference in dysuria compared with placebo.
	Vaginal estrogen vs. no treatment 36 weeks	RCT: 1 (108) ⁸⁹ ↔ 1 trial	One trial found more patients (%) with symptom resolution from baseline to treatment termination in the vaginal estrogen versus no treatment group, though the difference was not statistically significant.	Low ⊕⊕○○ ^{a,d}	Vaginal estrogen may result in little to no difference in dysuria compared with no treatment.
	Vaginal estrogen ring vs. vaginal estrogen cream 12 weeks	RCT: 1 (194) ⁸³ ↔ 1 trial	One trial found no statistically significant differences for resolution or improvement rate between groups based on a 4-point severity scale.	Low ⊕⊕○○ ^{a,d}	A vaginal estrogen ring may result in little to no difference in dysuria compared with a vaginal estrogen cream.
Dyspareunia	Vaginal estrogen vs. placebo 8 or 12 weeks	RCT: 7 (2072†) ^{84, 86, 91, 92, 94, 95, 116} ↑ 2 trials ↔ 2 trials ↑↔ 1 trial ? 2 trials	Seven trials found mixed effects of vaginal estrogen compared with placebo using two measurement tools. Three trials used the FSFI pain domain; one trial ⁸⁶ found no significant difference between groups, one trial ⁸⁵ observed a significant benefit of 10 mcg but not 4 mcg vaginal estrogen compared with placebo, while the third trial ⁸⁴ did not provide a statistical comparison of change over time between arms. The other four trials used a 4-point severity scale; two trials ^{91, 92} reported significant improvement in the vaginal estrogen arm(s) compared with placebo, one trial ⁹⁵ found no significant difference between groups, and one trial ⁹⁴ did not provide a statistical comparison of the groups.	Low ⊕⊕○○ ^{a,b}	Vaginal estrogen may result in little to no difference in dyspareunia compared with placebo.

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Outcome	Intervention Vs. Comparator Followup	Study Design: No. Trials (N) Direction of Effect	Findings	Certainty of Evidence	Summary Statement
	Vaginal estrogen vs. no treatment 36 weeks	RCT: 1 (108) ⁸⁹ ↑ 1 trial	One trial found significantly more patients (%) with symptom resolution from baseline to treatment termination in the vaginal estrogen versus no treatment group.	Low ⊕⊕○○ ^{a,d}	Vaginal estrogen may improve dyspareunia compared with no treatment.
	Vaginal estrogen ring vs. vaginal estrogen cream 12 or 15 weeks	RCT: 2 (390) ^{83, 88} ↔ 2 trials	Two trials reported equivalence between groups in terms of symptom improvement or resolution. One trial ⁸³ used a 4-point severity scale to measure symptoms, while it was unclear what measurement tool the other trial used. ⁸⁸	Low ⊕⊕○○ ^{a,d}	A vaginal estrogen ring may result in little to no difference in dyspareunia compared with a vaginal estrogen cream.
Change in MBS	Vaginal estrogen vs. placebo 8 or 12 weeks	RCT: 4 (1003*) ^{86, 91, 92, 96} ↑ 2 trials ↔ 1 trial ? 1 trial	Four trials found mixed effects of vaginal estrogen compared with placebo using a 4-point severity scale. Two trials found a statistically significant improvement in MBS in the vaginal estrogen arm(s) compared with placebo, ^{91, 92} while another trial ⁸⁶ found no significant difference between groups. The fourth trial ⁹⁶ observed improvement in both groups but did not provide a statistical comparison of change over time between groups.	Low ⊕⊕○○ ^{a,c}	Vaginal estrogen may improve MBS compared with placebo.
QoL	Vaginal estrogen vs. placebo 12 weeks	RCT: 1 (195*) ⁸⁶ ↔ 1 trial	Authors reported no significant differences in all the DIVA domain scores for both the vaginal estrogen and placebo arm, with no significant differences between treatment arms.	Moderate ⊕⊕⊕○ ^d	Vaginal estrogen probably results in little to no difference in QoL compared with placebo.
Satisfaction with treatment	Vaginal estrogen vs. placebo 12 weeks	RCT: 1 (195*) ⁸⁶ ↑ 1 trial	Authors reported a statistically significant difference between groups in the proportion of participants reporting “meaningful benefit” from treatment.	Low ⊕⊕○○ ^{a,d}	Vaginal estrogen may result in higher treatment satisfaction compared with placebo.
	Vaginal estrogen ring vs. vaginal estrogen cream 12 or 15 weeks	RCT: 2 (390) ^{83, 88} ↑ 2 trials	Two trials reported significantly higher treatment satisfaction (either “good or excellent” in one trial ⁸³ or “very easy to use” and “excellent comfort” in the other trial ⁸⁸) in the vaginal estrogen ring group compared with the vaginal estrogen cream group.	Moderate ⊕⊕⊕○ ^a	A vaginal estrogen ring probably results in higher treatment satisfaction compared with a vaginal estrogen cream.
Adverse effects (any AE)	Vaginal estrogen vs. placebo 12 weeks	RCT: 5 (2070*) ^{85, 86, 91, 92, 95} ↔ 1 trial ? 4 trials	Authors found similar incidence of any AE/TEAE in the vaginal estrogen and placebo groups. Only one trial ⁸⁵ formally compared the incidence rates between groups, finding no clinically significant difference. The other four trials did not report on statistical or clinical significance.	Low ⊕⊕○○ ^{a,c}	Vaginal estrogen may result in little to no difference in adverse effects compared with placebo.

Abbreviations: AE=adverse effect; COMMA=Core Outcomes in Menopause; DIVA=Day-to-Day Impact of Vaginal Aging; FSFI=Female Sexual Function Index; MBS=most bothersome symptom; N/A=not applicable; OIS=optimal information size; QoL=quality of life; RCT=randomized controlled trial; RoB=risk of bias; TEAE=treatment-emergent adverse effect

*Total N includes only estrogen and placebo arms from Mitchell (2018).⁸⁶ See Section 3.3.4 for moisturizer arm results.

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[†]Total N includes only estrogen and placebo arms from Fernandes (2014).⁸⁴ See Sections 3.3.2 and 3.3.4 for testosterone and lubricant arm results, respectively.

[‡]Total N includes only estrogen and placebo arms from Lima (2013).⁹⁴ See Section 3.6 for more information on the isoflavone arm.

Direction of effect

↑: Intervention group had a statistically significantly better outcome than comparison group (e.g., improved symptoms, higher treatment satisfaction)

↓: Intervention group had a statistically significantly worse outcome than comparison group (e.g., worsened symptoms, lower treatment satisfaction)

↔: No statistically significant difference between groups

↑↔ or ↓↔: Mixed statistical significance of intervention group effect versus comparison group effect within multi-arm trials (e.g., one intervention dose/schedule had a statistically significantly better outcome than comparison group but there was no statistically significant difference between another intervention dose/schedule and comparison group)

?: No statistical comparison of change in time between groups provided

Certainty of evidence (COE)

Moderate (⊕⊕⊕○): We are moderately confident in the effect estimate; the true effect is likely to be close to the effect estimate, but there is a possibility that it is substantially different.

Low (⊕⊕○○): Our confidence in the effect estimate is limited; the true effect may be substantially different from the effect estimate.

Very low (⊕○○○): We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

Explanations

^aDowngraded one level for study limitations (one or more trials assessed as “some concerns” RoB)

^bDowngraded one level for inconsistency (effect varied across trials)

^cDowngraded one level for study limitations (one or more trials did not provide adequate statistical reporting)

^dDowngraded one level for imprecision (total sample size less than OIS of 400)

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3.3.1.3.1 Vulvovaginal Dryness

3.3.1.3.1.1 Vaginal Estrogen Vs. Placebo (7 Trials; Total N=2072)

Seven trials^{84-86, 91, 92, 94, 95} (9 publications^{84-86, 91, 92, 94, 95, 116, 117}) (N=2072) evaluated the effect of vaginal estrogen versus placebo on vaginal dryness at 8 or 12 weeks. Three trials used the Female Sexual Function Index (FSFI) lubrication domain and found mixed effects: one trial⁸⁶ found no significant difference between groups, one trial¹¹⁶ observed a significant benefit of 10 mcg but not 4 mcg vaginal estrogen compared with placebo, while the third trial⁸⁴ observed improvement in both groups but did not provide a statistical comparison of change over time. Six trials evaluated vulvovaginal dryness using a 4-point severity scale (two of which also used the FSFI lubrication domain). Three trials^{91, 95, 117} found statistically significant improvement in the vaginal estrogen arm(s) compared with placebo, one trial⁸⁶ found no significant difference between groups, while another trial⁹² observed a significant benefit of daily, but not twice weekly, vaginal estrogen versus placebo. A sixth trial⁹⁴ did not provide a statistical comparison of change over time in 4-point severity scores. Participants in placebo groups improved in all seven trials.

Constantine (2017)⁸⁵ (N=561) was a multi-arm trial of vaginal estradiol softgel doses (4 mcg, 10 mcg) compared with vaginal placebo softgel, which enrolled postmenopausal women with moderate to severe dyspareunia as their MBS and baseline vaginal atrophy on vaginal pH and cytology. On the FSFI lubrication domain (0 (worst) to 6 (best)), a secondary publication¹¹⁶ reported a significant ($P<0.05$) improvement for the 10 mcg dose, but not the 4 mcg dose, compared with placebo (4 mcg estradiol 1.8 and 10 mcg estradiol 2.2 vs. placebo 1.6). On a 4-point severity scale (0=none to 3=severe), they reported a significant ($P<0.05$) improvement for both vaginal estradiol softgel arms compared with placebo (4 mcg estradiol -1.3 and 10 mcg estradiol -1.5 vs. placebo -1.0). Simon (2019),¹¹⁷ a post-hoc analysis of Constantine (2017),⁸⁵ also reported a significant ($P<0.05$) difference between arms in the percentage of women with ≥ 2 levels of improvement in their 4-point severity score (4 mcg estradiol 41.3% and 10 mcg estradiol 51.1% vs. placebo 30.9%).

Mitchell (2018)⁸⁶ (N=195) enrolled women with at least one moderate to severe GSM symptom without verifying vaginal atrophy at enrollment, and compared vaginal estradiol 10 mcg tablet with vaginal placebo tablet; both trial arms also used vaginal hydroxyethylcellulose (placebo) gel. Using the FSFI lubrication domain, they found a non-significant change from baseline for vaginal estrogen tablet versus vaginal placebo tablet (estradiol 1.4 vs. placebo 1.2). Authors also reported vaginal dryness on a 4-point severity scale only among participants with a moderate to severe dryness score at baseline (N=160 with week 12 data) and found a non-significant ($P>0.05$) change from baseline to 12 weeks in vaginal estradiol tablet compared with vaginal placebo tablet (estradiol -1.4 vs. placebo -1.4).

Fernandes (2014)⁸⁴ (N=40) enrolled patients from a menopause clinic with any severity of GSM symptoms without verifying vaginal atrophy at enrollment, and compared vaginal conjugated estrogen cream to vaginal glycerin and hydroxyethylcellulose (placebo) gel. They used the FSFI lubrication domain (0 (worst) to 6 (best)) and found a statistically significant change from baseline to 12 weeks for conjugated estrogens cream (CEC) and for placebo (CEC 1.5 to 2.8 and placebo 1.9 to 2.9); they did not provide a statistical test comparing the change over time between treatment arms.

Archer (2018)⁹⁵ (N=488) compared vaginal estradiol cream to placebo vaginal cream among postmenopausal women with moderate to severe vaginal dryness as their MBS and baseline

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vaginal atrophy on vaginal pH and cytology. They used a 4-point severity scale and reported a significant ($P<0.05$) improvement in the vaginal estradiol cream arm compared with placebo (estradiol -1.4 vs. placebo: -1.2).

Freedman (2009)⁹¹ (N=305) enrolled participants with moderate-to-severe vulvovaginal atrophy (VVA) and evaluated CEC versus a placebo cream. Authors reported the proportion of participants whose symptoms improved from baseline to 12 weeks, as well as the proportion of participants who experienced symptom resolution. Compared with placebo, a significantly greater ($P<0.05$) proportion of participants in the estrogen arm experienced symptom improvement (estrogen 78.9% vs placebo 58.4%) and symptom resolution (estrogen 33.3% vs placebo 16%).

Bachmann (2009)⁹² (N=423) enrolled participants with moderate-to-severe VVA and evaluated vaginal conjugated estrogens cream versus vaginal placebo cream using two dosing regimens. Participants tracked their symptoms in a daily diary with a 4-point severity scale from baseline to 12 weeks. They reported a significantly ($P<0.05$) greater mean reduction in dryness severity after 12 weeks for estrogen compared with placebo using 21/7 dosing (estrogen -1.1 vs placebo -0.7) but not 2x/week dosing (estrogen -1.1 vs placebo -0.8).

Lima (2013)⁹⁴ (N=90) evaluated conjugated estrogens cream, placebo, and isoflavone (see Section 3.6) and reported the prevalence of dryness at each level on a 4-point severity scale from baseline to 12 weeks. Though improvements for the conjugated estrogens cream group appear to exceed those in the placebo group, authors did not provide any statistical test of significance.

We evaluated but did not include results from an eighth trial, Tanmahasamut (2020),⁹⁶ (N=80) which enrolled postmenopausal women with VVA and compared vaginal estradiol gel with placebo gel. Authors measured mean change from baseline to 8 weeks in both arms using the FSFI lubrication domain. Reported scores exceeded the standard ranges for this scale, so we did not include these results in the Grading of Recommendations Assessment, Development and Evaluation (GRADE) assessment.

Due to study limitations and inconsistency, we conclude that vaginal estrogen may improve vulvovaginal dryness compared with placebo (low COE).

3.3.1.3.1.2 Vaginal Estrogen Vs. No Treatment (1 Trial; Total N=108)

One trial⁸⁹ evaluated the effect of vaginal estrogen versus no treatment on vaginal dryness at 36 weeks. Eriksen (1999) (N=108) reported a significant ($P<0.05$) difference between the percentage of participants with mild, moderate, or severe vaginal dryness at baseline whose symptoms were resolved by the end of the trial in the vaginal ring (81%) and no treatment (17%) groups. Due to study limitations and imprecision, we conclude that vaginal estrogen may improve vaginal dryness compared with no treatment (low COE).

3.3.1.3.1.3 Vaginal Estrogen Delivery Method Comparison (2 Trials; Total N=390)

Two trials^{83, 88} (N=390) evaluated the effect of a vaginal estradiol ring versus vaginal conjugated estrogens cream on vaginal dryness at 12 or 15 weeks. Exact values were not reported for Ayton (1996)⁸³ (N=194) or Nachtigall (1995)⁸⁸ (N=196), but the authors state that equivalence was demonstrated between the two treatments in the responder rate at followup. Due to study limitations and imprecision, we conclude that a vaginal estradiol ring may result in little to no difference in vulvovaginal dryness compared with a vaginal conjugated estrogens cream (low COE).

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3.3.1.3.2 Vulvovaginal Discomfort/Irritation

3.3.1.3.2.1 Vaginal Estrogen Vs. Placebo (4 Trials; Total N=1777)

Four trials^{85, 91, 92, 95} (N=1777) evaluated the effect of vaginal estrogen versus placebo on vulvovaginal discomfort/irritation using a 4-point severity scale (0=none to 3=severe) at 12 weeks. Results were mixed. All trials verified vaginal atrophy at enrollment using vaginal pH and cytology. Freedman (2009)⁹¹ (N=305) observed a significant ($P<0.05$) benefit of conjugated estrogens cream versus vaginal placebo cream based on the proportion of participants whose symptoms improved from baseline to 12 weeks (CEC 88.3% vs. placebo 71.7%). Constantine (2017)⁸⁵ (N=561) enrolled women with moderate to severe dyspareunia as their MBS and found a significant improvement ($P<0.05$) in vulvar and/or vaginal itching or irritation for the 10 mcg vaginal estradiol softgel arm, but not the 4 mcg estradiol arm compared with placebo (4 mcg estradiol -0.8 and 10 mcg estradiol -0.8 vs. placebo -0.6; only rounded values provided). Archer (2018)⁹⁵ (N=488) enrolled women with moderate to severe vaginal dryness as their MBS. They only presented results graphically (showing an improvement of more than -0.5 in both arms) without data but stated that improvements in symptom severity were similar between estradiol cream and placebo arms. Bachmann (2009)⁹² (N=423) evaluated the effect of two schedules (21 days on/7 days off or 2x/week) of vaginal conjugated estrogens cream versus vaginal placebo cream on vaginal itching and burning on a 4-point severity scale. All statistical comparisons of change over time between arms were non-significant ($P>0.05$) (Itching: 2x/wk CEC -0.3 vs. placebo -0.2; Burning: 21/7 CEC -0.5 vs. placebo -0.4 and 2x/wk CEC -0.4 vs. placebo -0.2), except for 21/7 vaginal conjugated estrogens cream versus placebo on vaginal itching (21/7 CEC -0.2 vs. 21/7 placebo -0.5, $P<0.05$). In this case, the mean score of the placebo arm significantly improved compared with the vaginal estrogen arm.

Due to study limitations and inconsistency, we conclude that the evidence is very uncertain on the effect of vaginal estrogen on vulvovaginal discomfort/irritation compared with placebo (very low COE).

3.3.1.3.2.2 Vaginal Estrogen Vs. No Treatment (1 Trial; Total N=108)

One trial⁸⁹ evaluated the effect of vaginal estrogen versus no treatment on vulvovaginal discomfort/irritation at 36 weeks. Eriksen (1999) (N=108) reported a non-significant difference between the percentage of participants with mild, moderate or severe vulvar itching at baseline whose symptoms were resolved by the end of the study: 80 percent in the vaginal ring group and 53 percent in the no treatment group. Due to study limitations and imprecision, we conclude that vaginal estrogen may result in little to no difference in vulvovaginal discomfort/irritation compared with no treatment (low COE).

3.3.1.3.2.3 Vaginal Estrogen Delivery Method Comparison (1 Trial; Total N=196)

One trial⁸⁸ evaluated the effect of a vaginal estradiol ring versus a vaginal conjugated estrogens cream on vulvovaginal discomfort/irritation at 15 weeks. We were unable to extract data from Nachtigall (1995) (N=196) as the data were presented graphically without accompanying text. While exact values were not reported, authors stated that the equivalence criteria for symptom improvement was satisfied for vaginal burning. Due to study limitations and imprecision, we conclude that the evidence is very uncertain on the effect of a vaginal estradiol ring on vulvovaginal discomfort/irritation compared with a vaginal conjugated estrogens cream (very low COE).

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3.3.1.3.3 Dysuria

3.3.1.3.3.1 Vaginal Estrogen Vs. Placebo (1 Trial; Total N=488)

One trial⁹⁵ evaluated the effect of vaginal estrogen versus placebo on dysuria at 12 weeks on a 4-point severity scale (0=none to 3=severe). Archer (2018) (N=488) reported low ratings of baseline dysuria in the vaginal estradiol group (0.4) and the placebo group (0.3). They did not provide followup data but stated that improvements in dysuria severity were similar between the estradiol cream and placebo groups at all time points. Due to study limitations, we conclude that vaginal estrogen may result in little to no difference in dysuria compared with placebo (low COE).

3.3.1.3.3.2 Vaginal Estrogen Vs. No Treatment (1 Trial; Total N=108)

One trial⁸⁹ evaluated the effect of vaginal estrogen versus no treatment on dysuria at 36 weeks. Eriksen (1999) (N=108) reported a non-significant difference between the percentage of participants with mild, moderate or severe dysuria at baseline whose symptoms were resolved by the end of the study: 50 percent in the vaginal ring group and 44 percent in the no treatment group. Due to study limitations and imprecision, we conclude that vaginal estrogen may result in little to no difference in dysuria compared with no treatment (low COE).

3.3.1.3.3.3 Vaginal Estrogen Delivery Method Comparison (1 Trial; Total N=194)

One trial⁸³ evaluated the effect of a vaginal estrogen ring versus a vaginal estrogen cream on dysuria at 12 weeks, using a 4-point severity scale (0=none to 3=severe). Ayton (1996) (N=194) reported low prevalence of baseline dysuria in the vaginal estrogen ring group (20 patients) and the vaginal estrogen cream group (13 patients). Data were presented graphically without accompanying numbers, but authors stated that no statistically significant differences were demonstrated between the two treatments in the response or cure rates at follow up. Due to study limitations and imprecision, we conclude that vaginal estrogen rings may result in little to no difference in dysuria compared with vaginal estrogen cream (low COE).

3.3.1.3.4 Dyspareunia

3.3.1.3.4.1 Vaginal Estrogen Vs. Placebo (7 Trials; Total N=2072)

Seven trials^{84-86, 91, 92, 94, 95} (12 publications^{84-86, 91, 92, 94, 95, 116-120}) (N=2072) evaluated the effect of vaginal estrogen versus placebo on dyspareunia at 12 weeks. Three trials used the FSFI pain domain and found mixed effects: one trial⁸⁶ found no significant difference between groups, one trial¹¹⁶ observed a significant benefit of 10 mcg but not 4 mcg vaginal estradiol compared with placebo, while the third trial⁸⁴ observed improvement in both groups but did not provide a statistical comparison of change over time. Six trials evaluated dyspareunia using a 4-point severity scale (two of which also used the FSFI pain domain). Three trials^{85, 91, 92} found statistically significant improvement in the vaginal estrogen arm(s) compared with placebo, while two trials^{86, 95} found no significant difference between groups. A sixth trial⁹⁴ did not provide a statistical comparison of change over time in 4-point severity scores.

Mitchell (2018)⁸⁶ (N=195) compared vaginal estradiol 10 mcg tablet with vaginal placebo tablet; both trial arms also used vaginal hydroxyethylcellulose (placebo) gel. Using the FSFI pain domain (0 (worst) to 6 (best)), they found no significant difference in change from baseline to 12 weeks for vaginal estradiol tablet plus placebo gel compared with placebo tablet plus placebo gel (estradiol tablet 1.4 vs. placebo tablet 0.9). They also found no significant difference in

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improvement of pain with penetration using a 4-point severity scale (estradiol tablet -1.5 vs. placebo tablet -1.5). A secondary publication¹¹⁸ reported mean pain severity scores with sexual activity at 12 weeks, which was similar between arms, but did not provide a statistical comparison of change over time.

Constantine (2017)⁸⁵ (N=561) was a multi-arm trial of vaginal estradiol softgel (4 mcg or 10 mcg) compared with vaginal placebo softgel, which enrolled postmenopausal women with moderate to severe dyspareunia as their MBS. On the FSFI pain domain (0 (worst) to 6 (best)), a secondary publication¹¹⁶ reported a significant ($P<0.05$) improvement for the 10 mcg dose, but not the 4 mcg dose, compared with placebo (4 mcg estradiol 2.2 and 10 mcg estradiol 2.6 vs. placebo 1.9). The main trial publication reported dyspareunia on a 4-point severity scale and found a statistically significant ($P<0.05$) improvement in both vaginal estradiol softgel arms compared with placebo (4 mcg -1.52 and 10 mcg -1.69 estradiol vs. placebo -1.28). Three additional secondary publications from this trial reported a variety of results, including results stratified by baseline characteristics,¹²⁰ the percentage of participants whose symptoms improved by ≥ 2 severity categories, which was significantly different between groups (4 mcg 41.4% and 10 mcg 47.3% vs. placebo 35.8%),¹¹⁷ or baseline and 12-week values for the estradiol and placebo arms without change from baseline or a statistical comparison.¹¹⁹

Fernandes (2014)⁸⁴ (N=40) compared vaginal conjugated estrogens cream to vaginal glycerin and hydroxyethylcellulose (placebo) gel. They used the FSFI pain domain (0 (worst) to 6 (best)) and reported a significant ($P<0.05$) change from baseline to 12 weeks for conjugated estrogens cream but not for placebo (CEC 1.3 to 3.0 and placebo 2.1 to 3.1); they did not provide a statistical test comparing the change over time between treatment arms.

Bachmann (2009)⁹² (N=423) compared vaginal estrogen cream to placebo vaginal cream using two dosing regimens. Using a 4-point severity scale, they reported a significantly ($P<0.05$) greater mean reduction in dyspareunia severity after 12 weeks for estrogen compared with placebo using both 21/7 dosing (estrogen -1.4 vs placebo -0.4) and 2x/week dosing (estrogen -1.4 vs placebo -0.7).

Freedman (2009)⁹¹ (N=305) compared vaginal estrogen to placebo vaginal cream in postmenopausal women with moderate to severe VVA. Compared with placebo, a significantly greater ($P<0.05$) proportion of participants in the estrogen arm experienced dyspareunia improvement (estrogen 70% vs placebo 40%) and symptom resolution (estrogen 33.8% vs placebo 8.8%).

Finally, Archer (2018)⁹⁵ (N=488) compared vaginal estradiol cream to placebo vaginal cream among postmenopausal women with moderate to severe vaginal dryness as their MBS. Using a 4-point severity scale, they graphically reported no significant difference in improvement in the vaginal estradiol cream arm compared with placebo from baseline to 12 weeks (data not provided).

Due to study limitations and inconsistency, we conclude that vaginal estrogen may result in little to no difference in dyspareunia compared with placebo (low COE).

3.3.1.3.4.2 Vaginal Estrogen Vs. No Treatment (1 Trial; Total N=108)

One trial⁸⁹ evaluated the effect of vaginal estrogen versus no treatment on dyspareunia at 36 weeks. Eriksen (1999) (N=108) reported a significant ($P<0.05$) difference between the percentage of participants with mild, moderate or severe dyspareunia at baseline who were symptom-free by the end of the study in the vaginal ring (71%) and no treatment (10%) groups. Due to study limitations and imprecision, we conclude that vaginal estrogen may improve dyspareunia compared with no treatment (low COE).

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3.3.1.3.4.3 Vaginal Estrogen Delivery Method Comparison (1 Trial; Total N=390)

Two trials^{83, 88} (N=390) evaluated the effect of a vaginal estradiol ring versus a conjugated estrogens cream on dyspareunia at 12-15 weeks. We were unable to extract data on dyspareunia from either trial as the data were presented graphically without accompanying text. While exact values were not reported, Ayton (1996)⁸³ (N=194) reported that responder rates (i.e., proportion of participants who improved at least one point on the 0-3 severity scale) were equivalent at 12-week followup in the two arms. Similarly, Nachtigall (1995)⁸⁸ (N=196) reported that symptom improvement was equivalent in both arms at 15-week followup. Due to study limitations and imprecision, we conclude that a vaginal estradiol ring may result in little to no difference in dyspareunia compared with a vaginal conjugated estrogens cream (low COE).

3.3.1.3.5 Change in MBS

3.3.1.3.5.1 Vaginal Estrogen Vs. Placebo (4 Trials; Total N=1003)

Four trials^{86, 91, 92, 96} (N=1003) evaluated the effect of vaginal estrogen versus placebo on change in MBS at 12 weeks and reported mixed results. Two trials^{91, 92} reported statistically significant improvement in the vaginal estrogen arm(s) compared with the placebo arm, one trial⁹⁶ reported an improvement in both the vaginal estrogen arm and the placebo arm, but did not provide a statistical comparison, and a fourth trial⁸⁶ did not find any significant difference in the change from baseline to 12 weeks between the vaginal estrogen and placebo arms. All trials measured MBS with a 4-point severity scale (0=none to 3=severe) and included vaginal dryness and dyspareunia as symptoms; however, inclusion of other vulvovaginal symptoms for MBS assessment was variable. Two trials required vaginal pH ≥ 5 and $\leq 5\%$ superficial cells on vaginal maturation index for inclusion.^{91, 92}

Bachmann (2009)⁹² (N=423) enrolled postmenopausal women with at least one moderate to severe GSM symptom, verified atrophy with vaginal pH and cytology, and offered dryness, itching, burning, and dyspareunia as MBS options. They compared two dosing strategies of conjugated estrogens cream with placebo and reported a statistically significant ($P < 0.05$) mean change from baseline in both conjugated estrogens cream arms (21 days on/7 days off -1.3; 2x/week -1.4) compared with the placebo arms (21/7 -0.8, 2x/week -0.7). Freedman (2009)⁹¹ (N=305) enrolled postmenopausal women with at least one moderate to severe GSM symptom, verified atrophy with vaginal pH and cytology, and offered dryness, soreness, irritation, pain with intercourse, and bleeding after intercourse as their MBS options and also reported a statistically significant ($P < 0.05$) mean difference in the vaginal estrogen arm (-1.71) compared with placebo arm (-1.11).

Tanmahasamut (2020)⁹⁶ (N=80) enrolled postmenopausal women with any level of GSM symptoms, without verification of atrophy, and included dryness, soreness, irritation, discharge, and dyspareunia as their MBS options and reported a statistically significant mean change in both the vaginal estrogen arm (2.4 to 0.4) and the placebo arm (2.4 to 0.8), but did not provide a statistical comparison of change over time between groups. Finally, Mitchell (2018)⁸⁶ (N=195) compared vaginal estradiol tablet plus placebo gel with vaginal placebo tablet plus placebo gel among women with at least one moderate to severe GSM symptom; they offered itching, pain, dryness, irritation, or dyspareunia as their MBS options and reported no significant ($P > 0.05$) difference in the improvement in vaginal estrogen (-1.4) and placebo (-1.3) arms.

Due to study limitations, we conclude that vaginal estrogen may improve MBS compared with placebo (low COE).

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3.3.1.3.6 QoL (i.e., Distress, Bother, or Interference of Genitourinary Symptoms)

3.3.1.3.6.1 Vaginal Estrogen Vs. Placebo (1 Trial; N=195)

Two publications^{121, 122} from the Menopause Strategies: Finding Lasting Answers for Symptoms and Health (MsFLASH) trial⁸⁶ (N=195) evaluated the effect of vaginal estrogen versus placebo on quality of life at 12 weeks. Diem (2018)¹²¹ used the Menopause Specific Quality of Life (MENQOL) Questionnaire (1 (best) to 8 (worst)) and found a statistically significant ($P<0.05$) mean change in the vaginal estradiol arm (-1.0) versus the placebo arm (-0.7). Gibson (2020)¹²² reported the followup values and between-group differences in 4 Day-to-Day Impact of Vaginal Aging (DIVA) Questionnaire domain scores: none were statistically significant. We based our GRADE assessment on the DIVA results because DIVA is more specific to GSM symptoms. Due to imprecision, we conclude that vaginal estrogen probably results in little to no difference in QoL compared with placebo (moderate COE).

3.3.1.3.7 Satisfaction With Treatment

3.3.1.3.7.1 Vaginal Estrogen Vs. Placebo (1 Trial; N=195)

One trial⁸⁶ evaluated the effect of vaginal estrogen versus placebo on treatment satisfaction at 12 weeks using two measures with mixed results. Mitchell (2018) (N=195) used a study-specific, 11-point Likert scale (0=not satisfied to 10=completely satisfied) and reported that mean treatment satisfaction was similar between the two groups (8.6 versus 8.1); they did not provide a statistical comparison. They also reported the percentage of participants who reported “meaningful benefit” and found a statistically significant ($P<0.05$) higher proportion in the vaginal estrogen arm (80%) compared with the placebo arm (65%). We downgraded for study limitations and imprecision and conclude that vaginal estrogen may result in higher treatment satisfaction compared with placebo (low COE).

3.3.1.3.7.2 Vaginal Estrogen Delivery Method Comparisons (2 Trials; Total N=390)

Two trials^{83, 88} (N=390) evaluated the effect of a vaginal estrogen ring versus a vaginal estrogen cream on treatment satisfaction at 12 or 15 weeks. Both showed higher satisfaction with vaginal estrogen ring. Ayton (1996)⁸³ (N=194) used a study-specific grading of the estrogen delivery methods as either “excellent” or “good” and reported statistically significant ($P<0.05$) greater treatment satisfaction in the estrogen ring group (84%) compared with the estrogen cream (43%) group. Similarly, Nachtigall (1995)⁸⁸ (N=196) used a study-specific questionnaire to ask participants about the comfort and ease of use of the estrogen delivery methods. They reported a statistically significant ($P<0.05$) difference between the groups in both the ease of use (ring 85% vs. cream 35%) and the percentage of participants who rated the product’s comfort as excellent (ring 67% vs. cream 18%). Despite study limitations, we conclude that the vaginal estrogen ring probably results in greater treatment satisfaction compared with vaginal estrogen cream (moderate COE).

3.3.1.3.8 Adverse Effects

Fifteen trials evaluated the potential harms of vaginal estrogen in comparison with placebo (k=9),^{85, 86, 91, 92, 94-96, 98, 123} no treatment (k=1),⁸⁹ or oral oxybutynin (k=1);⁹³ in combination with tolterodine (k=1);⁹⁰ or in different doses⁸⁷ or routes of delivery⁸⁸ (k=3). All the trials that used a

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placebo comparator or compared different delivery methods had a follow up period of 12 weeks, except for one placebo-controlled trial⁹⁶ that assessed outcomes at 8 weeks. The trial that compared vaginal estrogen with no treatment⁸⁹ evaluated harms at 36 weeks. The two trials that used overactive bladder pharmaceuticals as either a comparator⁹³ or in combination with vaginal estrogen⁹⁰ assessed outcomes at 12 weeks. We captured when a trial reported any AE/treatment-emergent adverse effect (TEAE) (k=5), serious adverse effects (SAEs; k=6), discontinuation due to AEs (k=9), or clinically relevant, specific AEs (k=8). Two trials evaluated safety only to state that no AEs were reported⁹⁶ or observed⁹⁰ in either trial arm. Specific counts (when available) and detailed AE reporting can be found in Appendix Table C.13.

3.3.1.3.8.1 Any AE/TEAE

3.3.1.3.8.1.1 Vaginal Estrogen Vs. Placebo (5 Trials; Total N=2070)

We assessed the 5 trials^{84, 85, 92, 95} (N=2070) that reported proportions of participants who experienced any AE/TEAE using GRADE and downgraded two levels for study limitations (RoB and inadequate statistical reporting). The proportion of vaginal estrogen participants with AEs ranged from 46.9 percent to 71.4 percent across the five trials, while the proportion of placebo participants with AEs ranged from 45.3 percent to 69.1 percent. Only one trial⁸⁵ evaluated clinical significance and found no clinically significant difference between groups. The other trials described incidence rates of any AE/TEAE between groups as “comparable,”⁹⁵ “similar,”^{91, 92} or “not different.”⁸⁶ We conclude that vaginal estrogen may result in little to no difference in AE rates compared with placebo (low COE).

3.3.1.3.8.2 Serious AEs

3.3.1.3.8.2.1 Vaginal Estrogen Vs. Placebo (4 Trials; Total N=1875)

Four trials^{85, 91, 92, 95} (N=1875) of vaginal estrogen versus placebo reported SAEs, none of which were considered related to treatment. In Archer (2018), participants in both groups experienced SAEs (2 [0.7%] in both the estradiol cream and placebo arms). During the study period for Constantine (2017), participants in the 10-mcg vaginal estradiol capsule and placebo arms reported an SAE, but not the 4-mcg estradiol arm (4 mcg 0 and 10 mcg 4 [sinus node dysfunction, ankle fracture, arthralgia, and malignant melanoma] vs. placebo 1 [cervical myelopathy]). One participant in each arm of Freedman (2009) reported an SAE (CEC 1 [ventricular tachycardia] vs placebo 1 [Hodgkin disease]). Bachmann (2009) reported that a total of five (1.2%) participants experienced SAEs but did not provide a breakdown by study arms.

3.3.1.3.8.2.2 Vaginal Estrogen Vs. No Treatment (1 Trial; Total N=108).

One trial⁸⁹ of vaginal estradiol ring versus no treatment reported SAEs. In Eriksen (1999)⁸⁹ (N=108), participants in both groups experienced an SAE (estradiol 3 [upper respiratory tract infection, abdominal pain, malignant melanoma] vs. placebo 1 [angina pectoris]). The authors state that a causal relationship between the events and vaginal ring treatment is unlikely.

3.3.1.3.8.2.3 Vaginal Estrogen Delivery Method Comparison (1 Trial; Total N=196).

One trial⁸⁸ of vaginal estradiol ring versus vaginal conjugated estrogens cream reported SAEs, none of which were considered related to treatment. In Nachtigall (1995)⁸⁸ (N=196), one participant in each group reported an SAE (ring 1 [viral meningitis] vs. CEC 1 [fractured ankle]). They also reported one breast cancer at an unspecified point after the 12-week treatment period

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but noted “she had had a suspicious mammogram at baseline” (though a “normal” mammogram within 6 months of trial initiation was required for trial participation).

3.3.1.3.8.3 Discontinuation Due to AEs

3.3.1.3.8.3.1 Vaginal Estrogen Vs. Placebo (6 Trials; Total N=1975)

Six trials^{85, 91, 92, 94, 95, 123} (N=1975) of vaginal estrogen versus placebo reported discontinuation due to AEs. Though two trials^{94, 123} provided specific reasons for trial discontinuation, many^{85, 91, 92, 95} only used a participant disposition figure or results table to report participants who discontinued the treatment and/or trial due to AEs. Specific AEs leading to trial discontinuation in the vaginal estrogen arms included allergic vaginitis (n=1),¹²³ mastalgia (n=5),⁹⁴ and pelvic pain (n=2).⁹⁴ The proportion of vaginal estrogen participants who discontinued ranged from 0.5 to 23 percent, while 0 to 7.4 percent of placebo participants discontinued across the six trials.

3.3.1.3.8.3.2 Vaginal Estrogen Vs. No Treatment (1 Trial; Total N=108)

One trial⁸⁹ of vaginal estradiol ring versus no treatment reported discontinuation due to AEs. In Eriksen (1999) (N=108),⁸⁹ five participants in the estradiol ring group discontinued because of local discomfort (n=3), hot flushes (n=1), or more frequent urinary tract infections (UTIs) (n=1). No placebo participants discontinued due to AEs.

3.3.1.3.8.3.3 Vaginal Estrogen Delivery Method Comparison (2 Trials; Total N=390)

Two trials^{83,88} of vaginal estradiol ring versus vaginal conjugated estrogens cream reported discontinuation due to AEs. In Nachtigall (1995),⁸⁸ five participants in the estradiol ring group discontinued because of vaginal discomfort (n=4) or headache and nausea (n=1). No conjugated estrogens cream participants discontinued due to AEs. In Ayton (1996),⁸³ similar proportions of participants in the ring group (7%) and cream group (8%) discontinued due to AEs.

3.3.1.3.8.3.4 Vaginal Estrogen Vs. Overactive Bladder (OAB) Pharmaceutical (1 Trial; Total N=54)

One trial⁹³ of vaginal estradiol ring versus oral oxybutynin reported discontinuation due to AEs. In Nelken (2011),⁹³ no estradiol ring participants discontinued due to AEs, though four oral oxybutynin participants discontinued for an unspecified AE.

3.3.1.3.8.4 Specific AEs

3.3.1.3.8.4.1 Vaginal Estrogen Vs. Placebo (5 Trials; Total N=1815)

Five trials^{85, 86, 92, 95, 98} (N=1815) of vaginal estrogen versus placebo provided counts and/or proportions of participants reporting specific AEs. The most common AEs reported were urinary tract infection (UTI; k=3;^{85, 86, 95} vaginal estrogen 2.0-5.2% vs. placebo 2.1-5.9%), vaginal discharge (k=3;^{85, 86, 98} 2.0-16.0% vs. 0.0-6.8%), vaginal infection (k=2;^{92, 95} 4.9-11.4% vs. 1.0-7.4%), vulvovaginal itching (k=2;^{85, 86} 1.6-2.1% vs. 2.0-5.2%), and headache (k=2;^{85, 92} 6.3-9.8% vs. 7.8-17.6%). Mitchell (2018)⁸⁶ (N=195) also reported the proportion of participants with moderate to severe breast tenderness (3 vs. 2%). Detailed specific AE results can be found in Appendix Table C.13.

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3.3.1.3.8.4.2 Vaginal Estrogen Dose or Delivery Method Comparisons (2 Trials; Total N=246)

Two trials (N=246) compared vaginal estrogen doses or routes of delivery and reported on specific AEs. Nachtigall (1995)⁸⁸ (N=196) observed that breast symptoms were higher in the conjugated estrogens cream than estradiol ring group, although vaginal infections were higher in the vaginal ring group (no data reported). Goetsch (2023)⁸⁷ (N=50) similarly reported specific AEs for 50 mcg vs. 100 mcg estradiol cream: breast tenderness (12 vs. 14%), vaginal spotting and bleeding (4 vs. 0%), and stinging (8 vs. 9%) with cream application. Specific counts of these AEs are reported in Appendix Table C.13.

3.3.1.3.8.4.3 Vaginal Estrogen Vs. OAB Pharmaceutical (1 Trial; Total N=54)

One trial⁹³ compared a vaginal estradiol ring with oral oxybutynin and provided counts of specific AEs. Nelken (2011)⁹³ (N=54) reported the percentage of estradiol ring vs. oral oxybutynin participants who reported dry mouth (22 vs. 85%, P<0.05), headache (26 vs. 37%, P>0.05), constipation (7 vs. 52%, P<0.05), vaginal discharge (41 vs. 4%, P<0.05), blurry vision (19 vs. 44%, P<0.05), and nausea/vomiting (11 vs. 7%, P>0.05). Specific counts of these AEs are reported in Appendix Table C.13.

3.3.1.4 Endometrial Safety

3.3.1.4.1 Vaginal Estrogen Vs. Placebo or No Treatment (7 Trials; Total N=1105)

Seven trials^{84-86, 89, 94, 96, 98} (N=1105) evaluated endometrial outcomes for estrogen compared with placebo or no treatment. Constantine (2017)⁸⁵ (N=574) reported no cases of endometrial hyperplasia or endometrial cancer through biopsy at week 12. In Fernandes (2018)¹²³ (N=38) (a publication of Fernandes (2014)⁸⁴), Lima (2013)⁹⁴ (N=60), Rhaghunandan (2010)⁹⁸ (N=50), and Tanmahasamut (2020)⁹⁶ (N=80), there were no statistically significant changes in endometrial thickness on transvaginal ultrasound for vaginal estrogen groups in comparison with placebo, though there was a nominal increase of up to 0.5 mm in two trials. Mitchell (2018)⁸⁶ (N=195) reported no cases of vaginal bleeding after 12 weeks for estrogen or placebo groups, while Eriksen (1999)⁸⁹ (N=108) reported 3 cases in the vaginal estrogen group and none in the no treatment group after 36 weeks.

3.3.1.4.2 Vaginal Estrogen Dose or Delivery Method Comparisons (3 Trials; Total N=354)

Goetsch (2023)⁸⁷ (N=50) evaluated endometrial thickness on transvaginal ultrasound for two doses of vaginal estrogen and found no significant increase from baseline to 12-weeks (0.1 mm increase in the 50 mcg group and no increase in the 100 mcg group) or difference between the groups. Ayton (1996)⁸³ (N=194) and Nachtigall (1995)⁸⁸ (N=196) performed a progesterone challenge on all participants after 12 weeks of therapy and reported a withdrawal bleed occurred for 4 percent⁸³ or 3 percent⁸⁸ of estradiol ring users and 9 percent⁸³ or 21 percent⁸⁸ of vaginal estrogen cream users (cream dose was higher in Nachtigall (1995)⁸⁸). Across both trials, subsequent endometrial biopsies identified proliferative endometrium or hyperplasia in an endometrial polyp (n=1) for 4 estradiol ring users and endometrial proliferation for 4 estrogen cream users.

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Ayton (1996)⁸³ and Goetsch (2023)⁸⁷ also identified patients with vaginal bleeding during treatment. Goetsch (2023)⁸⁷ reported that women with bleeding had a thin endometrial stripe on ultrasound or no uterus, while Ayton (1996)⁸³ performed endometrial biopsies and identified proliferative endometrium in one woman in each trial arm (vaginal estrogen ring and cream).

3.3.1.5. Other Outcomes

Two trials^{90, 93} (N=139) evaluated the effect of vaginal estrogen on urinary symptoms in women with OAB at 12 weeks. Nelken (2011)⁹³ (N=59) compared vaginal estrogen ring with oral oxybutynin and reported on the voiding frequency of participants via a 24-hour voiding diary, the Urinary Distress Inventory-6 (UDI-6), and the Incontinence Impact Questionnaire (IIQ-7). Both groups improved, but the difference between the groups was not statistically significant ($P>0.05$). Tseng (2009)⁹⁰ (N=80) compared the combination of oral tolterodine plus vaginal estrogen cream with oral tolterodine alone. Both groups showed improvement in daytime urinary frequency, UDI-6, and IIQ-7 scores, with a statistically significant ($p<0.05$) difference in favor of the tolterodine plus estrogen group.

One trial⁸⁹ evaluated the effect of vaginal estrogen versus no treatment on urinary urge incontinence, urinary urgency, urinary frequency, and recurrent UTI at 36 weeks. Eriksen (1999) (N=108) reported that a higher proportion of participants in the vaginal estrogen group experienced symptom resolution of urge incontinence, urgency, and frequency (50%, 63%, and 53%, respectively) compared with the no-treatment group (16%, 38%, and 29%), though the difference between arms was only statistically significant ($P<0.05$) for urinary urge incontinence. Based on bacteriologic examination, Eriksen (1999) reported that fewer participants in the vaginal estrogen group had a recurrent UTI compared with the control group (51% vaginal estrogen vs. 80% control). The cumulative proportion of subjects remaining UTI-free during the 36-week trial period was statistically significantly different between groups (45% vaginal estrogen vs. 20% control; $P<0.05$).

One trial⁸⁷ evaluated the effect of 50 mcg and 100 mcg vaginal estrogen cream applied to the vulvar vestibule on urinary urge incontinence in women with dyspareunia at 12 weeks. Goetsch (2023) (N=50) reported a non-significant pooled mean improvement on the UDI-6 score for the 50 mcg and 100 mcg estradiol groups from baseline (19.6) to 12 weeks (14.8).

Three trials⁸⁴⁻⁸⁶ (N=755) evaluated the effect of vaginal estrogen versus placebo on sexual function at 8-12 weeks using the FSFI total score, with mixed results. Kingsberg (2016)¹¹⁶ (N=520), a secondary publication from Constantine (2017),⁸⁵ reported a statistically significant improvement in total FSFI score for 10 mcg, but not 4 mcg, vaginal estradiol softgel compared with placebo softgel. Mitchell (2018)⁸⁶ (N=195) reported no significant difference in the improvement seen for both 10 mcg vaginal estradiol tablet plus placebo gel and placebo tablet plus placebo gel. Finally, Fernandes (2014)⁸⁴ (N=40) reported a statistically significant improvement in FSFI total score from baseline to 12 weeks in the placebo arm, but not in the vaginal estrogen arm; they did not report a statistical test comparing the change in each group.

All 6 trials^{85, 86, 91, 92, 95, 96} (N=2052) that compared vaginal estrogen with placebo and measured vaginal pH and vaginal cytology (i.e., VMI) found that, compared with placebo, vaginal estrogen resulted in a more significant reduction in vaginal pH, increase in superficial cells, and reduction in parabasal cells. Similarly, Eriksen (1999)⁸⁹ (N=50) and Nelken 2011⁹³ (N=59) found that vaginal estrogen had a more significant impact on vaginal pH and cytology than no treatment or oxybutynin, respectively. Ayton (1996)⁸³ (N=194) and Nachtigall (1995)⁸⁸

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(N=196) both reported equivalence of vaginal estrogen ring and cream with respect to reduction in pH, and Ayton also reported equivalence for VMI.

One trial⁸⁶ evaluated the effect of a vaginal estrogen tablet versus placebo on anxiety and depression at 12 weeks. Diem (2018)¹²¹ (N=195), a secondary publication of Mitchell (2018),⁸⁶ used the Patient Health Questionnaire (PHQ-8) to measure symptoms of depression and the Generalized Anxiety Disorder questionnaire (GAD-7) to measure anxiety. There was no significant difference between groups in the change from baseline to followup for both depression mean difference and anxiety mean difference.

3.3.2 Non-Estrogen Hormonal Interventions

3.3.2.1 Key Messages

- Vaginal DHEA may improve vulvovaginal dryness, dyspareunia, and menopause-related QoL compared with placebo (low COE). The evidence is very uncertain on the effect of vaginal DHEA on vulvovaginal discomfort/irritation and MBS compared with placebo (very low COE). There were no data on the impact on dysuria or treatment satisfaction.
- The evidence is very uncertain on the effect of oral DHEA on menopause-related QoL compared with placebo (very low COE). There were no data on oral DHEA for vulvovaginal dryness, discomfort/irritation, dysuria, dyspareunia, MBS, or treatment satisfaction.
- Vaginal oxytocin probably results in little to no difference in MBS compared with placebo (moderate COE). The evidence is very uncertain regarding effects of oxytocin on vulvovaginal dryness, discomfort/irritation, and dyspareunia (very low COE). There were no data on menopause-related QoL, dysuria, or treatment satisfaction.
- Ospemifene improves treatment satisfaction (high COE) and may improve vulvovaginal dryness and dyspareunia (low COE), but results in little to no difference in vulvovaginal discomfort/irritation compared with placebo (high COE). There were no data on MBS, dysuria, or QoL.
- Oral raloxifene added to vaginal estrogen or moisturizer may result in little to no difference in vulvovaginal dryness, discomfort/irritation, dysuria, or dyspareunia compared with placebo added to vaginal estrogen or moisturizer (low COE). Oral bazedoxifene may improve menopause-related QoL less than placebo (low COE). No data are available for the effects of bazedoxifene on dryness and dyspareunia. The evidence is very uncertain on the effect of oral bazedoxifene or raloxifene on treatment satisfaction compared with placebo (very low COE). There were no data for bazedoxifene or raloxifene for MBS.
- The evidence is very uncertain on the effect of vaginal testosterone on vulvovaginal dryness and dyspareunia, compared with placebo (very low COE). There were no data on effects of vaginal testosterone compared with placebo on vulvovaginal discomfort/irritation, dysuria, MBS, QoL, or treatment satisfaction. There were no data on the effects of vaginal testosterone compared with vaginal estrogen for vulvovaginal dryness, dyspareunia, dysuria, MBS, QoL, or treatment satisfaction.

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- Systemic estrogen plus systemic testosterone may result in little to no difference in vulvovaginal dryness and dyspareunia compared with estrogen alone (low COE). There were no data on effects of systemic testosterone on vulvovaginal discomfort/irritation, dysuria, MBS, QoL, or treatment satisfaction.
- Vaginal DHEA may result in more AEs compared with placebo, while vaginal oxytocin and oral ospemifene may result in little to no difference in SAEs compared with placebo (low COE). Hot flushes and vulvovaginal candidiasis occurred at higher rates in participants receiving ospemifene compared with placebo.
- Evidence is very uncertain on the adverse effects of oral DHEA, systemic testosterone plus systemic estrogen, and vaginal testosterone compared with a variety of controls (very low COE).
- Endometrial safety was evaluated in trials of all non-estrogen hormonal interventions using ultrasound and/or endometrial biopsy, ranging from 8 to 52 weeks.
- Compared with placebo, ospemifene was associated with thickened endometrial lining, proliferative endometrial histology, and one case of endometrial hyperplasia. Trials of oxytocin, bazedoxifene, raloxifene, and vaginal testosterone reported no difference in endometrial outcomes between treatment and control participants.

3.3.2.2 Overview

Thirty-six publications reporting 23 RCTs of non-estrogen hormonal interventions were included. Thirty-five publications (22 RCTs) were assessed as low or some concerns RoB. One publication (1 RCT⁷⁴) was assessed as high RoB and will not be discussed further. Table 5 presents an overview of the trials assessed as low or some concerns RoB, including key trial, patient, and outcome reporting characteristics. Detailed RoB assessments can be found in Appendix Table C.1. Detailed trial characteristics are reported in Appendix Table C.5. Limited information about the high RoB trial is in Table 2 and Appendix Table C.9.

Most trials of vaginal DHEA, vaginal oxytocin, and oral ospemifene required VMI and pH to verify vaginal atrophy for trial inclusion. One trial¹²⁴ of vaginal DHEA and two trials^{97, 125} of vaginal testosterone enrolled current or treated cancer patients.

The 22 RCTs investigated four non-estrogen hormonal interventions: DHEA (k=5),^{124, 126-129} oxytocin (k=2),^{130, 131} selective estrogen receptor modulators (SERMs; k=8),¹³²⁻¹³⁹ and testosterone (k=7).^{84, 97, 98, 113-115, 125} DHEA and oxytocin were administered alone, while SERMs and testosterone were tested both alone and in combination with estrogen. The investigated SERMs included ospemifene (k=5),¹³²⁻¹³⁶ bazedoxifene (k=1),¹³⁷ and raloxifene (k=2).^{138, 139}

All five DHEA trials^{124, 126-129} used a placebo comparator (4 vaginal DHEA/placebo^{124, 126-128, 114, 116-118} 1 oral DHEA/placebo¹²⁹). Vaginal DHEA trials were large, randomizing between 200 and 600 participants. Both oxytocin trials^{130, 131} compared vaginal oxytocin gel with placebo gel. All four ospemifene trials compared oral ospemifene with oral placebo tablets, and were large, randomizing 400 to 900 participants. The single bazedoxifene trial¹³⁷ was a 4-arm trial of oral bazedoxifene alone, oral bazedoxifene in combination with two doses of oral estrogen, and placebo. One raloxifene trial¹³⁰ had four arms and evaluated the effect of oral raloxifene plus conjugated estrogens cream or non-hormonal moisturizer versus placebo plus conjugated estrogens cream or non-hormonal moisturizer. The other trial¹³¹ compared oral raloxifene plus an estradiol vaginal ring versus oral placebo tablet plus estradiol ring. Of the seven testosterone

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trials,^{84, 97, 98, 113-115, 125} all included fewer than 100 participants and most focused on sexual outcomes. Three studied systemic testosterone (two oral,^{113, 114} one transdermal¹¹⁵) in addition to oral estrogen, compared with oral estrogen alone; one compared vaginal testosterone versus vaginal estrogen;⁹⁷ two compared vaginal testosterone versus placebo vaginal cream or lubricant gel;^{84, 125} and one studied vaginal testosterone in addition to vaginal estrogen, compared with vaginal estrogen alone or lubricant alone.⁹⁸ The trial⁸⁴ that used lubricant (hydroxyethylcellulose gel) as the comparator included two additional arms of conjugated estrogens cream and polyacrylic acid cream compared with lubricant. For estrogen and moisturizer versus placebo/lubricant outcomes, see Sections 3.3.1 and 3.3.4, respectively.

None of the trials reported on all outcomes of interest and most only reported a single effectiveness outcome. Twenty-two publications (19 RCTs) evaluated harms outcomes. These 19 RCTs investigated four interventions: systemic and vaginal DHEA (k=5),^{124, 126-129} oxytocin (k=2),^{130, 131} SERMs (k=7),^{132-137, 139} and systemic and vaginal testosterone (k=5).^{84, 97, 98, 114, 115} Measures and methods used for outcomes and reporting varied widely. None of the trials were designed to adequately assess patient reported side effects. We were unable to perform a meta-analysis of results due to trial variability in populations, interventions, comparisons, outcomes, and reporting used, including length of followup. Certainty of evidence ratings for priority outcomes are listed in Table 6 (DHEA), Table 7 (oxytocin), Table 8 (SERMs), and Table 9 (testosterone). Complete outcomes data are presented in Appendix Tables C.14 to C.21.

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Table 5. Overview of included non-estrogen hormonal trials rated low or some concerns RoB

Category	Characteristics	Vaginal or Oral DHEA Vs. Placebo (k=5)	Vaginal Oxytocin Vs. Placebo (k=2)	Oral Bazedoxifene +/- Vaginal CEC Vs. Placebo (k=1)	Oral Ospemifene Vs. Placebo (k=4)	Oral Raloxifene Vs. Placebo* (k=2)	Oral or Transdermal Testosterone + Oral Estrogen Vs. Oral Estrogen (k=3)	Vaginal Testosterone Vs. Vaginal Estrogen and/or Placebo (k=4)	Total (k=21)
Sample Size	<100	1	1	0	0	1	3	4	10
	100-199	0	1	0	0	1	0	0	2
	200-499	3	0	0	1	0	0	0	4
	>500	1	0	1	3	0	0	0	5
VVA/GSM symptoms diagnosis	Clinical diagnosis	0	0	0	1	0	1	0	2
	Self-reported	5	2	1	3	1	1	4	17
	Study verified	0	0	0	0	1	1	0	2
Type of VVA/GSM symptom for inclusion	Vulvovaginal	0	1	0	2	2	0	0	5
	Sexual	3	0	0	0	0	2	0	5
	Vulvovaginal and Sexual	2	0	1	1	0	0	2	6
	Vulvovaginal, Urinary, and Sexual	0	1	0	0	0	0	2	3
	Not reported	0	0	0	1	0	1	0	2
Baseline VVA/GSM symptom severity	Mild, moderate or severe	1	1	0	0	1	0	0	3
	Moderate to severe	3	1	1	3	0	0	0	8
	Not reported	1	0	0	1	1	3	4	10
Other eligibility criteria	Included women s/p hysterectomy	5	Unclear	0	3	0	1	1	10
	Presence/hx of cancer	1	NR	0	0	0	0	2	3
	Treatment naïve/washout	5	2	1	2	2	2	2	16
Length of followup	8 weeks	0	1	0	0	0	2	0	3
	12 weeks	4	1	1	3	1	0	3	12
	26 weeks	0	0	0	0	1	0	1	2
	52 weeks	1	0	0	1	0	1	0	3
Outcomes Reported*	Vulvovaginal dryness	4	2	0	3	2	2	2	15
	Discomfort/irritation	1	1	0	1	2	0	0	5
	Dysuria	0	0	0	2	2	0	0	4
	Dyspareunia	4	2	0	3	2	1	2	14
	Change in MBS	2	1	0	0	0	0	0	3
	QoL	2	0	1	0	0	0	0	3
	Satisfaction with treatment	0	0	0	1	1	0	0	2

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Category	Characteristics	Vaginal or Oral DHEA Vs. Placebo (k=5)	Vaginal Oxytocin Vs. Placebo (k=2)	Oral Bazedoxifene +/- Vaginal CEC Vs. Placebo (k=1)	Oral Ospemifene Vs. Placebo (k=4)	Oral Raloxifene Vs. Placebo* (k=2)	Oral or Transdermal Testosterone + Oral Estrogen Vs. Oral Estrogen (k=3)	Vaginal Testosterone Vs. Vaginal Estrogen and/or Placebo (k=4)	Total (k=21)
	Adverse effects	4	1	1	4	1	2	3	16

Abbreviations: CEC=conjugated estrogens cream; DHEA=Dehydroepiandrosterone; GSM=genitourinary syndrome of menopause; hx=history; MBS=most bothersome symptom; NR=not reported; QoL=quality of life; RCT=randomized controlled trial; RoB=risk of bias; s/p=status post; VVA=vulvovaginal atrophy

*Both raloxifene trials were placebo-controlled. One trial¹³⁸ was a 4-arm trial that investigated the effect of oral raloxifene vs. placebo on the response to either vaginal estrogen or vaginal moisturizer. The other trial¹³⁹ was a 2-arm trial that investigated the effect of adding oral raloxifene vs. placebo to vaginal estrogen.

3.3.2.3 DHEA

3.3.2.3.1 COMMA Outcomes

Table 6. Summary of COMMA outcomes, findings, and certainty of evidence for DHEA

Outcome	Intervention Vs. Comparator Followup	Study Design: No. Trials (N) Direction of Effect	Findings	Certainty of Evidence	Summary Statement
Vulvovaginal dryness	Vaginal DHEA vs. placebo 12 weeks	RCT: 4 (1472) ^{124, 127, 140, 141} ↑ 4 trials	Four trials found consistent effects of vaginal DHEA compared with placebo using three measurement tools. All trials found a significant benefit using the FSFI lubrication domain (k=2), ^{124, 141} a 4-point severity scale (k=1), ¹²⁷ or the MENQOL “dryness during intercourse” score (k=1). ¹⁴⁰	Low ⊕⊕○○ ^{a,b}	Vaginal DHEA may improve vulvovaginal dryness compared with placebo.
Vulvovaginal discomfort/irritation	Vaginal DHEA vs. placebo 12 weeks	RCT: 1 (16) ¹²⁸ ↕ 1 trial	One trial used a 4-point severity scale and found a statistically significant difference only for the 0.5% DHEA dose versus placebo, not the 0.25% or 1.0% DHEA doses.	Very low ⊕○○○ ^{a,e}	The evidence is very uncertain on the effect of vaginal DHEA on vulvovaginal discomfort/irritation compared with placebo.
Dyspareunia	Vaginal DHEA vs. placebo 12 weeks	RCT: 4 (1472) ^{124, 127, 141, 142} ↑ 4 trials	Four trials found statistically significant improvement after vaginal DHEA compared with placebo using either the FSFI pain domain ^{124, 141} or a 4-point severity scale. ^{127, 142}	Low ⊕⊕○○ ^{a,b}	Vaginal DHEA may improve dyspareunia compared with placebo.
Change in MBS	Vaginal DHEA vs. placebo 12 weeks	RCT: 2 (659) ^{124, 128} ↑ 1 trial ↔ 1 trial	Two trials used a 4-point severity scale and found a greater improvement in MBS severity for vaginal DHEA than placebo, though only one comparison was statistically significant. ¹²⁸	Very low ⊕○○○ ^{a,b,c}	The evidence is very uncertain on the effect of vaginal DHEA on MBS compared with placebo.

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Outcome	Intervention Vs. Comparator Followup	Study Design: No. Trials (N) Direction of Effect	Findings	Certainty of Evidence	Summary Statement
QoL	Vaginal DHEA vs. placebo 12 weeks	RCT: 1 (216) ¹⁴⁰ ↑↔ 1 trial	One trial found greater improvement in the total MENQOL score for all three vaginal DHEA arms compared with placebo, though only two comparisons (0.25% and 1.0% DHEA vs. placebo) were statistically significant.	Low ⊕⊕○○ ^{a,d}	Vaginal DHEA may improve QoL compared with placebo.
	Oral DHEA vs. placebo 26 weeks	RCT: 1 (93) ¹²⁹ ↔ 1 trial	One trial found improvement in the total MENQOL score for both oral DHEA and placebo and no significant difference between arms.	Very low ⊕○○○ ^{b,e}	The evidence is very uncertain on the effect of oral DHEA on QoL compared with placebo.
Adverse effects (any AE)	Vaginal DHEA vs. placebo 12 weeks	RCT: 3 (1256) ^{124, 126, 127} ↔ 1 trial ? 2 trials	Two trials ^{126, 127} reported rates of participants with at least one AE. Both trials observed slightly higher rates in the DHEA arm(s) than the placebo arm, though neither trial provided a statistical test comparing DHEA with placebo. The third trial ¹²⁴ reported no statistically significant differences between arms in any AE but did not report the data.	Low ⊕⊕○○ ^{a,f}	Vaginal DHEA may result in more AEs compared with placebo.
	Oral DHEA vs. placebo 52 weeks	RCT: 1 (93) ¹²⁹ ? 1 trial	One trial reported total AEs but did not specify whether the counts represented participants or events. No information was provided regarding statistical significance versus placebo.	Very low ⊕○○○ ^{e,f}	The evidence is very uncertain on the effect of oral DHEA on AEs compared with placebo.

Abbreviations: AE=adverse effect; CI=confidence interval; COMMA=Core Outcomes in Menopause; DHEA=Dehydroepiandrosterone; FSFI=Female Sexual Function Index; GU=genitourinary; MBS=most bothersome symptom; MENQOL=Menopause-Specific Quality of Life; OIS=optimal information size; QoL=quality of life; RCT=randomized controlled trial; RoB=risk of bias; SD=standard deviation; SEM=standard error of mean

Direction of effect

↑: Intervention group had a statistically significantly better outcome than comparison group (e.g., improved symptoms, higher treatment satisfaction)

↓: Intervention group had a statistically significantly worse outcome than comparison group (e.g., worsened symptoms, lower treatment satisfaction)

↔: No statistically significant difference between groups

↑↔: Mixed statistical significance of intervention group effect versus comparison group effect within multi-arm trials (e.g., one intervention dose/schedule had a statistically significantly better outcome than comparison group but there was no statistically significant difference between another intervention dose/schedule and comparison group)

?: No statistical comparison of change in time between groups provided

Certainty of evidence (COE)

Low (⊕⊕○○): Our confidence in the effect estimate is limited; the true effect may be substantially different from the effect estimate.

Very low (⊕○○○): We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

^aDowngraded one level for study limitations (one or more trials assessed as “some concerns” RoB)

^bDowngraded one level for imprecision (SD crosses no-effect threshold)

^cDowngraded one level for inconsistency (effect varied across trials)

^dDowngraded one level for imprecision (total sample size less than OIS of 400)

^eDowngraded two levels for imprecision (total sample size much less than OIS of 400)

^fDowngraded one level for study limitations (one or more trials did not provide adequate statistical reporting)

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3.3.2.3.1.1 Vulvovaginal Dryness

3.3.2.3.1.1.1 Vaginal DHEA Vs. Placebo (4 Trials; Total N=1472)

Four trials^{124, 126-128} (6 publications^{124, 126, 127, 140, 141, 143}) (N=1472) evaluated the effect of vaginal DHEA versus placebo on vulvovaginal dryness at 12 weeks. All trials found statistically significant improvement in the vaginal DHEA arm(s) compared with the placebo arm across three different measures, except for a 0.25% DHEA arm in a 3-arm trial.¹²⁴ The three industry-sponsored trials¹²⁶⁻¹²⁸ excluded women with a presence or history of cancer, while the remaining government-funded trial¹²⁴ only recruited women with a history of breast or gynecological cancer.

Archer (2015) (N=255)¹²⁷ used a 4-point severity scale (0=none to 3=severe) to measure dryness and reported a statistically significant ($P<0.05$) difference in mean change from baseline between groups (0.25% DHEA -1.29 and 0.5% DHEA -1.45 vs. placebo -1.02). Labrie (2018)¹²⁶ (N=558) found similar effects using the same scale only among participants with at least moderate to severe dryness at baseline (0.5% DHEA -1.44 vs. placebo -1.17). Labrie (2018) also used the FSFI lubrication domain (0 (worst) to 6 (best)) to measure change from baseline and reported a statistically significant difference in favor of the DHEA group (0.5% DHEA 2.0 to 4.1 vs placebo 1.9 to 3.5).¹⁴¹ Barton (2018)¹²⁴ (N=443) also used the FSFI lubrication domain, and found a significant effect comparing improvement for 0.5% DHEA versus placebo, but not 0.25% DHEA versus placebo (0.5% DHEA 1.6 and 0.25% DHEA 1.3 vs. placebo 1.1). Labrie (2009)^{140, 143} (N=216) used the MENQOL question to assess dryness during intercourse and reported a significant difference in average percent change after treatment with 0.25%, 0.5%, and 1.0% DHEA compared with placebo (45%, 50%, and 54% change vs. 23%). Due to study limitations and imprecision, we conclude that vaginal DHEA may improve vulvovaginal dryness compared with placebo (low COE).

3.3.2.3.1.2 Vulvovaginal Discomfort/Irritation

3.3.2.3.1.2.1 Vaginal DHEA Vs. Placebo (1 Trial; Total N=16)

One trial¹²⁸ (N=16) evaluated the effect of vaginal DHEA versus placebo on vulvovaginal discomfort/irritation at 12 weeks. Labrie (2009) used a 4-point severity scale (0=none to 3=severe) to assess patients who identified at least moderate to severe irritation/itching at baseline and reported the proportion of patients in each arm describing symptom score change. Only 16 women identified irritation/itching as their MBS at baseline across 4 arms (placebo and 0.25%, 0.5%, and 1.0% DHEA). A statistically significant difference was observed only for the 0.5% DHEA dose versus placebo (data not shown). Due to study limitations and imprecision, the evidence is very uncertain on the effect of vaginal DHEA on vulvovaginal discomfort/irritation compared with placebo (very low COE).

3.3.2.3.1.3 Dysuria

No trials evaluated the effect of DHEA on dysuria.

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3.3.2.3.1.4 Dyspareunia

3.3.2.3.1.4.1 Vaginal DHEA Vs. Placebo (4 Trials; Total N=1472)

Four trials^{124, 126-128} (6 publications^{124, 126, 127, 141, 142, 144}) (N=1472) evaluated the effect of vaginal DHEA versus placebo on dyspareunia. Archer (2015)¹²⁷ and Labrie (2018)¹²⁶ (N=813) both enrolled only women for whom dyspareunia was at least moderate to severe at baseline and was their MBS. Both trials found a statistically significant ($P<0.05$) improvement on a 4-point severity scale (0=none to 3=severe) from baseline to 12 weeks (Archer 2015: 0.25% DHEA -1.01 and 0.5% DHEA -1.27 vs. placebo -0.87; Labrie 2018: 0.5% DHEA -1.42 vs. placebo -1.06). Labrie (2018)¹²⁶ also reported statistically significant FSFI pain domain (0 (worst) to 6 (best)) improvement over 12 weeks in a secondary paper¹⁴¹ (0.5% DHEA 2.21 vs. placebo 1.56).

The other two trials^{124, 128} did not require a specific level of dyspareunia for trial entry. Labrie (2009)¹²⁸ (N=216) reported a statistically significant ($P<0.05$) improvement in dyspareunia severity on a 4-point scale (0=none to 3=severe) from baseline to 12 weeks for DHEA 0.25%, 0.5%, and 1% versus placebo, for both the whole trial population¹⁴² (-1.2, -1.6, and -1.4 vs. -0.4) and the sub-group¹⁴⁴ who reported that dyspareunia was their MBS (-1.3, -1.6, and -1.4 vs. -0.4). Barton (2018)¹²⁴ (N=443) reported statistically significant ($P<0.05$) improvement in the FSFI pain domain (0 (worst) to 6 (best)) from baseline to 12 weeks (0.25% DHEA 1.4 and 0.5% DHEA 2.0 vs. placebo 1.0). Barton (2018)¹²⁴ also noted that use of an aromatase inhibitor (slightly more than half of trial participants) was not associated with any significant difference in change in FSFI pain domain. Due to study limitations and imprecision, we conclude that vaginal DHEA may improve dyspareunia compared with placebo (low COE).

3.3.2.3.1.5 Change in MBS

3.3.2.3.1.5.1 Vaginal DHEA Vs. Placebo (2 Trials; Total N=659)

Two trials^{124, 128} (N=659) evaluated the effect of vaginal DHEA versus placebo on a patient's self-identified MBS. Barton (2018)¹²⁴ offered two options (dyspareunia (51-60% of participants) or vulvovaginal dryness (40-49%)) for patients to select as their MBS and reported results for both symptom groups. Labrie (2009)¹²⁸ reported change in a composite MBS that included vulvovaginal dryness (31%), vulvovaginal discomfort/irritation (8%), and dyspareunia (61%).

Barton (2018)¹²⁴ (N=443) used a 5-point severity scale (1=none to 5=very severe) and found a statistically significant ($P<0.05$) difference in change from baseline for only 0.5% DHEA versus placebo, not 0.25% DHEA (0.25% DHEA -1.6 and 0.5% DHEA -1.8 vs. placebo -1.5). This trial¹²⁴ recruited women with a history of breast or gynecological cancer and noted that use of an aromatase inhibitor was not associated with any significant difference in change in MBS. Labrie (2009)¹²⁸ (N=216) used a 4-point severity scale (0=none to 3=severe) to measure the change in MBS after 12 weeks of treatment and found significant ($P<0.05$) improvement with all DHEA doses compared with placebo (0.25% DHEA -1.2, 0.5% DHEA -1.5, and 1.0% DHEA -1.3 vs. placebo -0.6). Due to study limitations, imprecision, and inconsistency, we conclude that the evidence is very uncertain on the effect of vaginal DHEA on MBS compared with placebo (very low COE).

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3.3.2.3.1.6 QoL (i.e., Distress, Bother, or Interference of Genitourinary Symptoms)

3.3.2.3.1.6.1 Vaginal DHEA Vs. Placebo (1 Trial; Total N=199 or 216)

One trial¹²⁸ (2 publications^{140, 143}) evaluated the effect of vaginal DHEA versus placebo on menopause-related QoL. In separate analyses, Labrie (2009) analyzed results for either only participants assessed at both baseline and week 12 (N=199)¹⁴³ or all participants with the last value obtained carried forward when data at week 12 were missing (N=216).¹⁴⁰ Both analyses found that the total MENQOL score (or proportion who improved) statistically significantly ($P<0.05$) improved (i.e., decreased) for 0.25% DHEA (-0.83, 27%¹⁴³ or 24%¹⁴⁰) and 1.0% (-0.64, 21% or 20%), but not for 0.5% DHEA (-0.48, 18% in both analyses) compared with placebo (-0.28, 10% or 9%). Notably, only 0.5% DHEA is FDA-approved for the treatment of GSM. Due to study limitations and imprecision, we conclude that vaginal DHEA may improve QoL compared with placebo (low COE).

3.3.2.3.1.6.2 Oral DHEA Vs. Placebo (1 Trial; Total N=93)

One trial¹²⁹ (N=93) evaluated the effect of oral DHEA versus placebo on menopause-related QoL. Panjari (2009) reported that the total MENQOL score improved (i.e., decreased) in both arms after 26 weeks of treatment, though the difference in change from baseline between arms (-0.4) was not significant ($P>0.05$). Due to considerable concerns with imprecision, we conclude that the evidence is very uncertain on the effect of oral DHEA on QoL compared with placebo (very low COE).

3.3.2.3.1.7 Satisfaction With Treatment

No trials evaluated the effect of DHEA on treatment satisfaction.

3.3.2.3.1.8 Adverse Effects

Five trials evaluated the potential harms of vaginal (k=4) or oral (k=1) DHEA. We captured when a trial reported any AE/TEAE (k=4), SAEs (k=1), discontinuation due to AEs (k=4), or clinically relevant, specific AEs (k=4). All the vaginal DHEA trials assessed harms at 12 weeks, while the oral DHEA trial¹²⁹ had a 52-week followup period. One trial¹²⁸ evaluated safety only to state that there were no drug-related SAEs in the trial and no AEs on labs (including liver tests and blood counts). Specific counts (when available) and detailed AE reporting can be found in Appendix Table C.15.

3.3.2.3.1.8.1 Any AE/TEAE

Vaginal DHEA Vs. Placebo (3 Trials; Total N=1256). We assessed the 3 trials¹²⁶⁻¹²⁸ (N=1256) that reported rates of participants who experienced any AE/TEAE using GRADE and downgraded two levels for study limitations (RoB and inadequate statistical reporting). Two trials^{126, 127} reported number (%) of participants with at least one AE. Both reported “no relevant difference” in frequency of AEs between trial arms, though neither trial provided a statistical test comparing the arms. In Archer (2015),¹²⁷ participants in both vaginal DHEA arms reported more AEs than placebo participants (3.25 mg 48 [55.8] and 6.5 mg 46 [52.9] vs. placebo 35 [43.8]). Labrie (2018)¹²⁸ also observed more AEs in the vaginal DHEA than the placebo arm (6.5 mg 179 [47.9] vs. placebo 77 [42.8]). Barton (2018)¹²⁴ reported no statistically significant differences between arms in any grade toxicity or common clinician graded side effects but did not report the

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data. We conclude that vaginal DHEA may result in more AEs compared with placebo (low COE).

Oral DHEA Vs. Placebo (1 Trial; Total N=93). We assessed one trial¹⁴⁵ of oral DHEA versus placebo that reported total AEs using GRADE and downgraded three levels for imprecision and study limitations. Panjari (2009)¹²⁹ (N=93) reported total AEs by arm (DHEA 31 vs. placebo 24) and identified the AEs as androgenic (DHEA 5 vs. placebo 0) or nonandrogenic (DHEA 26 vs. placebo 24) but did not specify whether the counts represented participants or events. No information was provided regarding statistical significance versus placebo. We conclude that the evidence is very uncertain on the effect of oral DHEA on AEs compared with placebo (very low COE).

3.3.2.3.1.8.2 Serious AEs

Vaginal DHEA Vs. Placebo (1 Trial; Total N=255). One trial¹²⁷ of vaginal DHEA versus placebo reported SAEs. In Archer (2015)¹²⁷ (N=255), only participants in the DHEA group (3.25 mg 3.5% and 6.5 mg 1.1%) reported SAEs, none of which were considered to be drug related. No placebo participants reported SAEs.

Oral DHEA Vs. Placebo (1 Trial; Total N=93). One trial¹⁴⁵ of oral DHEA versus placebo evaluated SAEs. Panjari (2009)¹²⁹ (N=93) found no SAEs in either group.

3.3.2.3.1.8.3 Discontinuation Due to AEs

Vaginal DHEA Vs. Placebo (3 Trials; Total N=1256). Three trials^{124, 126, 127} (N=1256) of vaginal DHEA versus placebo reported discontinuation due to AEs. In Archer (2015)¹²⁷ and Labrie (2018),¹²⁶ specific AEs leading to discontinuation of vaginal DHEA treatment included hot flushes (n=1), vaginal intraepithelial lesion (n=1), application site discharge (n=3), vaginal bleeding (n=1), and suicidal ideation (n=1). The proportion of vaginal DHEA participants who discontinued treatment ranged from 1.5 to 3.5 percent, while 1.2 to 1.9 percent of placebo participants discontinued across these two trials. Barton (2018)¹²⁴ used a participant disposition figure to report participants (n, %) who discontinued the trial due to AEs but did not specify what the AEs were (3.25 mg DHEA 13 [8.8] and 6.5 mg DHEA 17 [11.4] vs. placebo 14 [9.5]).

Oral DHEA Vs. Placebo (1 Trial; Total N=93). One trial of oral DHEA versus placebo reported trial discontinuation due to AEs. In Panjari (2009)¹²⁹ (N=93), specific AEs leading to trial discontinuation in the oral DHEA arm (n=6 total) included facial hair and acne (n=1), skin rash (n=1), facial hair (n=1), vaginal discharge (n=1), and vaginal bleeding (n=2). Three participants in the placebo arm withdrew from the trial due to unspecified AEs.

3.3.2.3.1.8.4 Specific AEs

Vaginal DHEA Vs. Placebo (3 Trials; Total N=1256). Three trials^{124, 126, 127} (N=1256) of vaginal DHEA versus placebo provided counts and/or proportions of participants reporting specific AEs. Archer (2015)¹²⁷ and Labrie (2018)¹²⁶ reported rates of application site discharge (5.7-7.0% vs. 5.6-6.3%), UTI (4.5-7.0% vs. 2.8-5.0%), headache (4.7-5.7% vs. 1.3%), and/or hot flushes (1.6% vs. 3.9%). Barton (2018)¹²⁴ (N=443) stated that self-reported side effects of voice change and headache were statistically significantly worse in the vaginal DHEA group than the

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moisturizer group, which they attributed to androgen-related side effects. Detailed specific AE results can be found in Appendix Table C.15.

Oral DHEA Vs. Placebo (1 Trial; Total N=93). One trial¹²⁹ of oral DHEA versus placebo provided counts of participants reporting specific AEs. Panjari (2009)¹²⁹ (N=93) reported rates of acne (n=3 vs. n=0) and increased facial hair (n=2 vs. n=0). Detailed specific AE results can be found in Appendix Table C.15.

3.3.2.3.2 Endometrial Safety

In Archer (2015)¹²⁷ (N=255) nearly all participants (99%) underwent endometrial biopsies at 12 weeks. Insufficient tissue was noted in 18 percent of DHEA 0.50% participants, 8 percent of 0.25% DHEA participants, and 7 percent of placebo participants. For remaining adequate samples, all showed atrophic endometrium. Labrie (2009)¹²⁸ (N=216) also completed endometrial biopsies at 3 months and reported no effect on endometrial histology, though data was not shown.

Panjari (2009)¹⁴⁵ monitored breakthrough vaginal bleeding and measured endometrial thickness using transvaginal ultrasound over 52 weeks in a subgroup of 73 un-hysterectomized women. Breakthrough vaginal bleeding was similar across both arms (oral DHEA 3 vs. placebo 2) and no significant adverse endometrial effects were observed. Detailed results can be found in Appendix Table C.15.

3.3.2.3.3 Other Outcomes

Three trials^{124, 126, 128} (4 publications^{124, 140, 141, 143}) evaluated the effect of vaginal DHEA versus placebo on more comprehensive measures of sexual function at 12 weeks. Overall, there appeared to be improved sexual function based on various measures (e.g., average percent improvement in Abbreviated Sexual Function Questionnaire [ASFQ], FSFI total score) for vaginal DHEA versus placebo. One trial¹²⁹ concluded that oral DHEA was not effective for treatment of sexual function compared with placebo due to lack of statistically significant improvement after 26 weeks.

One trial¹²⁸ evaluated the effect of vaginal DHEA versus placebo on other psychological symptoms and reported changes from baseline to 12 weeks for each arm, but did not provide a statistical test comparing the two trial arms. Another trial¹²⁹ evaluated the effect of oral DHEA versus placebo on other psychological symptoms after 26 weeks and found little change from baseline or versus placebo for oral DHEA.

Three trials¹²⁶⁻¹²⁸ evaluated the effect of vaginal DHEA on vaginal atrophy compared with placebo. Each trial measured vaginal pH and collected vaginal cytology smears during gynecological exams at baseline and week 12, classified cells as parabasal or superficial squamous cell types, and reported the percentage of each based on a 100-cell count. Each trial reported a statistically significant reduction in vaginal pH, and a shift toward superficial cells and away from parabasal cells (both consistent with a reduction in vaginal atrophy) from baseline to week 12 for vaginal DHEA compared with placebo. Detailed results can be found in Appendix Table C.14.

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3.3.2.4 Oxytocin

3.3.2.4.1 COMMA Outcomes

Table 7. Summary of COMMA outcomes, findings, and certainty of evidence for vaginal oxytocin

Outcome	Comparator Followup	Study Design: No. Trials (N) Direction of Effect	Findings	Certainty of Evidence	Summary Statement
Vulvovaginal dryness	Placebo gel 8-12 weeks	RCT: 2 (243) ^{130, 146} ↑ 1 trial ↔ 1 trial	Two trials found mixed effects of vaginal oxytocin compared with placebo. One trial ¹⁴⁶ used the FSFI lubrication domain and reported a statistically significant difference between arms, while the second trial ¹³⁰ reported no significant difference between arms in mean change on a 4-point severity scale.	Very low ⊕○○○ ^{a,b,c}	The evidence is very uncertain on the effect of vaginal oxytocin on vulvovaginal dryness compared with placebo.
Vulvovaginal discomfort/irritation	Placebo gel 8 weeks	RCT: 1 (86) ¹³¹ ↑ 1 trial	One trial reported statistically significant improvement in mean trial-specific checklist scores after vaginal oxytocin compared with placebo.	Very low ⊕○○○ ^{b,d}	The evidence is very uncertain on the effect of vaginal oxytocin on vulvovaginal discomfort/irritation compared with placebo.
Dyspareunia	Placebo gel 8-12 weeks	RCT: 2 (243) ^{130, 146} ↑ 1 trial ↔ 1 trial	Two trials found mixed effects of vaginal oxytocin compared with placebo. One trial ¹⁴⁶ used the FSFI pain domain and reported a statistically significant difference between arms, while the second trial ¹³⁰ reported no significant difference between arms in mean change on a 4-point severity scale.	Very low ⊕○○○ ^{a,b,c}	The evidence is very uncertain on the effect of vaginal oxytocin on dyspareunia compared with placebo.
Change in MBS	Placebo gel 12 weeks	RCT: 1 (157) ¹³⁰ ↔ 1 trial	One trial found no significant effect of vaginal oxytocin compared with placebo using a 4-point severity scale.	Moderate ⊕⊕⊕○ ^a	Vaginal oxytocin probably results in little to no difference in MBS compared with placebo.
Adverse effects (SAEs)	Placebo gel 12 weeks	RCT: 1 (157) ¹³⁰ ? 1 trial	One trial reported SAEs in the oxytocin and aqueous Hypromellose-based gel groups but did not provide a statistical comparison of the two groups.	Low ⊕⊕○○ ^{a,e}	Vaginal oxytocin may result in little to no difference in SAEs compared with placebo.

Abbreviations: COMMA=Core Outcomes in Menopause; FSFI=Female Sexual Function Index; GU=genitourinary; MBS=most bothersome symptom; OIS=optimal information size; RCT=randomized controlled trial; RoB=risk of bias; SAE=serious adverse effect; SD=standard deviation

Direction of effect

↑: Intervention group had a statistically significantly better outcome than comparison group (e.g., improved symptoms, higher treatment satisfaction)

↓: Intervention group had a statistically significantly worse outcome than comparison group (e.g., worsened symptoms, lower treatment satisfaction)

↔: No statistically significant difference between groups

?: No statistical comparison of change in time between groups provided

Certainty of evidence (COE)

Moderate (⊕⊕⊕○): We are moderately confident in the effect estimate; the true effect is likely to be close to the effect estimate, but there is a possibility that it is substantially different.

Low (⊕⊕○○): Our confidence in the effect estimate is limited; the true effect may be substantially different from the effect estimate.

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Very low (⊕○○○): We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

^aDowngraded one level for imprecision (total sample size smaller than OIS of 400)

^bDowngraded one level for study limitations (one or more trials assessed as some concerns RoB)

^cDowngraded one level for inconsistency (effect varied across trials)

^dDowngraded two levels for imprecision (total sample size much smaller than OIS of 400)

^eDowngraded one level for study limitations (one or more trials did not provide adequate statistical reporting)

3.3.2.4.1.1 Vulvovaginal Dryness

3.3.2.2.1.1.1 Vaginal Oxytocin Vs. Placebo (2 Trials; Total N=243)

Two trials^{130, 131} (N=243) evaluated the effect of vaginal oxytocin gel versus placebo on vulvovaginal dryness at either 8 or 12 weeks and reported mixed results. Fianu Jonasson (2020)¹³⁰ (N=157) required self-reported vulvovaginal, urinary, or sexual symptoms of any severity at baseline, while Zohrabi (2020)¹³¹ required at least mild vulvovaginal symptoms. Abedi (2020)¹⁴⁶ (N=86) reported on vulvovaginal dryness for the Zohrabi (2020) trial.¹³¹ Neither trial specified eligibility criteria for history/risk of breast cancer or prior hysterectomy. Fianu Jonasson (2020)¹³⁰ assessed vaginal dryness with a 4-point severity scale (0=none to 3=severe) and found no significant ($P>0.05$) difference in mean change at 12 weeks between vaginal oxytocin and placebo (oxytocin -1.15 vs. placebo -1.21). Abedi (2020)¹⁴⁶ used the FSFI lubrication domain (0 (worst) to 6 (best)) and found a statistically significant ($P<0.05$) improvement in the mean score for vaginal oxytocin compared with placebo (oxytocin 2.8 to 4.53 vs. placebo 3.02 to 3.48) at 8 weeks. Due to concerns with study limitations, imprecision, and inconsistency, we conclude that the evidence is very uncertain on the effect of oxytocin gel on vulvovaginal dryness compared with placebo gel (very low COE).

3.3.2.4.1.2 Vulvovaginal Discomfort or Irritation

3.3.2.2.1.2.1 Vaginal Oxytocin Vs. Placebo (1 Trial; Total N=86)

One trial¹³¹ (N=86) evaluated the effect of vaginal oxytocin gel versus placebo on vulvovaginal discomfort or irritation at 8 weeks using a study checklist (decreased score indicates improvement). Zohrabi (2020) reported statistically significant ($P<0.05$) improvement in mean scores after vaginal oxytocin compared with placebo (oxytocin 6.2 to 0.38 vs. placebo 6.54 to 4.9). Due to concerns with study limitations and imprecision, we conclude that the evidence is very uncertain on the effect of oxytocin on vaginal/vulvar irritation compared with placebo (very low COE).

3.3.2.4.1.3 Dysuria

No trials evaluated the effect of vaginal oxytocin on dysuria.

3.3.2.4.1.4 Dyspareunia

3.3.2.4.1.4.1 Vaginal Oxytocin Vs. Placebo (2 Trials; Total N=243)

Two trials^{130, 131} (3 publications^{130, 131, 146}) (N=243) evaluated the effect of vaginal oxytocin gel versus placebo on dyspareunia and found mixed results. Fianu Jonasson (2020)¹³⁰ (N=157) used a 4-point scale (0=none to 3=severe) at 12 weeks and found no statistically significant ($P>0.05$) difference in mean change for vaginal oxytocin versus placebo (oxytocin -0.88 vs. placebo -1.05). A second trial¹³¹ (N=86) reported a statistically significant ($P<0.05$)

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improvement in the vaginal oxytocin arm compared with the placebo arm after 8 weeks, as measured by 2 different tools in 2 publications.^{131, 146} Zohrabi (2020)¹³¹ used a study checklist to record the proportion of patients experiencing no dyspareunia after 8 weeks (oxytocin 89% vs. placebo 7%), mild (11% vs. 45%), moderate (0 vs. 31%), or severe (0 vs. 17%) dyspareunia. Abedi (2020)¹⁴⁶ also found a significant improvement in the mean FSFI pain domain score (0 (worst) to 6 (best)) for vaginal oxytocin compared with placebo (oxytocin 3.3 to 5.53 vs. placebo 3.07 to 3.62). Due to study limitations, imprecision, and inconsistency, we conclude that the evidence is very uncertain on the effect of oxytocin gel on dyspareunia compared with placebo gel (very low COE).

3.3.2.4.1.5 Change in MBS

3.3.2.4.1.5.1 Vaginal Oxytocin Vs. Placebo (1 Trial; Total N=157)

One trial¹³¹ (N=157) evaluated the effect of vaginal oxytocin gel versus placebo on patients' self-identified MBS at 12 weeks. At baseline, patients were asked to identify their MBS among vaginal dryness, vulvovaginal irritation/itching, dysuria, or dyspareunia. Fianu Jonasson (2020) observed no significant ($P>0.05$) difference in mean change over 12 weeks on a 4-point severity scale (0=none to 3=severe) between the oxytocin gel and placebo arms (oxytocin -1.16 vs. placebo -1.28). Despite concerns with imprecision, we conclude that oxytocin probably results in little to no difference in MBS compared with placebo gel (moderate COE).

3.3.2.4.1.6 QoL (i.e., Distress, Bother, or Interference of Genitourinary Symptoms)

No trials evaluated the effect of vaginal oxytocin on QoL.

3.3.2.4.1.7 Satisfaction With Treatment

No trials evaluated the effect of vaginal oxytocin on treatment satisfaction.

3.3.2.4.1.8 Adverse Effects

Two trials^{130, 131} evaluated the potential harms of vaginal oxytocin. We captured when a trial reported any AE/TEAE ($k=1$), SAEs ($k=1$), discontinuation due to AEs ($k=2$), or clinically relevant, specific AEs ($k=1$). The followup period was either 8 weeks¹³¹ or 12 weeks.¹³⁰ Specific counts (when available) and detailed AE reporting can be found in Appendix Table C.17.

3.3.2.4.1.8.1 Any AE/TEAE

Vaginal Oxytocin Vs. Placebo (1 Trial; Total N=161). One trial¹³⁰ reported rates of participants who experienced any AE/TEAE. Fianu Jonasson (2020)¹³⁰ (N=161) reported n (%) of any AE in each arm but did not provide a statistical comparison between the two arms (oxytocin 32 [39.5] vs. placebo 27 [33.8]).

3.3.2.4.1.8.2 Serious AEs

Vaginal Oxytocin Vs. Placebo (1 Trial; Total N=161). We assessed one trial¹³⁰ of vaginal oxytocin versus placebo that reported SAEs using GRADE and downgraded two levels for imprecision and study limitations. Fianu Jonasson (2020)¹³⁰ (N=161) evaluated SAEs in the oxytocin (1 SAE "assessed as unlikely [to be] related to the study compound") and placebo groups (0 SAEs). No information was provided regarding statistical significance versus placebo.

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We conclude that vaginal oxytocin may result in little to no difference in SAEs compared with placebo (low COE).

3.3.2.4.1.8.3 Discontinuation Due to AEs

Vaginal Oxytocin Vs. Placebo (2 Trials; Total N=257). Two trials^{130, 131} (N=257) of vaginal oxytocin versus placebo reported discontinuation due to AEs. In Zohrabi (2020),¹³¹ vaginal burning caused one participant in each arm to withdraw from the trial. Fianu Jonasson (2020)¹³⁰ reported the number of participants who discontinued treatment due to unspecified AEs (n=3, all in vaginal oxytocin group) and assessed the AEs as possibly related (n=1), unlikely related (n=1), and not related (n=1) to treatment.

3.3.2.4.1.8.4 Specific AEs

Vaginal Oxytocin Vs. Placebo (1 Trial; Total N=161). One trial¹³⁰ of vaginal oxytocin versus placebo reported on specific AEs. Fianu Jonasson (2020)¹³⁰ (N=161) recorded the most frequently reported AEs (vaginal discharge, urinary tract infection, and vaginal odor) but did not provide the data. Despite no major differences in AE reporting between the two treatment arms, nearly twice as many participants in the vaginal oxytocin gel arm reported the most frequent AEs compared with the placebo arm.

3.3.2.4.2 Endometrial Safety

Fianu Jonasson (2020)¹³⁰ (N=161) measured endometrial thickness with transvaginal ultrasound (TVU). No safety concerns were identified in participants treated with either oxytocin gel or placebo. Detailed results were not reported.

3.3.2.4.3 Other Outcomes

One trial¹³¹ found a significant improvement in sexual function after 8 weeks of treatment with vaginal oxytocin compared with placebo using the FSFI total. Two trials^{130, 131} evaluated the effect of vaginal oxytocin versus placebo on vaginal atrophy based on either the percentage of superficial cells on vaginal cytology or the VMI, respectively. The first trial¹³⁰ found no statistically significant difference between the two arms in change from baseline to week 12, while the second trial¹³¹ reported that the number of superficial cells increased significantly in the oxytocin gel arm compared with placebo. Detailed results can be found in Appendix Table C.16.

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3.3.2.5 SERMs

3.3.2.5.1 COMMA Outcomes

Table 8. Summary of COMMA outcomes, findings, and certainty of evidence for SERMs

Outcome	Intervention Vs. Comparator Followup	Study Design: No. Trials (N) Direction of Effect	Findings	Certainty of Evidence	Summary Statement
Vulvovaginal dryness	Oral ospemifene vs. placebo 12 weeks	RCT: 3 (1771) ^{132, 133, 136} ↑ 2 trials ↔ 1 trial	Three trials found mixed effects of oral ospemifene compared with placebo using 2 measurements tools. Two trials ^{132, 136} reported significant improvement in either the FSFI lubrication domain or a 4-point severity scale, while the third trial ¹³³ reported no significant difference in mean change on a 4-point severity scale.	Low ⊕⊕○○ ^{a,b}	Oral ospemifene may improve vulvovaginal dryness compared with placebo.
	Oral raloxifene vs. placebo* 3 or 6 months	RCT: 2 (274) ^{138, 139} ↔ 2 trials	Two trials found no significant effect of oral raloxifene compared with placebo using a 4-point severity scale.	Low ⊕⊕○○ ^{b,c}	Oral raloxifene may result in little to no difference in vulvovaginal dryness compared with placebo.
Vulvovaginal discomfort/ irritation	Oral ospemifene vs. placebo 12 weeks	RCT: 1 (627) ¹³² ↔ 1 trial	One trial found no significant effect of oral ospemifene compared with placebo using a 4-point severity scale.	High ⊕⊕⊕⊕	Oral ospemifene results in little to no difference in vulvovaginal irritation compared with placebo.
	Oral raloxifene vs. placebo* 3 or 6 months	RCT: 2 (274) ^{138, 139} ↔ 2 trials	Two trials found no significant effect of oral raloxifene compared with placebo using a 4-point severity scale.	Low ⊕⊕○○ ^{b,c}	Oral raloxifene may result in little to no difference in vulvovaginal discomfort/ irritation compared with placebo.
Dysuria	Oral raloxifene vs. placebo* 3 or 6 months	RCT: 2 (274) ^{138, 139} ↔ 2 trials	Two trials found no significant effect of oral raloxifene compared with placebo using a 4-point severity scale.	Low ⊕⊕○○ ^{b,c}	Oral raloxifene may result in little to no difference in dysuria compared with placebo.

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Outcome	Intervention Vs. Comparator Followup	Study Design: No. Trials (N) Direction of Effect	Findings	Certainty of Evidence	Summary Statement
Dyspareunia	Oral ospemifene vs. placebo 12 weeks	RCT: 3 (2062) ^{132, 136, 147} ↑ 2 trials ↕ 1 trial	Three trials found consistent effects of oral ospemifene compared with placebo using 2 measurement tools (either the FSFI pain domain ^{132, 147} or a 4-point severity scale ¹³⁶). All trials reported a significant improvement after 60 mg ospemifene compared with placebo, though one trial ¹³⁶ also evaluated 30 mg ospemifene and found no significant effect compared with placebo.	Low ⊕⊕○○ ^{a,b}	Oral ospemifene may improve dyspareunia compared with placebo.
	Oral raloxifene vs. placebo* 3 or 6 months	RCT: 2 (187) ^{139, 148} ↔ 2 trials	Two trials found no significant effect of oral raloxifene compared with placebo using a 4-point severity scale.	Low ⊕⊕○○ ^{b,c}	Oral raloxifene may result in little to no difference in dyspareunia compared with placebo.
QoL	Oral BZA vs. placebo 12 weeks	RCT: 1 (215**) ¹⁴⁹ ↓ 1 trial	One trial reported that the total MENQOL score for both arms improved, though the change in total score was significantly smaller for oral bazedoxifene compared with placebo.	Low ⊕⊕○○ ^{b,c}	Oral BZA may improve QoL less than placebo.
Satisfaction with treatment	Oral ospemifene vs. Placebo 12 weeks	RCT: 1 (419) ¹³² ↑ 1 trial	One trial reported a significantly greater mean score on a 5-point Likert scale for oral ospemifene compared with placebo.	High ⊕⊕⊕⊕	Oral ospemifene results in higher treatment satisfaction compared with placebo.
	Oral BZA or raloxifene* vs. placebo 12 weeks	RCT: 2 (393**) ^{138, 149} ↔ 1 trial ? 1 trial	One bazedoxifene trial ¹⁴⁹ reported % of satisfied participants, with significantly more in the placebo arm. The raloxifene trial ¹³⁸ found an increase in satisfaction across all groups on a 7-point Likert scale compared to baseline but did not provide a statistical comparison of change over time between groups.	Very low ⊕○○○ ^{b,c,d}	The evidence is very uncertain on the effect of oral BZA or raloxifene on treatment satisfaction compared with placebo.
Adverse effects (SAEs)	Oral ospemifene vs. placebo 12 weeks	RCT: 4 (2372) ^{132-134, 136} ? 4 trials	Two trials ^{132, 136} reported more SAEs in the ospemifene group than in the placebo group. The other two trials ^{133, 134} reported either fewer or the same amount of SAEs in the ospemifene group than in the placebo group. None of the trials provided statistical tests of comparisons.	Low ⊕⊕○○ ^{b,d}	Oral ospemifene may result in little to no difference in SAEs compared with placebo.

Abbreviations: BZA=bazedoxifene; CI=confidence interval; COMMA=Core Outcomes in Menopause; FSFI=Female Sexual Function Index; GU=genitourinary; MBS=most bothersome symptom; MENQOL=Menopause-Specific Quality of Life; NR=not reported; OIS=optimal information size; QoL=quality of life; RCT=randomized controlled trial; RoB=risk of bias; SAE=serious adverse effect; SAQ=Sexual Activity Questionnaire; SD=standard deviation; SERM=selective estrogen receptor modulator

*Both raloxifene trials were placebo-controlled. One trial¹³⁸ was a 4-arm trial that investigated the effect of oral raloxifene vs. placebo on the response to either vaginal estrogen or vaginal moisturizer. The other trial¹³⁹ was a 2-arm trial that investigated the effect of adding oral raloxifene vs. placebo to vaginal estrogen.

**Total N includes only bazedoxifene and placebo arms from Bachmann (2010),¹⁴⁹ which reported results for Kagan (2010).¹³⁷

Direction of effect

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↑: Intervention group had a statistically significantly better outcome than comparison group (e.g., improved symptoms, higher treatment satisfaction)

↓: Intervention group had a statistically significantly worse outcome than comparison group (e.g., worsened symptoms, lower treatment satisfaction)

↔: No statistically significant difference between groups

?: No statistical comparison of change in time between groups provided

Certainty of evidence (COE)

High (⊕⊕⊕⊕): We are very confident that the true effect lies close to that of the estimate of the effect.

Low (⊕⊕○○): Our confidence in the effect estimate is limited; the true effect may be substantially different from the effect estimate.

Very low (⊕○○○): We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

^aDowngraded one level for inconsistency (effect varied across trials)

^bDowngraded one level for study limitations (one or more trials assessed as some concerns RoB)

^cDowngraded one level for imprecision (total sample size less than OIS of 400)

^dDowngraded one level for study limitations (one or more trials did not provide adequate statistical reporting)

3.3.2.5.1.1 Vulvovaginal Dryness

3.3.2.5.1.1.1 Oral Ospemifene Vs. Placebo (3 Trials; Total N=1771)

Three trials^{132, 133, 136} (N=1771) evaluated the effect of oral ospemifene versus placebo on vulvovaginal dryness at 12 weeks. All 3 trials observed an improvement from baseline in symptom severity using a 4-point scale (0=none to 3=severe), though only 2 found a statistically significant difference in change from baseline between arms. Archer (2019),¹³² Bachmann (2010),¹³⁶ and Portman (2014)¹³³ assessed only participants with at least moderate to severe vulvovaginal dryness, and for whom dryness was their MBS. All trials randomized participants to an oral ospemifene 60 mg tablet or placebo; Bachmann (2010)¹³⁶ also evaluated an oral ospemifene 30 mg tablet. Archer (2019)¹³² (N=631) and Bachmann (2010)¹³⁶ (N=826) reported a statistically significant ($P<0.05$) improvement for oral ospemifene compared with placebo (Archer 2019: 60 mg -1.29 vs. placebo -0.91; Bachmann 2010: 30 mg -1.22 and 60 mg -1.26 vs. placebo -0.84), while Portman (2014)¹³³ (N=314) reported a non-significant ($P>0.05$) difference (60 mg -1.3 vs. placebo -1.1). Archer (2019)¹³² also reported a statistically significant ($P<0.05$) improvement in the FSFI lubrication domain (0 (worst) to 6 (best)) from baseline to 12 weeks compared with placebo (difference of least square mean [LSM] 0.40). Due to inconsistency and study limitations, we conclude that oral ospemifene may improve vulvovaginal dryness compared with placebo (low COE).

3.3.2.5.1.1.2 Oral Raloxifene Vs. Placebo (2 Trials; Total N=274)

Two trials^{138, 139} (N=274) evaluated the effect of oral raloxifene versus placebo on vulvovaginal dryness at either 3 or 6 months. Parsons (2003)¹³⁸ (N=187) excluded women at a high risk of breast or gynecological cancers and women who had previously undergone hysterectomy, and evaluated the effect of oral raloxifene versus a matching placebo on the response to conjugated estrogens cream or non-hormonal moisturizer at 3 months. Pinkerton (2003)¹³⁹ (N=87) excluded women with a history of breast or endometrial cancer and who had undergone prior hysterectomy. The study team verified signs of vaginal atrophy via pelvic examination at baseline and investigated the effect of adding oral raloxifene versus placebo to a low-dose vaginal estradiol ring for 6 months. Both trials used a 4-point severity scale to assess vulvovaginal dryness and stated that there was no significant difference between groups, though neither trial reported data. Kessel (2003)¹⁴⁸ reported on dryness outcomes for a sexually active

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subset (N=82) of Parsons (2003)¹³⁸ and reported the difference between arms based on a Sexual Activity Questionnaire (SAQ) question (“*How frequently did you notice dryness [during intercourse]?*”; 0=very much to 3=not at all) was not statistically significant ($P>0.05$) (raloxifene 0.77 vs. placebo 0.98). Due to imprecision and study limitations, we conclude that oral raloxifene may result in little to no difference in vulvovaginal dryness compared with placebo (low COE).

3.3.2.5.1.2 Vulvovaginal Discomfort/Irritation

3.3.2.5.1.2.1 Oral Ospemifene Vs. Placebo (1 Trial; Total N=627)

One trial¹³² (N=627) evaluated the effect of oral ospemifene versus placebo on vulvovaginal irritation at 12 weeks. Archer (2019)¹³² used a 4-point severity scale (0=none to 3=severe) and found no significant ($P>0.05$) difference in score change for 60 mg ospemifene compared with placebo (60 mg -1.4 vs. placebo -1.4). We conclude that ospemifene results in little to no difference in vulvovaginal discomfort/irritation compared with placebo (high COE).

3.3.2.5.1.2.2 Oral Raloxifene Vs. Placebo on Vaginal Estrogen or Moisturizer (2 Trials; Total N=274)

Two trials^{138, 139} (N=274) evaluated the effect of oral raloxifene versus placebo on vaginal itching at either 3 or 6 months. Both Parsons (2003)¹³⁸ (N=187) and Pinkerton (2003)¹³⁹ (N=87) used a 4-point severity scale to assess vaginal itching and stated that there was no significant difference between groups, though neither trial reported data. Due to imprecision and study limitations, we conclude that oral raloxifene may result in little to no difference in vulvovaginal discomfort/irritation compared with placebo (low COE).

3.3.2.5.1.3 Dysuria

3.3.2.5.1.3.1 Oral Raloxifene Vs. Placebo (2 Trials; Total N=274)

Two trials^{138, 139} (N=274) evaluated the effect of oral raloxifene versus placebo on dysuria at either 3 or 6 months. Both Parsons (2003)¹³⁸ (N=187) and Pinkerton (2003)¹³⁹ (N=87) used a 4-point severity scale to assess dysuria and stated that there was no significant difference between groups, though neither trial reported data. Due to imprecision and study limitations, we conclude that oral raloxifene may result in little to no difference in dysuria compared with placebo (low COE).

3.3.2.5.1.4 Dyspareunia

3.3.2.5.1.4.1 Oral Ospemifene Vs. Placebo (3 Trials; Total N=2062)

Three trials^{132, 134, 136} (4 publications^{132, 134, 136, 147}) (N=2062) evaluated the effect of oral ospemifene versus placebo on dyspareunia at 12 weeks. All trials found a significant ($P<0.05$) improvement after 60 mg ospemifene compared with placebo, though Bachmann (2010)¹³⁶ did not find a significant difference between 30 mg ospemifene and placebo. Bachmann (2010)¹³⁶ (N=826) and Portman (2013)¹³⁴ (N=605) used a 4-point severity scale (0=none to 3=severe) to assess only participants for whom dyspareunia was their MBS (Bachmann 2010: 30 mg -1.02 and 60 mg -1.19 vs. placebo -0.89; Portman 2013: 60 mg -1.5 vs. placebo -1.2). Archer (2019)¹³² (N=631) used both a 4-point severity scale (60 mg -1.6 vs. placebo -1.2) and the FSFI pain domain (0 (worst) to 6 (best)) (difference of LSM 0.45). Constantine (2015)¹⁴⁷ is a secondary

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paper that reports overarching findings for 2 strata from related trials described in Portman (2013)¹³⁴ (dyspareunia stratum) and Portman (2014)¹³³ (dryness stratum). Though the FSFI pain domain improved significantly for the full intention-to-treat trial population (N=919)¹⁴⁷ and the dyspareunia stratum (n=605),¹³⁴ it did not improve significantly among the dryness stratum (n=314).¹³³ Due to inconsistency and study limitations, we conclude that oral ospemifene may improve dyspareunia compared with placebo (low COE).

3.3.2.5.1.4.2 Oral Raloxifene Vs. Placebo on Vaginal Estrogen or Moisturizer (2 Trials; Total N=274)

Two trials^{138, 139} (N=274) evaluated the effect of oral raloxifene versus placebo on dyspareunia at either 3 or 6 months. Both Parsons (2003)¹³⁸ (N=187) and Pinkerton (2003)¹³⁹ (N=87) used a 4-point severity scale to assess dyspareunia and stated that there was no significant difference between groups, though neither trial reported data. Parsons (2003)¹³⁸ also asked a subset of sexually active participants (N=82) an SAQ question (“*Did you feel pain on penetration?*”; 0=very much to 3=not at all) and found no significant (P>0.05) difference between arms (raloxifene 0.77 vs. placebo 0.86), as reported in a publication by Kessel (2003).¹⁴⁸ Due to imprecision and study limitations, we conclude that oral raloxifene may result in little to no difference in dyspareunia compared with placebo (low COE).

3.3.2.5.1.5 Change in MBS

No trials evaluated the effect of SERMs on a composite MBS.

3.3.2.5.1.6 QoL (i.e., Distress, Bother, or Interference of GSM symptoms)

3.3.2.5.1.6.1 Oral Bazedoxifene Vs. Placebo (1 Trial; Total N=215)

One trial¹³⁷ (N=215) evaluated the effect of oral bazedoxifene on menopause-related QoL compared with placebo at 12 weeks. Bachmann (2010)¹⁴⁹ published QoL outcomes for Kagan (2010)¹³⁷ and reported a significantly (P<0.05) smaller change in total MENQOL score (1 (best) to 8 (worst)) for bazedoxifene compared with placebo (bazedoxifene -0.37 vs. placebo -0.67). Due to study limitations and imprecision, we conclude that bazedoxifene may improve QoL less than placebo (low COE).

3.3.2.5.1.7 Satisfaction With Treatment

3.3.2.5.1.7.1 Oral Ospemifene Vs. Placebo (1 Trial; Total N=419)

One trial¹³² (N=419) evaluated treatment satisfaction after 12 weeks of oral ospemifene versus placebo. Archer (2019) used a 5-point Likert scale and found a significantly (P<0.05) greater proportion of oral ospemifene participants rated their treatment satisfaction as “very/moderately satisfied” compared with placebo participants (ospemifene 69.7% vs. placebo 53.5%). Oral ospemifene results in higher satisfaction with treatment compared with placebo (high COE).

3.3.2.5.1.7.2 Oral Bazedoxifene Vs. Placebo OR Oral Raloxifene Vs. Placebo With Vaginal Estrogen or Moisturizer (2 Trials; Total N=393)

One trial¹³⁷ (N=215) evaluated treatment satisfaction after 12 weeks of oral bazedoxifene versus placebo. Kagan (2010)¹³⁷ used the Menopause Symptoms Treatment Satisfaction Questionnaire (0 (worst) to 4 (best)) and found a lower proportion of bazedoxifene participants

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reported overall satisfaction compared with placebo participants (bazedoxifene 40.4% vs. placebo 47.4%, statistical comparison not reported), as reported in a publication by Bachmann (2010).¹⁴⁹

One trial¹³⁸ (N=178) evaluated treatment satisfaction after 12 weeks of either oral raloxifene or placebo in combination with conjugated estrogens cream or non-hormonal moisturizer. Parsons (2003)¹³⁸ used a 7-point Likert scale (1 (worst) to 7 (best)) and found an increase in treatment satisfaction across all arms, with no significant differences between raloxifene and placebo treatment pairs. Individual arm values were not reported, though the trial authors noted that the median score across treatment arms was 4.00 at baseline (ie, neutral to mild satisfaction), which increased by 1.00 after treatment.

Due to study limitations and imprecision, we conclude that the evidence is very uncertain on the effect of oral bazedoxifene or raloxifene on treatment satisfaction compared with placebo (low COE).

3.3.2.5.1.8 Adverse Effects

Seven trials^{132-137, 139} (8 publications^{132-137, 139, 150}) evaluated the potential harms of SERMs (k=5 oral ospemifene, k=1 bazedoxifene, k=1 raloxifene). We captured when a trial reported any AE/TEAE (k=6), SAEs (k=6), discontinuation due to AEs (k=7), or a clinically relevant, specific AE (k=5). Most of the oral ospemifene trials assessed harms at 12 weeks; one trial¹⁵⁰ conducted a safety extension up to 52 weeks and another trial¹³⁵ also evaluated outcomes at 52 weeks. The bazedoxifene trial¹³⁷ followed up at 12 weeks, while the raloxifene trial¹³⁹ evaluated harms at 26 weeks. Results are reported below by these four categories, then type of comparison. Specific counts (when available) and detailed AE reporting can be found in Appendix Table C.19.

3.3.2.5.1.8.1 Any AE/TEAE

Oral Ospemifene Vs. Placebo (5 Trials; Total N=2372 at 12 weeks, N=606 at 52 weeks).

Four trials^{132-134, 136} (N=2372) of oral ospemifene versus placebo reported rates of participants who experienced any AE/TEAE during a 12-week treatment period. Archer (2019) (60 mg 35.3% vs. placebo 33.2%),^{132, 136} Portman (2013) (61.4% vs. 51.0%),¹³⁴ and Portman (2014)^{133, 135} (65.0% vs. 50.6%) reported a higher rate of AEs in the 60 mg ospemifene group than in the placebo group. Bachmann (2010)¹¹⁹ reported more AEs in both the 30 mg arm and the 60 mg group compared with placebo (30 mg 64.5% and 60 mg 59.4% vs. placebo 52.2%). None of the trials provided statistical tests of comparison.

Two trials^{135, 150} (N=606) reported AEs at 52 weeks. Simon (2013),¹⁵⁰ a safety extension of Bachmann (2010),¹³⁶ found that a higher proportion of participants in both ospemifene arms experienced AEs than placebo participants (30 mg 61.3% and 60 mg 63.8% vs. placebo 44.9%). Goldstein (2014)¹³⁵ also reported a higher rate of AEs in the 60 mg ospemifene group than in the placebo group (84.6% vs. 75.8%). Neither trial provided statistical tests of comparison.

Oral Bazedoxifene Vs. Placebo (1 Trial; Total N=215). One trial¹³⁷ of oral bazedoxifene versus placebo reported rates of participants who experienced any AE/TEAE during a 12-week treatment period. Kagan (2010)¹³⁷ (N=215) observed a higher rate of AEs in the 20 mg bazedoxifene arm than the placebo arm (81.8% vs. 71.4%; P>0.05).

3.3.2.5.1.8.2 Serious AEs

Oral Ospemifene Vs. Placebo (5 Trials; Total N=2372 at 12 Weeks, N=606 at 52 Weeks).

We assessed the four trials^{132-134, 136} (N=2372) of oral ospemifene versus placebo that reported

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SAEs at 12 weeks using GRADE and downgraded two levels for study limitations. Archer (2019)^{132, 136} reported a higher rate of SAEs in the 60 mg ospemifene group than in the placebo group (1.6% vs. 1.0%), though none of the SAEs were considered related to treatment. Bachmann (2010)¹¹⁹ reported more SAEs in the 30 mg arm but not the 60 mg group compared with placebo (30 mg 1.8% and 60 mg 0% vs. placebo 1.5%). Portman (2014)^{133, 135} reported a lower rate of SAEs in the 60 mg ospemifene group than in the placebo group (1.3% vs. 1.9%); one of the SAEs (a deep venous thrombosis) in the ospemifene group was considered probably related to treatment. Portman (2013)¹³⁴ observed the same rate of SAEs in both groups (1.3%) and did not consider any SAE to be related to treatment. None of the trials provided statistical tests of comparison. We conclude that oral ospemifene may result in little to no difference in SAEs compared with placebo (low COE).

Two trials^{135, 150} (N=606) reported SAEs at 52 weeks. Simon (2013),¹⁵⁰ a safety extension of Bachmann (2010),¹³⁶ found that a higher proportion of participants in both ospemifene arms experienced SAEs than placebo participants (30 mg 3.2% and 60 mg 7.2% vs. placebo 2.0%). Goldstein (2014)¹³⁵ reported a lower rate of SAEs in the 60 mg ospemifene group than in the placebo group (4.9% vs. 6.5%). Neither trial provided statistical tests of comparison.

3.3.2.5.1.8.3 Oral Bazedoxifene Vs. Placebo (1 Trial; Total N=215). One trial¹³⁷ of oral bazedoxifene versus placebo reported rates of participants who experienced any SAEs during a 12-week treatment period. Kagan (2010)¹³⁷ (N=215) reported that more placebo participants experienced an SAE than 20 mg bazedoxifene participants (n=4 [3.0%] vs. n=2 [0.9%]) but did not provide a statistical test of comparison. None of the SAEs were considered related to the study medication.

3.3.2.5.1.8.3 Discontinuation Due to AEs

Oral Ospemifene Vs. Placebo (5 Trials; Total N=2372 at 12 Weeks, N=606 at 52 Weeks).

Four trials^{132-134, 136} (N=2372) of oral ospemifene versus placebo reported trial^{132, 136} or treatment^{133, 134} discontinuation due to AEs during a 12-week treatment period. Archer (2019)^{132, 136} reported n (%) of participants who discontinued the trial due to unspecified AEs (5 [1.6] vs. 3 [1.0]) and noted that 3 (0.9%) 60 mg ospemifene participants and 1 (0.1%) placebo participant discontinued the trial due to hot flushes. Bachmann (2010)¹¹⁹ also reported n (%) of participants who discontinued the trial due to unspecified AEs (30 mg 15 [5.3] and 60 mg 13 [4.7] vs. placebo 13 [4.9]) and highlighted discontinuation due to hot flushes (30 mg 3 [1.1] and 60 mg 1 [0.4] vs. placebo 2 [0.7]). Portman (2013)¹³⁴ and Portman (2014)^{133, 135} reported treatment discontinuation due to AEs for 60 mg ospemifene and placebo (14 [4.6]/12 [7.5] vs. placebo 10 [3.3]/5 [3.2]). Both also noted the number of ospemifene participants who discontinued treatment due to hot flushes (n=1/n=3).

Two trials^{135, 150} (N=606) reported treatment discontinuation due to AEs over 52 weeks. Simon (2013),¹⁵⁰ a safety extension of Bachmann (2010),¹³⁶ and Goldstein (2014)¹³⁵ both reported n (%) of total participants (30 mg 3 [4.8] and 60 mg 4 [5.8]/49 [13.5] vs. placebo 1 [2.0]/6 [9.7]) and those who discontinued due to hot flushes (1.6% overall/60 mg 8 [2.2] vs. placebo 0).

Oral Bazedoxifene Vs. Placebo (1 Trial; Total N=215). One trial¹³⁷ of oral bazedoxifene versus placebo reported treatment discontinuation due to AEs over 12 weeks. Kagan (2010)¹³⁷

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(N=215) reported that rates were not significantly different among treatment groups (20 mg bazedoxifene 8 [7.3] vs. placebo 7 [6.7], $P>0.05$).

Oral Raloxifene Vs. Placebo on Vaginal Estrogen (1 Trial; Total N=91). One trial¹³⁹ investigated the effect of oral raloxifene versus placebo on a low-dose vaginal estradiol ring and reported trial discontinuation due to AEs. Pinkerton (2003)¹³⁹ (N=91) reported that four total participants withdrew from the trial because of AEs (raloxifene n=2 [hypertonia and moniliasis] vs. placebo n=2 [edema and vaginitis], $P>0.05$).

3.3.2.5.1.8.4 Specific AEs

Oral Ospemifene Vs. Placebo (4 Trials; Total N=1767 at 12 Weeks, N=606 at 52 Weeks).

Three trials^{132, 134, 136} (N=1767) of oral ospemifene versus placebo reported specific AEs observed over the 12-week treatment period. In Archer (2019)¹³², hot flushes (60 mg ospemifene 6.3% vs. placebo 2.6%) were the most frequent AE. Other common AEs included UTIs (60 mg 2.2% vs. placebo 3.2%), headache (60 mg 1.6% vs. placebo 2.3%). Bachmann (2010)¹³⁶ also reported the proportion of participants in the ospemifene 30 mg, 60 mg, and placebo groups who experienced hot flushes (30 mg 9.6%, 60 mg 8.3% vs. placebo 3.4%), UTI (30 mg 4.6%, 60 mg 7.2% vs. placebo 2.2%), and headache (30 mg 6.0%, 60 mg 2.5% vs. placebo 5.2%). Portman (2013)¹³⁴ evaluated 60 mg ospemifene versus placebo and reported common AEs including hot flushes (6.6% vs. 4.3%), UTI (5.6% vs. 3.6%), headache (3.3% vs. 4.0%), vaginal discharge (4.6% vs. 0.7%), vaginal candidiasis (4.6% vs. 0.3%), and vulvovaginal mycotic infection (4.3% vs. 0.3%).

Two trials^{135, 150} of ospemifene versus placebo provided 52-week follow up safety data. Goldstein (2014)¹³⁵ found that common AEs included hot flushes (60 mg 12.6% vs. placebo 6.5%; 1.9% of ospemifene recipients rated their hot flushes severe), UTI (60 mg 16.8% vs. placebo 24.2%), and vaginal candidiasis (60 mg 9.6% vs. placebo 3.2%). Vaginal discharge, insomnia, and cystitis were each reported by n=19-20 (>5%) of 60 mg ospemifene participants and 0 placebo participants. Simon (2013),¹⁵⁰ a safety extension of Bachmann (2010),¹³⁶ reported the proportion of participants in the ospemifene 30 mg, 60 mg, and placebo groups who experienced hot flushes (30 mg 3.2%, 60 mg 7.2% vs. placebo 4.1%) and UTI (30 mg 6.5%, 60 mg 8.7% vs. placebo 8.2%).

3.3.2.5.2 Endometrial Safety

Four trials^{132, 134-136} (6 publications^{132-136, 150}) (N=2411) of oral ospemifene versus placebo monitored endometrial safety with both transvaginal ultrasound and endometrial biopsy. TVU measurements for ospemifene participants increased by an average of 0.4 to 1.1 mm; placebo group mean changes ranged from -0.23 to 1.1 mm. In two trials, 6 percent of ospemifene participants had an endometrial lining ≥ 5 mm at 12 weeks¹³³ or 52 weeks¹³⁵ (compared with <2% of placebo participants). Endometrial hyperplasia was seen in one trial participant across all ospemifene trials,¹³⁵ no endometrial cancer was observed. Three trials^{132, 135, 150} provided more detailed endometrial biopsy outcomes at followup. Proliferative endometrial findings (weakly proliferative, active proliferative, atypical epithelial proliferation, and proliferative pattern, disordered type) were found almost exclusively in ospemifene participants (30 total cases across 3 trials), compared with one case of weakly proliferative endometrium in placebo.

One bazedoxifene and one raloxifene trial assessed endometrial safety with both transvaginal ultrasound and endometrial biopsy. The raloxifene trial¹³⁹ (N=91) reported no significant difference between intervention and placebo groups for change in endometrial lining

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thickness from baseline to 6 months, and no hyperplasia, carcinoma, or “clinically significant endometrial proliferation” in either group. The bazedoxifene trial¹³⁷ (N=215) did not report any endometrial safety results.

3.3.2.5.3 Other Outcomes

Three trials^{132, 138, 147} (3 publications^{132, 147, 148}) evaluated the effect of SERMs on sexual function. Archer (2019),¹³² Portman (2013),¹³⁴ and Portman (2014)¹³³ (published in Constantine [2015]¹⁴⁷) measured the effect of oral ospemifene versus placebo on change in FSFI total score from baseline to 12 weeks. Kessel (2003)¹⁴⁸ evaluated the effect of either oral raloxifene or placebo in combination with conjugated estrogens cream or non-hormonal moisturizer, assessed 3 domain scores from the SAQ at 3 months, and reported on sexual function outcomes for Parsons (2003).¹³⁸ Both ospemifene trials reported significant improvement in the ospemifene arm compared with the placebo arm, while the raloxifene trial only reported on changes from baseline and found a statistically significant change for raloxifene and placebo.

Six trials^{132-136, 138} (7 publications^{133-136, 138, 150, 151}) evaluated the effect of SERMs on vaginal atrophy using objective measures like vaginal pH, a vaginal smear (i.e., VMI/vaginal maturation value [VMV]) or a 4-point scale during a gynecological exam). All 5 ospemifene trials^{10-12, 29, 33, 34} observed a significant reduction in atrophy after ospemifene compared with placebo, while the single raloxifene trial¹³⁸ found no significant differences between the raloxifene and placebo arms. Bachmann (2010)¹³⁶ reported percentage of superficial and parabasal cells at baseline and the change after 12 weeks of treatment, while a safety extension¹⁵⁰ of this trial reported observed changes in petechiae, pallor, friability, vaginal dryness, and vaginal redness. Goldstein (2019)¹⁵¹ used the Vaginal Health Index (VHI) during visual examination and reported on 12-week vaginal atrophy outcomes for Archer (2019),¹³² which also reported VMI and pH. Goldstein (2014),¹³⁵ Portman (2013),¹³⁴ and Portman (2014)¹³³ all reported measures of vaginal maturation and vaginal pH. Parsons (2003)¹³⁸ reported results on two measures of vaginal atrophy at 3 months, including change in the VMV and evaluations of the vaginal mucosa with five domains. Detailed results can be found in Appendix Table C.18.

3.3.2.6 Testosterone

3.3.2.6.1 COMMA Outcomes

Table 9. Summary of COMMA outcomes, findings, and certainty of evidence for testosterone

Outcome	Intervention Vs. Comparator Followup	Study Design: No. Trials (N) Direction of Effect	Findings	Certainty of Evidence	Summary Statement
Vulvovaginal dryness	Vaginal testosterone vs. placebo 12 or 26 weeks	RCT: 2 (84*) ^{84, 125} ↔ 1 trial ? 1 trial	Two trials used the FSFI lubrication domain; one trial ¹²⁵ found a non-significant difference between arms after 26 weeks, while the other trial ⁸⁴ observed improvement in both arms after 12 weeks but did not provide a statistical comparison between arms for change over time.	Very low ⊕○○○ ^{a,c}	The evidence is very uncertain on the effect of vaginal testosterone on vulvovaginal dryness compared with placebo.

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Outcome	Intervention Vs. Comparator Followup	Study Design: No. Trials (N) Direction of Effect	Findings	Certainty of Evidence	Summary Statement
	Systemic testosterone plus systemic estrogen vs. systemic estrogen alone 8 weeks or 12 months	RCT: 2 (130) ^{113, 114} ↔ 1 trial ? 1 trial	Two trials reported either a non-significant difference between arms based on the FSFI lubrication domain after 8 weeks or a proportion of participants who experienced vaginal dryness over 12 months, which was not compared between arms.	Low ⊕⊕○○ ^{a,b}	Systemic estrogen plus systemic testosterone may result in little to no difference in vulvovaginal dryness compared with systemic estrogen alone.
Dyspareunia	Vaginal testosterone vs. placebo 12 or 26 weeks	RCT: 2 (84*) ^{84, 125} ↔ 1 trial ? 1 trial	Two trials used the FSFI pain domain; one trial ¹²⁵ found a non-significant difference between arms after 26 weeks, while the other trial ⁸⁴ observed improvement in both arms after 12 weeks but did not provide a statistical comparison between arms for change over time.	Very low ⊕○○○ ^{a,c}	The evidence is very uncertain on the effect of vaginal testosterone on dyspareunia compared with placebo.
	Systemic testosterone plus systemic estrogen vs. systemic estrogen alone 8 weeks	RCT: 1 (70) ¹¹⁴ ↔ 1 trial	One trial used the FSFI pain domain and reported a non-significant mean change after 8 weeks of treatment with systemic testosterone plus estrogen versus systemic estrogen alone.	Low ⊕⊕○○ ^c	Systemic estrogen plus systemic testosterone may result in little to no difference in dyspareunia compared with systemic estrogen alone.
Adverse effects	Vaginal testosterone vs. placebo 4-12 weeks	RCT: 1 (40*) ¹²³ ? 1 trial	Authors stated that topical testosterone participants did not show androgenic side effects such as acne, increased hair growth, and clitoral hypertrophy but did not provide any data.	Very low ⊕○○○ ^{b,c}	The evidence is very uncertain on the effect of vaginal testosterone on AEs compared with placebo.
	Vaginal testosterone vs. vaginal estrogen 12 weeks	RCT: 1 (76) ⁹⁷ ? 1 trial	Authors reported the treatment-related AEs that occurred in >2% of participants (n, %) but did not provide information on the statistical significance of the difference between arms.	Very low ⊕○○○ ^{b,c}	The evidence is very uncertain on the effect of vaginal testosterone on AEs compared with vaginal estrogen.
	Systemic testosterone + systemic estrogen vs. systemic estrogen alone** 8 weeks	RCT: 2 (140) ^{114, 115} ↔ 1 trial ? 1 trial	Two trials reported patient-reported specific AEs by arm. The first trial ¹¹⁴ observed similar rates of acne, hirsutism, and vaginal bleeding. The second trial ¹¹⁵ reported on acne, with a slightly higher proportion of participants in the testosterone plus estrogen arm compared with the estrogen alone arm. However, the difference between arms was not statistically significant.	Very low ⊕○○○ ^{a,b,d}	The evidence is very uncertain on the effect of testosterone plus estrogen on AEs compared with estrogen alone.

Abbreviations: AE=adverse effect; COMMA=Core Outcomes in Menopause; FSFI=Female Sexual Function Index; GU=genitourinary; MBS=most bothersome symptom; MENQOL=Menopause-Specific Quality of Life; OIS=optimal information size; RCT=randomized controlled trial; RoB=risk of bias; SD=standard deviation

*Total N includes only testosterone and placebo arms from Fernandes (2014)⁸⁴ and Fernandes (2018).¹²³ See Sections 3.3.1 and 3.3.4 for conjugated estrogens cream and polyacrylic acid cream arm results, respectively.

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**Route of delivery for testosterone + estrogen vs. estrogen alone comparison is either transdermal testosterone gel + oral estrogen tablet¹¹⁵ or oral testosterone + oral estrogen.¹¹⁴

Direction of effect

↔: No statistically significant difference between groups

?: No statistical comparison of change in time between groups provided

Certainty of evidence (COE)

Low (⊕⊕○○): Our confidence in the effect estimate is limited; the true effect may be substantially different from the effect estimate.

Very low (⊕○○○): We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

^aDowngraded one level for imprecision (total sample size less than OIS of 400)

^bDowngraded one level for study limitations (one or more trials did not provide adequate statistical reporting)

^cDowngraded two levels for imprecision (total sample size much less than OIS of 400)

^dDowngraded one level for study limitations (one or more trials assessed as some concerns RoB)

3.3.2.6.1.1 Vulvovaginal Dryness

3.3.2.6.1.1.1 Vaginal Testosterone Vs. Placebo (2 Trials; Total N=84)

Two trials^{84, 125} (N=84) evaluated the effect of vaginal testosterone cream versus placebo on vulvovaginal dryness at either 12 or 26 weeks. Results were mixed. Davis (2018)¹²⁵ (N=84) enrolled only women with invasive breast cancer taking aromatase inhibitors. Fernandes (2014)⁸⁴ randomized 80 total participants to 4 arms: vaginal testosterone cream, vaginal conjugated estrogens cream, vaginal polyacrylic acid cream, or vaginal lubricant. Only the testosterone (n=20) and lubricant (ie, placebo) (n=20) arms will be discussed in this section. Detailed results for the estrogen and moisturizer arms are in Sections 3.3.1 and 3.3.4, respectively. Both trials used the FSFI lubrication domain (0 (worst) to 6 (best)) to assess dryness during intercourse. Davis (2018)¹²⁵ (N=44) reported a median change from baseline to 26 weeks for both arms. The difference between arms was non-significant ($P>0.05$) when adjusted for baseline differences (linear regression beta coefficient 0.76). Fernandes (2014)⁸⁴ reported an improvement in the mean score for both arms (testosterone 1.6 to 3.9; placebo 1.9 to 2.88), but did not provide a statistical comparison of change over time between arms. Davis (2018)¹²⁵ also used a 4-point severity scale (0=none to 3=severe) and observed a significant ($P<0.05$) improvement after testosterone compared with placebo (ordinal regression for treatment 0.14). Due to imprecision and study limitations, we conclude that the evidence is very uncertain on the effect of vaginal testosterone cream on vulvovaginal lubrication compared with placebo (very low COE).

3.3.2.6.1.1.2 Oral Testosterone Vs. Placebo on Oral Estrogen (2 Trials; Total N=130)

Two trials^{113, 114} (N=130) evaluated the effect of adding oral testosterone versus placebo to oral estrogen on vulvovaginal dryness at either 8 weeks or 12 months. Tungmunsakulchai (2015)¹¹⁴ (N=70) used the FSFI lubrication domain at 8 weeks and found no significant difference in the change over time for the estrogen plus testosterone arm, compared with estrogen plus placebo (E+T 3.27 to 5.08 vs. E+P 2.80 to 4.64). Penteado (2008)¹¹³ (N=60) recorded the proportion of participants experiencing vaginal dryness at baseline and 12 months and found statistically significant improvement for both the estrogen plus testosterone (81% to 19%) and estrogen alone (67% to 21%) arms but did not report a statistical comparison test of the change from baseline between trial arms. Due to study limitations and imprecision, we conclude that the oral testosterone plus oral estrogen may result in little to no difference in vulvovaginal dryness compared with oral estrogen alone (low COE).

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3.3.2.6.1.2 Vulvovaginal Discomfort/Irritation

No trials evaluated the effect of testosterone on vulvovaginal discomfort/irritation.

3.3.2.6.1.3 Dysuria

No trials evaluated the effect of testosterone on dysuria.

3.3.2.6.1.4 Dyspareunia

3.3.2.6.1.4.1 Vaginal Testosterone Vs. Placebo (2 Trials; Total N=84)

Davis (2018)¹²⁵ and Fernandes (2014)⁸⁴ compared vaginal testosterone versus placebo as described above, evaluated dyspareunia, and found mixed results. Both trials used the FSFI pain domain (0 (worst) to 6 (best)), though at 2 different lengths of followup (26 or 12 weeks). Davis (2018)¹²⁵ (N=44) did not find a statistically significant difference in mean change over time for testosterone compared with placebo (linear regression beta coefficient 0.76), while Fernandes (2014)⁸⁴ (N=40) observed an improvement in mean score for both arms (testosterone 1.5 to 4.3; placebo 2.1 to 3.1) but did not provide a statistical comparison of change over time between arms. However, Davis (2018)¹²⁵ did find a statistically significant ($P<0.05$) improvement for testosterone compared with placebo using a 4-point severity scale (0=none to 3=severe) (ordinal regression for treatment 0.21). Due to imprecision and study limitations, we conclude that the evidence is very uncertain on the effect of vaginal testosterone cream on dyspareunia compared with placebo (very low COE).

3.3.2.6.1.4.2 Oral Testosterone Vs. Placebo on Oral Estrogen (1 Trial; Total N=70)

One trial¹¹⁴ (N=70) evaluated the effect of adding oral testosterone versus placebo to oral estrogen on dyspareunia at 8 weeks. Tungmunsakulchai (2015) used the FSFI pain domain (0 (worst) to 6 (best)) and found no significant ($P>0.05$) difference in the mean score change between arms (E+T 2.33 vs. E+P 2.03). Due to imprecision, we conclude that systemic estrogen plus systemic testosterone may result in little to no difference in dyspareunia compared with systemic estrogen alone (low COE).

3.3.2.6.1.5 Change in MBS

No trials evaluated the effect of testosterone on a composite MBS.

3.3.2.6.1.6 QoL (i.e., Distress, Bother, or Interference of Genitourinary Symptoms)

No trials evaluated the effect of testosterone on QoL.

3.3.2.6.1.7 Satisfaction With Treatment

No trials evaluated the effect of testosterone on treatment satisfaction.

3.3.2.6.1.8 Adverse Effects

Five trials^{84, 97, 98, 114, 115} evaluated the potential harms of both vaginal and systemic testosterone (alone or in combination with estrogen). We captured when a trial reported any AE/TEAE (k=1), SAEs (k=2), discontinuation due to AEs (k=2), or clinically relevant, specific AEs (k=4). Two trials^{98, 123} evaluated safety only to state that no AEs were reported or observed in either trial arm. Specific counts (when available) and detailed AE reporting can be found in Appendix Table C.21.

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3.3.2.6.1.8.1 Any AE/TEAE

Vaginal Testosterone Vs. Placebo (1 Trial; N=38). We used GRADE to assess the one trial⁸⁴ of vaginal testosterone cream versus placebo that recorded side effects as they appeared during 12 weeks of treatment. Fernandes (2014)⁸⁴ (N=38) stated that no androgenic adverse effects were seen but did not provide data or report other AEs. Due to study limitations and imprecision, the evidence is very uncertain on the effect of vaginal testosterone cream compared with placebo on adverse effects (very low COE).

3.3.2.6.1.8.2 Serious AEs

Systemic Testosterone Plus Systemic Estrogen Vs. Systemic Estrogen Alone (2 Trials; Total N=140). Two trials^{114, 115} (N=140) investigated the effect of adding systemic testosterone versus placebo to systemic estrogen and evaluated SAEs, reporting that there were none.

3.3.2.6.1.8.3 Discontinuation Due to AEs

Vaginal Testosterone Vs. Vaginal Estrogen (1 Trial; N=76). One trial⁹⁷ compared vaginal testosterone cream versus vaginal estradiol ring in patients with early-stage breast cancer and reported treatment discontinuation due to AEs. Melisko (2017)⁹⁷ (N=76) reported that one participant discontinued the testosterone cream due to vulvar irritation and one participant discontinued the estradiol ring due to vaginal odor/discomfort.

Systemic Testosterone Plus Systemic Estrogen Vs. Systemic Estrogen Alone (1 Trial; Total N=70). One trial¹¹⁵ investigated the effect of adding systemic testosterone versus placebo to systemic estrogen and reported trial discontinuation due to AEs. Chaikittisilpa (2019)¹¹⁵ (N=70) reported that two participants in both groups discontinued due to nausea.

3.3.2.6.1.8.4 Specific AEs

Vaginal Testosterone Vs. Placebo (1 Trial; Total N=50). One trial⁹⁸ evaluated the effect of vaginal testosterone on vaginal estrogen and monitored specific androgenic AEs like acne, hirsutism, weight gain, and voice change. Raghunandan (2010)⁹⁸ (N=50) stated that vaginal testosterone was not associated with any of the listed side effects but did not provide any data or report any other form of AEs for vaginal testosterone.

Vaginal Testosterone Vs. Vaginal Estrogen (1 Trial; N=76). We used GRADE to assess the one trial⁹⁷ that evaluated vaginal testosterone cream versus vaginal estradiol ring in patients with early-stage breast cancer and monitored AEs during a 12-week period. Melisko (2017)⁹⁷ (N=76) reported TEAEs occurring in >2 percent of patients: vaginal discharge (testosterone: n=2 vs. estradiol: n=4), facial hair growth (n=5 vs. n=1), vulvovaginal itching and/or irritation (n=0 vs. n=4), vaginal odor (n=3 vs. n=0), and UTI/yeast infection (n=3 vs. n=1). However, they did not provide a statistical comparison of the two groups for any TEAE. Due to study limitations and imprecision, the evidence is very uncertain on the effect of vaginal testosterone on AEs compared with vaginal estrogen (very low COE).

Systemic Testosterone Plus Systemic Estrogen Vs. Systemic Estrogen Alone (2 Trials; Total N=140). We used GRADE to assess the two trials^{114, 115} (N=140) that investigated systemic testosterone plus systemic estrogen versus systemic estrogen alone (1 oral testosterone plus oral estrogen¹¹⁴ and 1 transdermal testosterone gel plus oral estrogen¹¹⁵) and reported harms at the end of an 8-week treatment period. Tungmunsakulchai (2015)¹¹⁴ recorded n (%) of participants

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who reported acne (testosterone plus estrogen 6 [17.6] vs. estrogen alone: 5 [14.2]) and hirsutism (3 [8.8] vs. 3 [8.5]) but did not provide a statistical comparison of the two groups. Chaikittisilpa (2019)¹¹⁵ also reported acne proportions (42% vs 29%, $P=0.3$). Due to study limitations and imprecision, the evidence is very uncertain on the effect of systemic testosterone plus systemic estrogen compared with systemic estrogen alone on AEs (very low COE).

3.3.2.6.2 Endometrial Safety

Two trials^{84, 115} ($N=108$) of vaginal or systemic testosterone monitored endometrial thickness with TVU. Chaikittisilpa (2019)¹¹⁵ ($N=70$) a trial of oral estradiol combined with either transdermal testosterone or placebo, reported that endometrial thickness increased in both arms, but the change from baseline to 8 weeks was not significant. Two participants in the oral estrogen alone arm had vaginal bleeding. Fernandes (2014)⁸⁴ ($N=38$) reported that endometrial thickness was not significantly different between vaginal testosterone cream versus placebo at 12 weeks and neither arm had cases of vaginal bleeding. Detailed results can be found in Appendix Table C.21.

3.3.2.6.3 Other Outcomes

All seven testosterone trials assessed sexual function. Three trials¹¹³⁻¹¹⁵ ($N=200$) compared systemic testosterone plus systemic estrogen versus systemic estrogen alone: 2 small trials^{114, 115} in Thailand used the FSFI total at 8 weeks, while the third small trial¹¹³ in Brazil used 3 different measurement tools at 12 months: study interviews, patient monthly calendars, and the Sexual Energy Scale. Chaikittisilpa (2019)¹¹⁵ and Tungmunsakulchai (2015)¹¹⁴ both required an FSFI total score (2 (worst) to 36 (best)) less than 26.5 at baseline for trial inclusion and observed an improvement (ie, increase) in total score from baseline to 8 weeks. Penteado (2008)¹¹³ reported improvements in sexual energy with the addition of oral testosterone to oral estrogen plus medroxyprogesterone, but no improvement in orgasmic capacity. They reported improvements in other parameters, including sexual desire, excitement, and intercourse, for both trial arms over time from baseline to 12 months, but did not provide a statistical test comparing the change between trial arms.

Two trials^{84, 125} ($N=84$) compared vaginal testosterone cream with a placebo, one of which enrolled only women with invasive breast cancer taking aromatase inhibitors.¹²⁵ That trial reported a significant improvement in sexual function outcomes for testosterone compared with placebo using the FSFI satisfaction domain at 26 weeks, as well as the Female Sexual Distress Scale-Revised (FSDS-R) (after adjusting for baseline differences). On the Profile of Female Sexual Function (PFSF), the sexual concerns and responsiveness domains improved statistically significantly more for testosterone compared with placebo at 26 weeks, though other domains (desire, arousal, pleasure, orgasm, and self-image) did not. The other trial⁸⁴ of vaginal testosterone versus placebo found a statistically significant improvement in FSFI total score from baseline 9.9 to 24.9 at 12 weeks for testosterone, while the lubricant group improved from 13.1 to 15.8.

One trial⁹⁷ randomly assigned ($N=76$) women with hormone receptor-positive breast cancer taking aromatase inhibitors to either vaginal testosterone or vaginal estrogen. The trial, described as open-label and “noncomparative,” used the Cancer Rehab Evaluation System (CARES) to measure sexual dysfunction, interest, and satisfaction at baseline, 4, and 12 weeks. Both the vaginal testosterone and vaginal estrogen groups improved in sexual interest and sexual dysfunction, but only the vaginal estrogen group improved on the single-item Cancer

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Rehabilitation Evaluation System sexual satisfaction subscale. The authors did not provide a statistical test comparing the change from baseline in the two trial arms.

Finally, one trial⁹⁸ studied the addition of vaginal testosterone to vaginal estrogen, compared with vaginal estrogen alone or lubricant alone (also described in Section 3.3.1). They used an adapted sexuality score to measure 7 components of sexual function on a scale of 0 to 3, including satisfaction in sexual activities, orgasm, intensity of desire, self-classification of sexual life, frequency of arousal, sexual activity, and sexual fantasies. They reported a significantly better improvement in composite sexuality score from baseline to 12 weeks for the vaginal testosterone plus vaginal estrogen group, compared with either vaginal estrogen alone or with lubricant.

One trial¹²⁵ measured vaginal pH and vaginal epithelial maturation at baseline and 12 weeks among participants with breast cancer taking aromatase inhibitors who were randomized to either vaginal testosterone or placebo cream and reported no difference between the treatment arms. They attributed this finding to the effects of aromatase inhibitors.

One trial⁹⁷ evaluated the effect of vaginal testosterone cream or vaginal estradiol ring on genital signs. Melisko (2017) used a 4-point scale during gynecological examinations at baseline and week 12 and reported changes in rugae, pallor, petechiae, elasticity, and dryness. Changes were characterized as none (0), mild (1), moderate (2), or severe (3) compared with normal epithelium. Both the testosterone cream and estradiol ring reduced signs of vaginal atrophy, with statistically significant improvement across all atrophy scores in both groups. The authors did not provide a statistical test comparing the change from baseline in the two trial arms. Detailed results can be found in Appendix Table C.20.

3.3.3. Energy-Based Interventions

3.3.3.1 Key Messages

- Compared with sham laser, CO₂ laser may result in little to no difference in MBS, dysuria, or menopause-related QoL (low COE). The evidence is very uncertain on the effect of CO₂ laser on vulvovaginal dryness, vulvovaginal irritation, dyspareunia, and treatment satisfaction compared with sham laser (very low COE).
- Compared with vaginal conjugated estrogens cream, CO₂ laser may result in little to no difference in vulvovaginal dryness, vulvovaginal irritation, dysuria, dyspareunia, or menopause-related QoL (low COE). The evidence is very uncertain on the effect of CO₂ laser on treatment satisfaction compared with vaginal estrogen cream (very low COE).
- The evidence is very uncertain on the effect of the combination of CO₂ laser and hyaluronic acid gel on vulvovaginal dryness, vulvovaginal irritation, dysuria, dyspareunia, or menopause-related QoL compared with CO₂ laser alone (very low COE).
- The evidence is very uncertain on the effect of CO₂ laser or radiofrequency on menopause-related QoL compared with placebo (very low COE).
- Erbium-doped yttrium aluminum garnet (Er:YAG) laser may result in little to no difference in menopause-related QoL compared with sham laser (low COE).

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- The evidence is very uncertain on the effect of Er:YAG laser on vulvovaginal dryness, dyspareunia, menopause-related QoL, or treatment satisfaction compared with hyaluronic acid suppositories (very low COE).
- The evidence is very uncertain on the effect of Er:YAG laser on dyspareunia compared with Er:YAG laser hyperstack protocol (very low COE).
- The evidence is very uncertain on the effect of Er:YAG vaginal erbium laser (VEL) on AEs compared with Er:YAG hyperstack or compared with hyaluronic acid (very low COE).
- The evidence is very uncertain on the effect of CO₂ laser on SAEs compared with sham, vaginal conjugated estrogens cream, or CO₂ laser plus hyaluronic acid gel (very low COE).
- The evidence is very uncertain on the effect of Er:YAG laser on SAEs compared with sham (very low COE).
- All energy-based interventions and comparators (sham, vaginal estrogen, hyaluronic acid, or a different energy protocol) reported zero SAEs.
- AEs were infrequent and may not differ between intervention and comparator.
- Nonrandomized studies suggest that attrition may exceed 20% at 12-24 months followup.

3.3.3.2 Overview

Thirty-four publications reporting 32 studies (16 RCTs, one quasi-randomized trial, and 15 non-controlled observational studies) of energy-based interventions were included.^{77, 78, 111, 112, 152-177} Five publications^{111, 112, 152, 156, 161} (5 RCTs) were assessed as low RoB and five publications^{153, 154, 157, 158, 160} (5 RCTs) were assessed as some concerns RoB. Seven publications^{77-82, 159} (6 RCTs) were assessed as high RoB and will not be discussed further. One quasi-randomized trial by Alvisi (2022) was rated as moderate RoB.¹⁵⁵ Sixteen publications (15 non-controlled observational studies) were assessed as either serious¹⁷⁷ or critical¹⁶²⁻¹⁷⁶ RoB. Table 10 presents an overview of the trials assessed as low or some concerns RoB, including key trial, patient, symptom, and outcome reporting characteristics. Detailed RoB assessments can be found in Appendix Tables C.1 and C.2. Detailed trial characteristics can be found in Appendix Table C.7. Limited information about the high RoB trials is in Table 2 and Appendix Table C.11.

One trial required VHI<15¹⁵⁵ for inclusion; no other trial required an objective measure to verify vaginal atrophy. Two trials enrolled breast cancer survivors^{153, 154} while three excluded cancer survivors^{111, 157} or those with prior pelvic malignancy.¹⁶¹

The ten RCTs investigated either CO₂ laser (k=7) or Er:YAG laser (k=3) interventions. For CO₂ laser, comparators included sham (k=4),^{152, 156-158} vaginal conjugated estrogens cream (k=2),^{111, 112} or radiofrequency or placebo (k=1 trial with 3 arms; the placebo was not described).¹⁶⁰ For Er:YAG laser, comparators included sham laser (k=1),¹⁶¹ hyaluronic acid suppositories (k=1),¹⁵⁴ or an Er:YAG laser hyperstack protocol (k=1).¹⁵³ The quasi-randomized trial compared CO₂ laser with CO₂ laser plus hyaluronic acid gel.¹⁵⁵

One trial reported on all outcomes of interest.¹⁵² Overall, dyspareunia, vulvovaginal dryness, and menopause-related QoL were most frequently reported (by 9, 8, and 7 trials, respectively). Five trials reported more than three outcomes of interest.^{111, 152, 154-157, 160} Most trials used a visual analog scale (VAS) or FSFI subscale for symptom assessment. A variety of established scales were used for quality of life and treatment satisfaction. Timing of outcome assessment ranged from 3 to 12 months with over one-half of trials reporting outcomes at 3 to 6 months post-

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intervention. All 11 trials (10 RCTs, 1 quasi-randomized) reported harms outcomes. The 15 non-randomized studies reported long-term (≥ 1 year) harms outcomes and were included to supplement harms reporting by RCTs and prospective observational studies. We were unable to perform a meta-analysis of results due to trial variability in populations, interventions, comparisons, outcomes, and reporting used including length of followup. Certainty of evidence ratings for priority outcomes are listed in Table 11 (CO₂ laser) and Table 12 (Er:YAG laser). Complete outcomes data are presented in Appendix Tables C.24 to C.27.

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Table 10. Overview of included energy-based trials rated low or some concerns RoB

Category	Characteristics	CO ₂ Laser Vs. Sham Laser (k=4)	CO ₂ Laser Vs. Vaginal CEC (k=2)	CO ₂ Laser Vs. Laser + Moisturizer (k=1)	CO ₂ Laser Vs. Radiofrequency and Placebo (k=1)	Er:YAG Laser Vs. Sham Laser (k=1)	Er:YAG Laser VEL Vs. Er:YAG Hyperstack Laser (k=1)	Er:YAG Laser Vs. Hyaluronic Acid (k=1)	Total (k=11)
Sample size	≤50	0	0	1	0	1	1	1	4
	51-74	2	2	0	0	0	0	0	4
	75-250	2	0	0	1	0	0	0	3
Diagnosis of VVA/GSM symptoms	Clinical diagnosis	1	0	1	1	1	0	0	4
	Self-reported	2	2	0	0	1	1	1	7
	Study verified	1	0	0	0	0	0	0	1
Type of VVA/GSM symptom for inclusion	Vulvovaginal	3	1	1	1	1	1	1	9
	Urinary	0	0	0	1	1	0	1	3
	Sexual	2	0	0	1	0	0	1	4
	Vulvovaginal, Urinary, and Sexual	0	0	0	0	0	0	0	0
	Not reported	0	1	0	0	0	0	0	1
Baseline VVA/GSM symptom severity	Mild, moderate, or severe	0	0	0	0	0	0	0	0
	Moderate to severe	2	0	0	0	0	0	0	2
	Not reported	2	2	1	1	1	1	1	9
Other eligibility criteria	Included women s/p hysterectomy	1	1	0	0	0	0	0	2
	Presence/hx of cancer	0	0	0	0	0	1	1	2
	Treatment naïve/washout period	4	2	1	0	0	1	1	9
Length of followup	3 months	1*	1	1	0	1	1	1	6
	4 months	1	0	0	0	0	0	0	1
	6 months	1	1	0	0	0	0	0	2
	≥12 months	1	0	0	0	0	0	0	1
COMMA outcomes reported	Vulvovaginal dryness	4	2	1	0	0	0	1	8
	Discomfort/irritation	3	1	1	0	0	0	0	5
	Dysuria	3	1	1	0	0	0	0	5
	Dyspareunia	3	2	1	0	0	1	1	8
	QoL	3	1	1	1	1	0	1	8
	Satisfaction with treatment	2	1	0	0	0	0	1	4
	Adverse effects	4	2	1	1	1	1	1	11

Abbreviations: CEC=conjugated estrogens cream; CO₂=carbon dioxide; COMMA=Core Outcomes in Menopause; Er:YAG=Erbium-doped yttrium aluminum garnet laser; hx=history; QoL=quality of life; s/p=status post; RoB=risk of bias; VEL=vaginal erbium laser; VVA/GSM=Vulvovaginal atrophy/genitourinary syndrome of menopause

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3.3.3.3 CO₂ Laser

3.3.3.3.1 COMMA Outcomes

Table 11. Summary of COMMA outcomes, findings, and certainty of evidence for CO₂ laser interventions

Outcome	Comparator Followup (Post-Baseline)	Study Design: No. Trials (N Randomized) Direction of Effect	Findings	Certainty of Evidence	Summary Statement
Vulvovaginal dryness/lubrication	Sham laser 3-12 months	RCT: 4 (293) ^{152, 156-158} ↑ 1 trial ↔ 1 trial ? 2 trials	Four trials found mixed effects of CO ₂ laser compared with sham laser on vulvovaginal dryness using 3 measurement tools. One trial reported a significant improvement in FSFI lubrication for the laser group compared with sham. ¹⁵⁷ Three trials reported no significant difference in mean change from baseline using VAS ^{152, 156} or median scores 3 months post-baseline using ICIQ-VS ¹⁵⁸ for CO ₂ laser compared with sham; two did not provide a statistical comparison of change over time.	Very low ⊕○○○ ^{a,b,c}	The evidence is very uncertain on the effect of CO ₂ laser on vulvovaginal dryness compared with sham laser.
	Vaginal conjugated estrogens cream 6 months	RCT: 2 (119) ^{111, 112} ↔ 1 trial ? 1 trial	One trial ¹¹¹ reported no significant difference in mean change from baseline using a 10-point VAS between groups. The other trial ¹¹² reported FSFI lubrication domain mean scores at followup, without a statistical comparison of change over time between groups.	Low ⊕⊕○○ ^{c,e}	CO ₂ lasers may result in little to no difference in vulvovaginal dryness compared with vaginal conjugated estrogens cream.
	CO ₂ laser plus hyaluronic acid gel 3 months	Quasi-randomized: 1 (50) ¹⁵⁵ ↔ 1 trial	One trial reported no significant difference in mean change from baseline using a 10-point VAS between CO ₂ laser versus CO ₂ laser plus hyaluronic acid gel.	Very low ⊕○○○ ^{a,d}	The evidence is very uncertain on the effect of adding hyaluronic acid gel to CO ₂ laser on vulvovaginal dryness compared with CO ₂ laser alone.
Vulvovaginal discomfort/irritation	Sham laser 3-12 months	RCT: 3 (205) ^{152, 156, 157} ↑ 1 trial ↔ 1 trial ? 1 trial	Three trials found mixed effects of CO ₂ laser compared with sham laser on vulvovaginal discomfort/irritation using VAS. One trial reported a significant improvement from baseline in burning and itching using a 10-point VAS for CO ₂ laser compared with sham. ¹⁵⁷ One trial reported no significant difference in mean change from baseline for burning and itching using a 100-point VAS. ¹⁵⁶ One trial reported no difference in mean change from baseline on a 10-point VAS but did not report a statistical comparison over time. ¹⁵²	Very low ⊕○○○ ^{a,b,c}	The evidence is very uncertain on the effect of CO ₂ laser on vulvovaginal discomfort/irritation compared with sham laser.

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Outcome	Comparator Followup (Post-Baseline)	Study Design: No. Trials (N Randomized) Direction of Effect	Findings	Certainty of Evidence	Summary Statement
	Vaginal conjugated estrogens cream 6 months	RCT: 1 (69) ¹¹¹ ↔ 1 trial	One trial reported no significant differences in mean change from baseline in VAS for itching or irritation after CO ₂ laser compared with vaginal conjugated estrogens cream.	Low ⊕⊕○○ ^d	CO ₂ lasers may result in little to no difference in vulvovaginal discomfort/irritation compared with vaginal conjugated estrogens cream.
	CO ₂ laser + hyaluronic acid gel 3 months	Quasi-randomized: 1 (50) ^{†155} ↔ 1 trial	One trial reported no significant differences in mean change from baseline in VAS for burning or itching after CO ₂ laser compared with CO ₂ laser plus hyaluronic acid gel.	Very low ⊕○○○ ^{a,d}	The evidence is very uncertain on the effect of CO ₂ laser on vulvovaginal discomfort/irritation compared with CO ₂ laser plus hyaluronic acid gel.
Dysuria	Sham laser 3-12 months	RCT: 3 (205) ^{152, 156, 157} ↔ 2 trials ? 1 trial	Three trials reported no significant difference in dysuria after CO ₂ laser compared with sham laser on a VAS. Two trials reported no statistically significant difference between arms in mean change in VAS, ^{152, 156, 157} while the third trial reported no difference between groups but did not report a statistical comparison over time. ¹⁵²	Low ⊕⊕○○ ^{a,c}	CO ₂ laser may result in little to no difference in dysuria compared with sham laser.
	Vaginal conjugated estrogens cream 6 months	RCT: 1 (69) ¹¹¹ ↔ 1 trial	One trial reported no significant difference in mean improvement from baseline in VAS for dysuria after CO ₂ laser compared with vaginal conjugated estrogens cream.	Low ⊕⊕○○ ^d	CO ₂ lasers may result in little to no difference in dysuria compared with vaginal conjugated estrogens cream.
	CO ₂ laser plus hyaluronic acid gel 3 months	Quasi-randomized: 1 (50) ^{†155} ↔ 1 trial	One trial reported no significant difference in mean change in VAS after CO ₂ laser compared with CO ₂ laser plus hyaluronic acid gel.	Very low ⊕○○○ ^{a,d}	The evidence is very uncertain on the effect of CO ₂ laser on dysuria compared with CO ₂ laser plus hyaluronic acid gel.
Dyspareunia	Sham laser 3-12 months	RCT: 3 (205) ^{152, 156, 157} ↑ 1 trial ↔ 1 trial ? 1 trial	Three trials reported mixed results for dyspareunia (FSFI pain domain or VAS) following CO ₂ laser compared with sham laser. One trial reported a significant improvement in FSFI pain domain for CO ₂ laser compared with sham, ¹⁵⁷ while the other two trials reported no significant difference in mean change in VAS between groups; ^{152, 156} one did not report a statistical comparison of change over time between groups. ¹⁵²	Very low ⊕○○○ ^{a,b,c}	The evidence is very uncertain on the effect of CO ₂ laser on dyspareunia compared with sham laser.
	Vaginal conjugated estrogens cream 6 months	RCT: 2 (119) ^{111, 112} ↔ 1 trial ? 1 trial	One trial reported no significant difference in mean change in FSFI pain domain after CO ₂ laser compared with vaginal conjugated estrogens cream. ¹¹¹ The other trial reported mean FSFI pain domain scores after CO ₂ laser and vaginal conjugated estrogens cream, but did not provide a statistical comparison of change over time between groups. ¹¹²	Low ⊕⊕○○ ^{c,e}	CO ₂ laser may result in little to no difference in dyspareunia compared with vaginal conjugated estrogens cream.

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Outcome	Comparator Followup (Post-Baseline)	Study Design: No. Trials (N Randomized) Direction of Effect	Findings	Certainty of Evidence	Summary Statement
	CO ₂ laser + hyaluronic acid gel 3 months	Quasi-randomized: 1 (50 [†]) ¹⁵⁵ ↔ 1 trial	One trial reported no significant difference in mean change in FSFI pain domain after CO ₂ laser compared with CO ₂ laser plus hyaluronic acid gel for sexually active women (N=25).	Very Low ⊕○○○ ^{a,d}	The evidence is very uncertain of the effect of CO ₂ laser on dyspareunia compared with CO ₂ laser plus hyaluronic acid gel.
Change in MBS	Sham laser 3-12 months	RCT: 1 (60) ¹⁵² ↔ 1 trial	One trial reported no significant difference in mean change in overall MBS severity after CO ₂ laser compared with sham laser.	Low ⊕⊕○○ ^{a,c}	CO ₂ laser may result in little to no difference in MBS compared with sham laser.
QoL	Sham laser 3-12 months	RCT: 3 (205) ^{152, 156, 157} ↔ 2 trials ? 1 trial	Three trials did not report significant differences in QoL assessed with either the ICIQ-OAB, ¹⁵² the AQoL-6D, ¹⁵⁶ or the UDI-6 ¹⁵⁷ for CO ₂ laser vs sham laser. Two trials found no difference and one trial did not report a statistical comparison of change over time between groups. ¹⁵²	Low ⊕⊕○○ ^{a,c}	CO ₂ laser may result in little to no difference in QoL compared with sham laser.
	Vaginal conjugated estrogens cream 6 months	RCT: 1 (69) ¹¹¹ ↔ 1 trial	One trial reported no significant difference in mean change in UDI-6 and DIVA after CO ₂ compared with vaginal conjugated estrogens cream.	Low ⊕⊕○○ ^d	CO ₂ laser may result in little to no difference in QoL compared with vaginal conjugated estrogens cream.
	CO ₂ laser + hyaluronic acid gel 3 months	Quasi-randomized: 1 (50 [†]) ¹⁵⁵ ? 1 trial	One trial reported a significant change in FSDS and MENQOL after CO ₂ laser and CO ₂ laser plus hyaluronic acid gel but did not report a statistical comparison of change over time between groups.	Very low ⊕○○○ ^{a,d,e}	The evidence is very uncertain on the effect of CO ₂ laser on QoL compared with CO ₂ laser plus hyaluronic acid gel.
	Radiofrequency, 3 months	RCT: 1 (246) ¹⁶⁰ ↔ 1 trial	One trial reported no significant difference in mean change of ICIQ-SF (MUI) scores after CO ₂ laser compared with radiofrequency.	Very low ⊕○○○ ^{a,c,e}	The evidence is very uncertain on the effect of CO ₂ laser or radiofrequency on QoL compared with placebo.
	Placebo* 3 months	RCT: 1 (246) ¹⁶⁰ ↔ 1 trial	One trial reported no significant difference in mean change of ICIQ-SF (MUI) scores after CO ₂ laser compared with placebo.	Very low ⊕○○○ ^{a,c,e}	The evidence is very uncertain on the effect of CO ₂ laser or radiofrequency on QoL compared with placebo.
Satisfaction with treatment	Sham laser 3 months	RCT: 2 (148) ^{152, 158} ? 2 trials	One trial ¹⁵² reported no significant difference in PGI-I after CO ₂ or sham laser, while the other trial reported a higher percentage of people “very satisfied or satisfied” on a 5-point Likert scale after CO ₂ laser than sham laser. ¹⁵⁸	Very low ⊕○○○ ^{a,c,e}	The evidence is very uncertain on the effect of CO ₂ laser on treatment satisfaction compared with sham laser.

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Outcome	Comparator Followup (Post-Baseline)	Study Design: No. Trials (N Randomized) Direction of Effect	Findings	Certainty of Evidence	Summary Statement
	Vaginal conjugated estrogens cream 6 months	RCT: 1 (69) ¹¹¹ ? 1 trial	One trial reported PGI-I scores after CO ₂ laser and vaginal conjugated estrogens cream and reported “no obvious difference” between the two groups.	Very low ⊕○○○ ^{d,e}	The evidence is very uncertain on the effect of CO ₂ laser on treatment satisfaction compared with vaginal conjugated estrogens cream.
Adverse effects	Sham laser 3 to 12 months	RCT: 4 (293) ^{152, 156-158}	Four trials reported no difference in SAEs after CO ₂ laser compared with sham laser. No SAEs were reported in any of the four trials.	Very low ⊕○○○ ^{a,c,f}	The evidence is very uncertain on the effect of CO ₂ laser on SAEs compared with sham laser.
	Vaginal conjugated estrogens cream 6 months	RCT: 2 (119) ^{111, 112}	Two trials reported no difference in SAEs after CO ₂ laser compared with vaginal conjugated estrogens cream. No SAEs were reported in either of the trials.	Very low ⊕○○○ ^{d,f}	The evidence is very uncertain on the effect of CO ₂ laser on SAEs compared with vaginal conjugated estrogens cream.
	CO ₂ laser + hyaluronic acid gel 3 months	Quasi-randomized: 1 (50) ¹⁵⁵	One trial reported no difference in SAEs after CO ₂ laser compared with CO ₂ laser plus hyaluronic acid gel. No SAEs were observed in either arm.	Very low ⊕○○○ ^{a,d,f}	The evidence is very uncertain on the effect of CO ₂ laser on SAEs compared with CO ₂ laser plus hyaluronic acid gel.

Abbreviations: AE=adverse effect; AQoL-6D=Assessment of Quality of Life – 6D; CO₂=carbon dioxide; DIVA=Day-to-day Impact of Vaginal Aging; COMMA=Core Outcomes in Menopause; EORTC SHQ-C22=European Organization for the Research and Treatment of Cancer Sexual Health Questionnaire; FSFI=Female Sexual Function Index; FSDS: Female Sexual Distress Score; GSM=genitourinary syndrome of menopause; ICIQ-OAB=International Consultation on Incontinence Questionnaire Overactive Bladder; ICIQ-SF=International Consultation on Incontinence Questionnaire Short Form; ICIQ-VS=International Consultation on Incontinence Questionnaire Vaginal Symptoms; MBS=most bothersome symptom; MENQOL=Menopause-Specific Quality of Life; MUI=mixed urinary incontinence; OIS=optimal information size; PGI-I=Patient Global Impression of Improvement; QoL=quality of life; RCT=randomized controlled trial; RoB=risk of bias; SAE=serious adverse effect; UDI-6=Urogenital Distress Inventory 6; VAS=visual analog scale

*Placebo not defined

†Laser plus estriol group from Alvisi (2022)¹⁵⁵ not included

Direction of effect

↑: Intervention group had a statistically significantly better outcome than comparison group (e.g., improved symptoms, higher treatment satisfaction)

↔: No statistically significant difference between groups

?: No statistical comparison of change in time between groups provided

Certainty of evidence (COE)

Low (⊕⊕○○): Our confidence in the effect estimate is limited; the true effect may be substantially different from the effect estimate.

Very low (⊕○○○): We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

^aDowngraded one level for study limitations (one or more trials assessed as “some concerns” RoB)

^bDowngraded one level for inconsistency (effect varied across trials)

^cDowngraded one level for imprecision (total sample size less than OIS of 400)

^dDowngraded two levels for imprecision (total sample size much less than OIS of 400)

^eDowngraded one level for study limitations (one or more trials did not provide adequate statistical reporting)

^fDowngraded one level for imprecision (zero or few events)

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3.3.3.3.1.1 Vulvovaginal Dryness

3.3.3.3.1.1.1 CO₂ Laser Vs. Sham Laser (4 Trials; Total N=293)

Four trials^{152, 156-158} (N=293) compared the effect of CO₂ laser vs. sham laser on vaginal dryness using three different measures and reported mixed results. One trial¹⁵⁷ found a significant improvement in dryness with CO₂ laser compared with sham laser; one trial¹⁵⁶ found a non-significant difference; and 2 trials^{152,158} reported only change from baseline to followup within treatment arms but no statistical test comparing the change between groups. Salvatore (2021)¹⁵⁷ (N=60) enrolled women with dryness and dyspareunia as their two most bothersome symptoms and used a 10-point VAS (0=best to 10=worst). They reported significantly (P<0.05) greater reduction in dryness on a 10-point VAS at 4 months post-baseline in the CO₂ laser group than in the sham group (Laser -5.6 vs. Sham -1.9). They also reported a significantly (P<0.05) greater improvement based on change from baseline in the FSFI lubrication domain (0 (worst) to 6 (best)) (Laser 2.5 vs. Sham 0.7).¹⁵⁷ Li (2021)¹⁵⁶ (N=85) enrolled women with at least one GSM symptom “severe enough” to seek treatment and used a 100-point VAS (0=best to 100=worst). They reported no statistically significant (P>0.05) difference between groups in mean change from baseline to 12 months (Laser -18.0 vs. Sham -12.0). Page (2022)¹⁵² (N=60) enrolled women with moderate to severe GSM symptoms and used a 10-point VAS (0=best to 10=worst). They reported “no obvious inter-group difference” between groups in mean change from baseline at 12 weeks (Laser -0.69; Sham -0.00; no statistical test provided). They¹⁵² also measured vaginal dryness on a 4-point severity scale (0=none to 3=severe) and reported a reduction in dryness severity for both the laser and sham groups (Laser -1.5 vs. Sham -0.3); they did not provide a statistical test comparing the change between arms. Ruanphoo (2020)¹⁵⁸ (N=88) included women with moderate to severe symptoms of vaginal atrophy and assessed dryness using a single question from the International Consultation on Incontinence Modular Questionnaire – Vaginal Symptoms (ICIQ-VS). They found a statistically significant improvement from baseline to 12 weeks for the laser group, but not the sham group (Laser 5.0 to 3.2 and Sham 4.0 to 2.0); they did not provide a statistical test comparing the change from baseline to followup between groups. Due to study limitations, inconsistency, and imprecision, we conclude the evidence is very uncertain on the effect of CO₂ laser on vulvovaginal dryness compared with sham laser (very low COE).

3.3.3.3.1.1.2 CO₂ Laser Vs. Vaginal Conjugated Estrogens Cream (2 Trials; Total N=119)

Two trials^{111, 160} (N=119) evaluated the effect of CO₂ laser versus vaginal conjugated estrogens cream on vulvovaginal dryness, assessed with a VAS or the FSFI Lubrication domain. Paraiso (2020)¹¹¹ (N=69) enrolled women with baseline dryness ≥7 on a 10-point VAS (0=best to 10=worst). Trial enrollment was stopped early due to the FDA requiring the sponsor to obtain and maintain an Investigational Device Exemption, and they did not reach statistical significance for a finding of “non-inferiority” of laser compared with estrogen. They reported that mean changes from baseline to 6 months did not differ significantly (P>0.05) between the laser and estrogen groups using a 10-point VAS (Laser -5.48 vs. CEC -5.76) or the FSFI Lubrication domain (0 (worst) to 6 (best)) (Laser 0.11 vs. CEC 0.35). Eftekhari (2020)¹¹² (N=50), enrolled sexually active women with any severity of GSM symptoms. They reported mean scores at baseline and 6-month followup for the FSFI Lubrication domain (Laser 3.1 to 3.1 and CEC 2.3 to 3.0) but did not provide a statistical test comparing the change over time between trial groups. We downgraded for imprecision and study limitations and conclude that CO₂ laser may result in little to no difference in vulvovaginal dryness compared with vaginal CEC (low COE).

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3.3.3.3.1.1.3 CO₂ Laser Vs. CO₂ Laser + Hyaluronic Acid Gel (1 Trial; Total N=50)

One quasi-randomized trial¹⁵⁵ (N=50) evaluated the effect of CO₂ laser versus combination CO₂ laser plus hyaluronic acid gel (moisturizer) on vulvovaginal dryness and found no difference. Alvisi (2022)¹⁵⁵ enrolled women with VHI scores <15 (possible range of scores 5 to 25) at baseline. They assessed vulvovaginal dryness using a 10-point VAS (0=best to 10=worst) and reported no statistically significant difference ($P>0.05$) between CO₂ laser and combination CO₂ laser plus hyaluronic acid gel (moisturizer) in change from baseline to 3 months post-baseline (Laser -3.3 vs Laser with Moisturizer -2.6). Among the subgroup of sexually active participants (N=25), the change in FSFI Lubrication domain (0 (worst) to 6 (best)) scores also did not differ significantly ($P>0.05$) between treatment groups at 3 months post-baseline (Laser 0.5 vs Laser with Moisturizer 1.0). After downgrading for RoB and imprecision, we conclude the evidence is very uncertain on the effect of adding hyaluronic acid gel to CO₂ laser, compared with CO₂ laser alone, on vulvovaginal dryness (very low COE).

3.3.3.3.1.2 Vulvovaginal Discomfort/Irritation

3.3.3.3.1.2.1 CO₂ Laser Vs. Sham Laser (3 Trials; Total N=205)

Three trials^{152, 156, 157} (N=205) assessed vaginal burning and vaginal itching using 2 measures with mixed results. One trial¹⁵⁷ found a significant improvement in burning and itching with CO₂ laser compared with sham laser; one trial¹⁵⁶ found a non-significant difference; and 1 trial¹⁵² reported only change from baseline to followup within treatment arms but no statistical test comparing the change between groups. Salvatore (2021)¹⁵⁷ (N=60) reported statistically significantly ($P<0.05$) greater improvement from baseline to 4 months post-baseline in the CO₂ laser group using a 10-point VAS (0=best to 10=worst) for both burning (Laser -2.3 vs. Sham -1.0) and itching (Laser -2.9 vs. Sham -1.4). Using a 100-point VAS (0=best to 100=worst), Li (2021) (N=85) reported no statistically significant ($P>0.05$) difference between groups in mean change from baseline to 12 months for either burning (Laser -21.9 vs. Sham -16.0) or itching (Laser -15.4 vs. Sham -8.3). Page (2022)¹⁵² (N=60) reported “no obvious intergroup differences” without a statistical test comparing mean improvement on a 10-point VAS for either burning (Laser -1.03 vs. Sham -1.38) or itching (Laser -0.24 vs. -1.55) at 3 months post-baseline.¹⁵² We downgraded for RoB, inconsistency, and imprecision and conclude the evidence is very uncertain on the effect of CO₂ laser on vaginal/vulvar irritation compared with sham laser (very low COE).

3.3.3.3.1.2.2 CO₂ Laser Vs. Vaginal Conjugated Estrogens Cream (1 Trial; Total N=69)

Paraiso (2020)¹¹¹ (N=69), reported no significant difference ($P>0.05$) between CO₂ laser and vaginal estrogen in mean improvement on a 10-point VAS (0=best to 10=worst) from baseline to 6 months post-baseline for itching (Laser -1.84 vs. CEC -1.24) or irritation (Laser -3.29 vs. CEC -3.49). Due to concerns about imprecision, we conclude that CO₂ lasers may result in little to no difference in itching or irritation compared with estrogen cream (low COE).

3.3.3.3.1.2.3 CO₂ Laser Vs. CO₂ Laser + Hyaluronic Acid Gel (1 Trial; Total N=50)

The single trial of CO₂ laser vs. CO₂ laser plus hyaluronic acid gel by Alvisi (2022)¹⁵⁵ (N=50) reported no statistically significant differences ($P>0.05$) using a 10-point VAS (0=best to 10=worst) in mean improvement for burning from baseline to 3 months post-baseline (Laser -2.3 vs Laser with Moisturizer -2.1). For itching, the corresponding changes were also not significantly different ($P>0.05$) (Laser -1.4 vs Laser with Moisturizer -1.4). We downgraded for RoB and imprecision and conclude the evidence is very uncertain on the effect adding hyaluronic acid gel to CO₂ laser, compared with CO₂ laser alone, on vaginal/vulvar irritation (very low COE).

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3.3.3.3.1.3 Dysuria

3.3.3.3.1.3.1 CO₂ Laser Vs. Sham Laser (3 Trials; Total N=205)

Three trials^{152, 156, 157} (N=205) evaluated the effect of CO₂ laser versus sham laser on dysuria using a VAS. Two trials^{157, 156} found no significant improvement in dysuria with CO₂ laser compared with sham laser; one trial¹⁵² reported only change from baseline to followup within treatment arms but did not provide a statistical test comparing the change between groups. At 4 months post-baseline, Salvatore (2021)¹⁵⁷ (N=60) reported no statistically significant ($P>0.05$) difference between groups in the reduction of dysuria severity on a 10-point VAS (0=best to 10=worst), (Laser -0.9 vs. Sham -0.3). Li (2021)¹⁵⁶ (N=85) used a 100-point VAS (0=best to 100=worst) and reported no statistically significant difference ($P>0.05$) between treatment arms in dysuria change from baseline to 12 months (Laser -11.4 vs. Sham 2.2). Page (2022)¹⁵² (N=60) used a 10-point VAS and reported “no obvious intergroup difference” between treatment arms in the change from baseline to 3 months (Laser -0.62 vs. Sham -0.43; no statistical test provided). After downgrading for RoB and imprecision, we conclude that CO₂ laser may result in little to no difference in dysuria compared with sham laser (low COE).

3.3.3.3.1.3.2 CO₂ Laser Vs. Vaginal Conjugated Estrogens Cream (1 Trial; Total N=69)

Paraíso (2020)¹¹¹ (N=69), reported no significant difference ($P>0.05$) between CO₂ laser and vaginal estrogen in mean improvement on a 10-point VAS (0=best to 10=worst) from baseline to 6 months post-baseline for dysuria (Laser -1.4 vs. CEC -2.1). Due to concerns about imprecision, we conclude that CO₂ lasers may result in little to no difference in dysuria compared with estrogen cream (low COE).

3.3.3.3.1.3.3 CO₂ Laser Vs. CO₂ Laser + Hyaluronic Acid Gel (1 Trial; Total N=50)

In a single trial, using a 10-point VAS (0=best to 10=worst), Alvisi (2022)¹⁵⁵ (N=50) reported that mean change in dysuria at 3 months post-baseline did not differ significantly ($P>0.05$) between CO₂ laser and the combination of CO₂ laser plus hyaluronic acid gel groups (Laser -0.1 vs Laser with Moisturizer -0.4). Due to concerns with RoB and imprecision, we downgraded three levels and conclude the evidence is very uncertain on the effect of a combination of CO₂ laser plus hyaluronic acid gel on dysuria compared with CO₂ laser alone (very low COE).

3.3.3.3.1.4 Dyspareunia

3.3.3.3.1.4.1 CO₂ Laser Vs. Sham Laser (3 Trials; Total N=205)

Three trials^{152, 156, 157} (N=205) evaluated the effect of CO₂ laser versus sham laser on dyspareunia with mixed results. One trial¹⁵⁷ found a significant improvement in dyspareunia with CO₂ laser compared with sham laser; one trial¹⁵⁶ found a non-significant difference; and 1 trial¹⁵² reported only change from baseline to followup within treatment arms but no statistical test comparing the change between groups. Salvatore (2021)¹⁵⁷ (N=60) reported significantly ($P<0.05$) greater improvement in dyspareunia using a 10-point VAS (0=best to 10=worst) at 4 months post-baseline in the CO₂ laser group than in the sham laser group (Laser -6.0 vs Sham -1.1).¹⁵⁷ They also reported a significantly ($P<0.05$) greater improvement in the mean FSFI pain domain (0 (worst) to 6 (best)) score (Laser 3.1 vs Sham 0.4). Li (2021)¹⁵⁶ (N=85) used a 100-point VAS (0=best to 100=worst). They reported no statistically significant ($P>0.05$) difference between groups in mean change from baseline to 12 months (Laser -15.0 vs. Sham -3.5). Page (2022)¹⁵² (N=60) used a 10-point VAS and reported “no obvious intergroup difference” between treatment arms in the change from baseline to 3 months (Laser -2.3 vs. Sham -2.2; no statistical test provided). They¹⁵² also measured dyspareunia on a 4-point severity scale (0=none to 3=severe) and reported a reduction in dyspareunia severity for both the laser and sham groups (Laser -0.6 vs. Sham -0.4); they did not provide a statistical test

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comparing the change between arms. We downgraded for RoB, inconsistency, and imprecision and conclude the evidence is very uncertain on the effect of CO₂ laser compared with sham laser on dyspareunia (very low COE).

3.3.3.3.1.4.2 CO₂ Laser Vs. Vaginal Conjugated Estrogens Cream (2 Trials; Total N=119)

Two trials^{111, 160} (N=119) evaluated the effect of CO₂ laser versus vaginal CEC on dyspareunia using the FSFI pain domain (0 (worst) to 6 (best)). Paraiso (2020)¹¹¹ (N=69) reported no significant difference ($P>0.05$) between laser and CEC in the slight worsening of mean FSFI pain scores from baseline at 6 months post-baseline (Laser -0.59 vs CEC -0.04). Eftekhari (2020)¹¹² (N=50) reported mean scores at baseline and 6 months followup for the FSFI pain domain (Laser 2.5 to 4.4 and CEC 2.6 to 3.7), but did not provide a statistical test comparing the change over time between trial groups. After downgrading for imprecision and statistical insufficiency, we conclude the evidence CO₂ laser may result in little to no difference in dyspareunia compared with estrogen cream (low COE).

3.3.3.3.1.4.3 CO₂ Laser Vs. CO₂ Laser + Hyaluronic Acid Gel (1 Trial; Total N=50)

In a single small trial (N=50), Alvisi (2022)¹⁵⁵ evaluated the effect of CO₂ laser plus hyaluronic acid gel compared with CO₂ laser alone on dyspareunia using the FSFI pain domain (0 (worst) to 6 (best)) for the subgroup of participants who were sexually active (N=25). They reported no significant difference in dyspareunia between CO₂ laser and the combination of CO₂ laser plus hyaluronic acid gel in change from baseline to 3-month followup (Laser 0.7 vs Laser with Moisturizer 1.3). Downgrading for RoB and imprecision, we conclude the evidence is very uncertain on the effect of CO₂ laser and hyaluronic acid gel compared with CO₂ laser alone on dyspareunia (very low COE).

3.3.3.3.1.5 Change in MBS

3.3.3.3.1.5.1 CO₂ Laser Vs. Sham Laser (1 Trial; Total N=60)

A single trial by Page (2022)¹⁵² (N=60) evaluated the effect of CO₂ laser versus sham laser on change in MBS at 3 months. They measured MBS with a 4-point severity scale (0=none to 3=severe) and included vaginal dryness, itching, burning, dyspareunia, and dysuria. They reported no statistically significant ($P>0.05$) difference in improvement in overall MBS severity between the laser and sham groups (Laser 2.86 to 2.17 vs. Sham 2.90 to 2.52). Neither of the changes in severity reached a 45 percent reduction, a cut-off used by the trial authors in determining sample size. After downgrading for RoB and imprecision, we conclude CO₂ laser may result in little to no difference in change in MBS compared with sham laser (low COE).

3.3.3.3.1.6 QoL (i.e., Distress, Bother, or Interference of Genitourinary Symptoms)

3.3.3.3.1.6.1 CO₂ Laser Vs. Sham Laser (3 Trials; Total N=205)

Three trials^{152, 156, 157} (N=205) reported no effect of CO₂ laser on varied measures of menopause-related QoL. Li (2021)¹⁵⁶ (N=85) assessed global quality of life domains including independent living, relationships, mental health, coping, pain, and senses, using the Assessment of Quality of Life-6D (AQoL-6D) (scale standardized to 0-100; higher is better). They reported no statistically significant ($P>0.05$) mean difference between groups for change from baseline to 12 months post-baseline for the AQoL-6D (Laser 6.3 vs Sham 1.4). Two trials evaluated quality of life related to urinary symptoms associated with GSM and found no effect of CO₂ laser compared with sham laser. Salvatore (2021)¹⁵⁷ (N=60) used the UDI-6 (scale 0-25; lower is better) to measure how bothered participants are by urinary frequency, leakage, difficulty urinating, and pelvic pain or discomfort. They found no statistically significant ($P>0.05$) difference in

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improvement from baseline to 4 months post-baseline between groups (Laser -8.0 vs. Sham -2.6). Page (2022)¹⁵² (N=60) evaluated quality of life associated with urinary daytime frequency, nocturia, urgency, and urge incontinence, using the International Consultation on Incontinence Questionnaire Overactive Bladder (ICIQ-OAB) (scale 0-16; lower is better). They reported “no obvious intergroup difference” for change in ICIQ-OAB scores from baseline to 3 months post-baseline (Laser -0.55 vs Sham -0.31). After downgrading for RoB and imprecision, we conclude that CO₂ laser may result in little to no difference in menopause-related QoL compared with sham laser (low COE).

3.3.3.3.1.6.2 CO₂ Laser Vs. Vaginal Conjugated Estrogens Cream (1 Trial; Total N=69)

Paraiso (2020)¹¹¹ (N=69) evaluated the effect of CO₂ laser and vaginal CEC on quality of life related to urinary and vulvovaginal symptoms using the UDI-6 and the DIVA questionnaire. They reported no significant differences ($P>0.05$) between CO₂ laser and vaginal CEC for the change from baseline to 6 months post-baseline in either the UDI-6 (scale 0-25; lower is better) (Laser -9.4 vs CEC -6.2) or the DIVA (lower is better) (Laser -3.3 vs CEC -4.4). With downgrading for imprecision, we conclude that CO₂ laser may result in little to no difference in menopause-related QoL compared with estrogen cream (low COE).

3.3.3.3.1.6.3 CO₂ Laser Vs. CO₂ Laser + Hyaluronic Acid Gel (1 Trial; Total N=50)

Alvisi (2022)¹⁵⁵ (N=50) evaluated the effect of CO₂ laser plus hyaluronic acid gel compared with CO₂ laser alone on quality of life related to menopause and sexual function. They found a statistically significant improvement in the MENQoL sexual domain (scale 0-18, lower is better) for both CO₂ laser and CO₂ laser plus hyaluronic acid gel (Laser -1.7 vs Laser with Moisturizer -1.6); they did not provide a statistical test comparing the change between arms. In the subgroup of participants who were sexually active (N=25), they found a statistically significant improvement in FSDS scores (<15 is ‘normal’, lower is better) for both groups (Laser -7.5 vs Laser with Moisturizer -2.6) but did not provide a statistical test comparing the change between arms. Due to concerns with RoB and imprecision, we conclude the evidence is very uncertain on the effect of CO₂ laser on menopause-related QoL compared with a combination of CO₂ laser and hyaluronic acid gel (very low COE).

3.3.3.3.1.6.4 CO₂ Laser Vs. Radiofrequency, Placebo (1 Trial; Total N=246)

Eftekhari (2021)¹⁶⁰ (N=246) evaluated the effect of CO₂ laser, radiofrequency, and placebo, on quality of life related to urinary incontinence symptoms using the ICIQ-SF (Mixed Urinary Incontinence) (scale 0-21; lower is better). They found a statistically significant improvement from baseline to 3 months post-baseline in the CO₂ laser and radiofrequency groups but not the placebo group (Laser 6.5 to 4.9; Radiofrequency 7.6 to 4.1; Placebo 6.7 to 6.1) and reported that the mean change was statistically different ($P<0.05$) for radiofrequency versus placebo, but not for laser versus radiofrequency or laser versus placebo. We downgraded for RoB, imprecision, and statistical insufficiency and conclude the evidence is very uncertain on the effect of CO₂ laser compared with placebo (very low COE), CO₂ laser compared with radiofrequency (very low COE), and radiofrequency compared with placebo (very low COE).

3.3.3.3.1.7 Satisfaction With Treatment

3.3.3.3.1.7.1 CO₂ Laser Vs. Sham Laser (2 Trials; Total N=129)

Two trials^{152, 158} (N=129) evaluated the effect of CO₂ laser versus sham laser on treatment satisfaction with mixed results. Ruanphoo (2020)¹⁵⁸ (N=69) used a 5-point Likert scale (very dissatisfied, dissatisfied, neutral, satisfied, very satisfied) and reported a significantly ($P<0.05$) higher proportion of the CO₂ laser group was very satisfied or satisfied compared with sham (Laser 80% vs Sham 45%) at 3 months post-baseline. Page (2022)¹⁵² (N=60) used the Patient Global Impression of Improvement (PGI-I) 5-point Likert

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scale (1=much worse to 5=much better) and reported “no obvious difference” in the percentages of patients rating their condition at 3 months post-baseline as better or much better (Laser 41% vs Sham 34%). With downgrading for RoB, imprecision, and statistical insufficiency, we conclude the evidence is very uncertain on the effect of CO₂ laser on treatment satisfaction compared with sham laser (very low COE).

3.3.3.3.1.7.2 CO₂ Laser Vs. Vaginal Conjugated Estrogens Cream (1 Trial; Total N=69)

One trial¹¹¹ (N=69) found no statistically significant difference between groups in ratings of improvement and satisfaction at 6 months post-baseline. Paraiso (2020)¹¹¹ reported similar proportions of each group that rated improvement on the PGI-I 5-point Likert scale (1=much worse to 5=much better) as “better or much better.” Due to concerns about imprecision and statistical insufficiency, we conclude the evidence is very uncertain on the effect of CO₂ laser on treatment satisfaction compared with estrogen cream (very low COE).

3.3.3.3.1.8 Adverse Effects

Eight trials evaluated the potential harms of CO₂ laser therapy.^{111, 112, 152, 155-158, 160} We captured when a trial reported any AE/TEAE (k=0), SAEs (k=7), discontinuation due to AE (k=8), or a clinically relevant, specific AE (k=6). Results are reported below by these four categories, then type of comparison. Reporting varied widely – including when and what events were assessed. No trials provided statistical measures comparing effects of interventions with comparators. None of the trials were designed to adequately assess serious or severe AEs. Long-term harms outcomes from the non-controlled studies are described following the outcomes from the RCTs and quasi-randomized studies. Two trials evaluated safety only to state that no AEs were reported in either trial arm¹⁵⁵ or that there were no trial discontinuations due to AEs.¹⁶⁰ Specific counts (when available) and detailed AE reporting can be found in Appendix Table C.25.

3.3.3.3.1.8.1 Any AE/TEAE

One trial¹⁵⁵ of CO₂ laser versus CO₂ laser plus hyaluronic acid gel (N=50) stated that no AEs were reported in either trial arm. No other trials reported the overall count or proportion of participants who experienced any AE.

3.3.3.3.1.8.2 Serious AEs

We used GRADE to assess seven trials that evaluated SAEs, all of which reported that no SAEs occurred in any of the trial arms. Four trials^{138, 142-144} (N=293) investigated CO₂ laser versus sham laser,^{152, 156-158} two trials^{111, 112} (N=119) investigated CO₂ laser versus vaginal conjugated estrogens cream, and one trial investigated CO₂ laser versus CO₂ laser plus hyaluronic acid gel (N=50).¹⁵⁵ Due to study limitations and imprecision, the evidence is very uncertain on the effect of CO₂ laser on SAEs compared with sham laser, vaginal conjugated estrogens cream, or CO₂ laser plus hyaluronic acid gel (very low COE).

3.3.3.3.1.8.3 Discontinuation Due to AEs

Eight trials reported on discontinuation due to AEs. Six trials reported there were no discontinuations due to AEs, including two trials^{152, 156-158} (N=145) of CO₂ laser versus sham laser, two trials^{96, 97} (N=119) of CO₂ laser versus vaginal conjugated estrogen cream,^{111, 112} one trial¹⁵⁵ (N=50) of CO₂ laser versus CO₂ laser plus hyaluronic acid gel, and one trial¹⁶⁰ (N=246) of CO₂ laser versus radiofrequency. Two trials of CO₂ laser versus sham laser reported n (%) of trial discontinuation. In Page (2022),¹⁵² 3.3 percent (1/30) of sham participants discontinued the trial due to urogenital pain after the first session. Ruanphoo (2020)¹⁵⁸ reported that 2.3 percent (1/44) of participants in the intervention group discontinued after experiencing pain on vaginal probe insertion.

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3.3.3.3.1.8.4 Specific AEs

CO₂ Laser Vs. Sham Laser (4 Trials; Total N=313). Four trials^{138, 142-144} (N=313) of CO₂ laser versus sham laser provided proportions of specific AEs. The most common AEs reported were pain after procedure (k=3; 2.3%-100% vs. 0%-10.5%), vaginal bleeding/discharge (k=2; 0%-11.5% vs. 2.3%-2.6%), and dyspareunia (k=2; 0% vs. 0%). Li (2021)¹⁵⁶ reported how many participants experienced one or more of the following events: vaginal pain/discomfort, spotting, lower urinary tract symptoms/infection, vaginal discharge, and upper UTI after treatment. Detailed specific AE results can be found in Appendix Table C.25.

CO₂ Laser Vs. Vaginal Conjugated Estrogen Cream (2 Trials; Total N=119). Two trials^{96, 97} (N=119) of CO₂ laser versus conjugated estrogen cream reported proportions of specific AEs.^{111, 112} The most common AEs included vaginal bleeding (k=2; 0%-6.7% vs. 0%-6.3%) and vaginal discharge (k=2; 0%-3.3% vs. 0%). Paraiso (2020)¹¹¹ also reported the proportion of participants who experienced vaginal pain (3.3% vs. 0%), UTI (3.3% vs. 0%), migraine (0% vs. 3%), abdominal cramping (0% vs. 3%), and breast tenderness (0% vs. 3%). Detailed specific AE results can be found in Appendix Table C.25.

3.3.3.3.2 Other Outcomes

3.3.3.3.2.1 CO₂ Laser Vs. Sham Laser

Two trials^{156, 157} (N=145) reported mixed results on sexual function using total FSFI score (scale 2-36; higher is better) change from baseline. Salvatore (2021)¹⁵⁷ (N=60) reported a significantly (P<0.05) greater improvement in FSFI total score from baseline to 4 months post-baseline for CO₂ laser compared with sham. Page (2022)¹⁵² (N=60) reported “no obvious intergroup difference” in the change in FSFI scores from baseline to 3 months post-baseline. For both trials, mean FSFI scores at followup remained below standard cut points of 26.55 or 27 that define sexual dysfunction. Li (2021)¹⁵⁶ (N=85) reported no statistically significant difference (P>0.05) on change in Functional Social Support Questionnaire (FSSQ) from baseline to 12 months in the subset of women who were sexually active (N=42) for CO₂ laser compared with sham.

Two trials^{152, 156} (N=145) reporting mean change in VHI from baseline to followup found no significant difference between CO₂ laser and sham laser, while a third trial¹⁵⁸ (N=88) reported a significant difference between post-intervention means.¹⁵⁸

One trial¹⁵⁸ (N=88) reported mean scores at 3 months for a VAS that incorporated four symptoms (dyspareunia, dryness, irritation, and soreness). Scores were significantly lower (P<0.05) in the CO₂ laser group indicating more mild symptoms.

3.3.3.3.2.2 CO₂ Laser Vs. Vaginal Conjugated Estrogens Cream

Two trials^{111, 160} (N=119) reported mixed results for sexual function. Paraiso (2020)¹¹¹ (N=69) reported no significant difference in the change in total

FSFI scores from baseline to 6 months post-baseline for CO₂ laser compared with CEC. Mean FSFI values post-treatment were not reported. Eftekhari (2020)¹¹² (N=50) reported an increase in mean FSFI total scores from baseline to 6-month followup for both CO₂ laser and estrogen, but did not provide a statistical test comparing the change between groups. Mean values after treatment for both groups remained below the cut point indicating sexual dysfunction.

Paraiso (2020)¹¹¹ (N=69) reported that mean change in VHI scores did not differ significantly between CO₂ laser and estrogen cream groups at 6 months post-baseline. The authors also reported a significant change in VMI from baseline to 6 months post-baseline for estrogen compared with laser, which retained statistical significance after adjusting for age, menopausal status, prior estrogen use, and sexual activity.

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Eftekhari (2020)¹¹² (N=50) reported an increase in mean VHI scores from baseline to 6-month followup for both CO₂ laser and estrogen, but did not provide a statistical test comparing the change between groups.

3.3.3.3.2.3 CO₂ Laser Vs. CO₂ Laser + Hyaluronic Acid Gel

The small trial (N=25 sexually active) by Alvisi (2022)¹⁵⁵ reported no statistically significant difference in the change from baseline to 3 months post-baseline in sexual function using total FSFI scores between CO₂ laser compared with the combination of CO₂ laser plus hyaluronic acid gel. Mean values post-treatment for both groups were below the cut point indicating sexual dysfunction.

Alvisi (2022)¹⁵⁵ (N=50) also reported that mean change from baseline to 3 months post-baseline for VHI did not differ between CO₂ laser versus a combination of CO₂ laser plus hyaluronic acid gel.

3.3.3.3.2.4 CO₂ Laser Vs. Radiofrequency, Placebo

Eftekhari (2021)¹⁶⁰ (n=246) compared CO₂ laser, radiofrequency, and placebo reporting significantly improved mean ratings at followup in overall VAS (including irritation, itching, Dryness, dispersion, and dysuria) with significant differences (P<0.05) in mean change between laser and radiofrequency, laser and placebo, and radiofrequency and placebo. Mean scores for the Prolapse/Urinary Incontinence Sexual Questionnaire (PISQ-12) Physical Behavior outcome assessed 3 months post-baseline were improved from baseline following CO₂ laser and radiofrequency but not placebo. There was a statistically significant difference (P<0.05) in mean change between all 3 paired comparisons. This trial also reported a statistically significant difference in mean scores on the VHI 3 months post-baseline. Improvement from baseline was noted in CO₂ laser and radiofrequency groups; the difference in mean change was also statistically significant (P<0.05) for all 3 pairs of interventions.

3.3.3.4 Er:YAG Laser

3.3.3.4.1 COMMA Outcomes

Table 12. Summary of COMMA outcomes, findings, and certainty of evidence for Er:YAG laser interventions

Outcome	Comparator Followup (Post-Baseline)	Study Design: No. Trials (N Randomized) Direction of Effect	Findings	Certainty of Evidence	Summary Statement
Vulvovaginal dryness/lubrication	Hyaluronic acid suppositories 3 months	RCT: 1 (43) ¹⁵⁴ ? 1 trial	One trial observed no difference between groups in the proportion of participants reporting vaginal dryness on the EORTC SHQ-C22 without providing a statistical comparison of change over time between groups.	Very low ⊕○○○ ^{a,b,c}	The evidence is very uncertain on the effect of Er:YAG laser on vulvovaginal dryness compared with hyaluronic acid suppositories.
Dyspareunia	Hyaluronic acid suppositories 3 months	RCT: 1 (43) ¹⁵⁴ ? 1 trial	One trial reported no significant difference in median EORTC SHQ-C22 score and percentage of sexually active women with dyspareunia after Er:YAG or hyaluronic acid suppositories, but did not report a statistical comparison of change over time between groups.	Very low ⊕○○○ ^{a,b,c}	The evidence is very uncertain on the effect of Er:YAG laser on dyspareunia compared with hyaluronic acid suppositories.

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Outcome	Comparator Followup (Post-Baseline)	Study Design: No. Trials (N Randomized) Direction of Effect	Findings	Certainty of Evidence	Summary Statement
	Er:YAG hyperstack 6 months	RCT: 1 (68) ¹⁵³ ↑ 1 trial	One trial reported significantly greater improvement in VAS scores after Er:YAG hyperstack compared with a standard Er:YAG protocol.	Very low ⊕○○○ ^{a,b}	The evidence is very uncertain on the effect of Er:YAG laser on dyspareunia compared with Er:YAG hyperstack.
QoL	Sham laser 3 months	RCT: 1 (50) ¹⁶¹ ↔ 1 trial	Authors found a greater improvement in the HRQoL score in the Er:YAG arm compared with the sham arm, though the difference between arms was non-significant.	Low ⊕⊕○○ ^b	Er:YAG laser may result in little to no difference in QoL compared with sham.
	Hyaluronic acid suppositories 3 months	RCT: 1 (43) ¹⁵⁴ ? 1 trial	One trial reported median scores on a numeric rating scale for post-treatment bother related to dyspareunia, dryness, OAB, and recurrent UTI for Er:YAG laser and hyaluronic acid suppositories but did not provide statistical comparisons over time between groups.	Very low ⊕○○○ ^{a,b,c}	The evidence is very uncertain on the effect of Er:YAG laser on QoL compared with hyaluronic acid suppositories.
Satisfaction with treatment	Hyaluronic acid suppositories 3 months	RCT: 1 (43*) ¹⁵⁴ ? 1 trial	One trial reported median ratings of satisfaction on PGI-I for both groups but did not provide a statistical comparison over time between groups.	Very low ⊕○○○ ^{a,b,c}	The evidence is very uncertain on the effect of Er:YAG laser on treatment satisfaction compared with hyaluronic acid suppositories.
Adverse effects	Sham Laser 3 months	RCT: 1 (50) ¹⁶¹	Authors found that more participants in the Er:YAG arm reported mild vaginal pain immediately after treatment compared with the sham arm but did not provide a statistical comparison. All cases were resolved after 3 months.	Very low ⊕○○○ ^{b,d}	The evidence is very uncertain on the effect of Er:YAG laser on SAEs compared with sham.
	Hyaluronic acid suppositories 3 months	RCT: 1 (43) ¹⁵⁴	One trial reported no difference in SAEs after Er:YAG compared with hyaluronic acid suppositories. No SAEs were observed in either arm.	Very low ⊕○○○ ^{a,b,d}	The evidence is very uncertain on the effect of Er:YAG on SAEs compared with hyaluronic acid suppositories.

Abbreviations: AE=adverse effect; COMMA=Core Outcomes in Menopause; EORTC SHQ-C22=European Organization for the Research and Treatment of Cancer Sexual Health Questionnaire; Er:YAG=Erbium-doped yttrium aluminum garnet laser; HRQoL=health-related quality of life; MBS=most bothersome symptom; OAB=overactive bladder; OIS=optimal information size; PGI-I=Patient Global Impression of Improvement; QoL=quality of life; RCT=randomized controlled trial; RoB=risk of bias; SAE=serious adverse effect; UTI=urinary tract infection; VAS=visual analog scale

Direction of effect

↑: Intervention group had a statistically significantly better outcome than comparison group (e.g., improved symptoms, higher treatment satisfaction)

↔: No statistically significant difference between groups

?: No statistical comparison of change in time between groups provided

Certainty of evidence (COE)

Low (⊕⊕○○): Our confidence in the effect estimate is limited; the true effect may be substantially different from the effect estimate.

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Very low (⊕○○○): We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

^aDowngraded one level for study limitations (one or more trials assessed as “some concerns” RoB)

^bDowngraded two levels for imprecision (total sample size much less than OIS of 400)

^cDowngraded one level for study limitations (one or more trials did not provide adequate statistical reporting)

^dDowngraded one level for imprecision (zero or few events)

3.3.3.4.1.1 Vulvovaginal Dryness

3.3.3.4.1.1.1 Er:YAG Laser Vs. Hyaluronic Acid Suppositories (1 Trial; Total N=43)

Gold (2023)¹⁵⁴ (N=43) enrolled women with urogenital atrophy and at least one GSM symptom after breast cancer treatment, about three-quarters of whom were taking an aromatase inhibitor or tamoxifen, and evaluated the effect of Er:YAG laser versus hyaluronic acid (moisturizer) suppository on vulvovaginal dryness. Using the European Organization for the Research and Treatment of Cancer Sexual Health Questionnaire (EORTC SHQ C22) single-item dryness domain, they reported that the Er:YAG laser and hyaluronic acid suppository groups did not differ in the proportion of patients reporting vaginal dryness ‘not at all’ or ‘a little’ from baseline to 3-month followup (Laser 0% to 27% vs. Moisturizer 12% to 47%) or the proportion reporting ‘quite a bit’ or ‘very much’ (Laser 100% to 74% vs. Moisturizer 88% to 53%). They also reported the overall proportion of patients reporting vaginal dryness at baseline and followup without any significant differences between groups (Laser 91% to 73% vs. Moisturizer 86% to 67%). Due to concerns about RoB, imprecision, and statistical insufficiency, we find the evidence is very uncertain on the effect of Er:YAG laser on vulvovaginal dryness compared with hyaluronic acid suppositories (very low COE).

3.3.3.4.1.2 Vulvovaginal Discomfort/Irritation

No trials evaluated the effect of Er:YAG laser on vulvovaginal discomfort or irritation.

3.3.3.4.1.3 Dysuria

No trials evaluated the effect of Er:YAG laser on dysuria.

3.3.3.4.1.4 Dyspareunia

3.3.3.4.1.4.1 Er:YAG Laser Vs. Hyaluronic Acid Suppositories (1 Trial; Total N=43). In the trial by Gold (2023)¹⁵⁴ (N=43), median EORTC-SHQ C22 sexual pain domain scores (0-100, lower is better) assessed at 3 months post-baseline were not statistically significantly different ($P>0.05$) between groups of women with a history of breast cancer receiving Er:YAG laser or hyaluronic acid suppositories (Laser: 33.3 vs. hyaluronic acid suppositories: 54.2).¹⁵⁴ They also reported the overall proportion of patients reporting dyspareunia at baseline and followup without any significant differences between groups (Laser 86% to 68% vs. Moisturizer 76% to 62%). We downgraded for RoB, imprecision, and statistical insufficiency and conclude the evidence is very uncertain on the effect of Er:YAG laser on dyspareunia compared with hyaluronic acid suppositories (very low COE).

3.3.3.4.1.4.2 Er:YAG Laser Vs. Er:YAG Laser Hyperstack (1 Trial; Total N=68)

In 68 women with a history of breast cancer, Fidecicchi (2023)¹⁵³ reported that a ‘hyperstack’ Er:YAG laser protocol was associated with significantly ($P<0.05$) greater reduction from baseline in mean 10-point VAS pain score (0=best to 10=worst) at 6 months post-baseline compared with a standard Er:YAG protocol (Laser Hyperstack -7.15 vs. Laser Standard -5.12). After downgrading for RoB and imprecision, we

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conclude the evidence is very uncertain on the effect of Er:YAG hyperstack laser on dyspareunia compared with standard Er:YAG laser (very low COE).

3.3.3.4.1.5 Change in MBS

No trials evaluated the effect of Er:YAG laser on change in MBS.

3.3.3.4.1.6 QoL (i.e., Distress, Bother, or Interference of GSM Symptoms)

3.3.3.4.1.6.1 Er:YAG Laser Vs. Sham Laser (1 Trial; Total N=50)

Chienthong (2023)¹⁶¹ (N=50) compared a single application of Er:YAG laser to sham laser in women diagnosed with OAB, at least one symptom of VVA, and no history of malignant disease. Symptom bother scores at 3 months (0-100, higher is increased bother), a domain of the OAB-questionnaire, did not differ significantly ($P>0.05$) between the groups (Laser 47.1 vs. Sham 53.2). The change from baseline in symptom bother was significant only for the laser group (Laser -8.4 vs Sham -4.2). Similar non-statistically different ($P>0.05$) results were reported for the Health-Related Quality of Life domain at 3 months (0-100, higher is better quality of life) (Laser 30.7 vs. Sham 42.7), with a significant change from baseline only for the laser group (Laser -9.4 vs. Sham -4.7). Downgrading two levels for imprecision, we conclude that Er:YAG laser may result in little to no difference in menopause-related QoL compared with sham (low COE).

3.3.3.4.1.6.2 Er:YAG Laser Vs. Hyaluronic Acid Suppositories (1 Trial; Total N=43)

Gold (2023)¹⁵⁴ (N=43) evaluated the effect of Er:YAG laser versus hyaluronic acid vaginal suppositories in breast cancer survivors, on quality of life related to various GSM symptoms. Median 10-point numeric rating scale (NRS) scores for bother associated with OAB with incontinence (OAB Wet) (0 vs 0), recurrent UTI (0 vs 0), dyspareunia (7 vs 5), and vaginal dryness (3 vs 2) did not differ significantly ($P>0.05$) between groups at 3 months post-baseline but a statistical comparison of change over time for the two groups was not reported. After downgrading for RoB, imprecision and statistical insufficiency, we conclude the evidence is very uncertain on the effect of Er:YAG laser on menopause-related QoL compared with hyaluronic acid suppositories (very low COE).

3.3.3.4.1.7 Satisfaction With Treatment

3.3.3.4.1.7.1 Er:YAG Laser Vs. Hyaluronic Acid Suppositories (1 Trial; Total N=43)

Gold (2023)¹⁵⁴ (N=43) compared Er:YAG laser with hyaluronic acid suppositories and reported no significant difference ($P>0.05$) between groups at 3 months post-baseline for ratings using the PGI-I or the Zurich Satisfaction Questionnaire (ZUF-8). We downgraded for RoB, imprecision and statistical insufficiency and conclude the evidence is very uncertain on the effect of Er:YAG laser on treatment satisfaction compared with hyaluronic acid suppositories (very low COE).

3.3.3.4.1.8 Adverse Effects

Three trials evaluated the potential harms of Er:YAG laser therapy.^{153, 154, 161} We captured when a trial reported any AE/TEAE (k=0), SAEs (k=3), discontinuation due to AE (k=3), or a clinically relevant, specific AE (k=1). Results are reported below by these four categories, then type of comparison. Reporting varied widely – including when and what events were assessed. No trials provided statistical measures comparing effects of interventions with comparators. None of the trials were designed to adequately assess serious or severe AEs. Long-term harms outcomes from the non-controlled studies are described following the outcomes from the RCTs and quasi-randomized studies. Two trials^{153, 154} evaluated safety only to state

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that no AEs were reported in either trial arm and that no participants discontinued due to AEs. Specific counts (when available) and detailed AE reporting can be found in Appendix Table C.27.

3.3.3.4.1.8.1 Any AE/TEAE

No trials reported the overall count or proportion of participants who experienced any AE.

3.3.3.4.1.8.2 Serious AEs

We used GRADE to assess the three trials^{153, 154, 161} that evaluated SAEs, all of which reported that no SAEs occurred in any of the trial arms. The trials investigated Er:YAG versus sham laser (N=50),¹⁴⁸ Er:YAG versus hyaluronic acid suppositories (N=43),¹⁵⁴ or Er:YAG versus Er:YAG hyperstack (N=68).¹⁵³ Due to study limitations and imprecision, the evidence is very uncertain on the effect of Er:YAG on SAEs compared with sham laser, hyaluronic acid suppositories, or Er:YAG hyperstack (very low COE).

3.3.3.4.1.8.3 Discontinuation Due to AEs

Three trials^{153, 154, 161} reported on discontinuation due to AE. There were no discontinuations due to AEs in any of the trials, which evaluated Er:YAG versus sham laser¹⁴⁸ (N=50), hyaluronic acid suppositories¹⁵⁴ (N=43), or Er:YAG hyperstack¹⁵³ (N=68).

3.3.3.4.1.8.4 Specific AEs

One trial¹⁴⁸ (N=50) of Er:YAG laser versus sham laser reported on proportions of specific AEs. Chiengthong (2023)¹⁴⁸ reported the percentage of participants who experienced vaginal pain after treatment (36% vs. 4%), vaginal bleeding (4% vs. 0%), and vaginal abrasions (0%). Detailed specific AE results can be found in Appendix Table C.27.

3.3.3.4.2 Other Outcomes

3.3.3.4.2.1 Er:YAG Laser Vs. Sham Laser

The trial by Chiengthong (2023)¹⁶¹ (N=50) reported a composite 4-point VAS for four vaginal symptoms (vaginal dryness, vaginal irritation, soreness, and dyspareunia) following a single Er:YAG laser application compared with sham. The median score at 3 months was statistically significantly lower for the laser group; change from baseline was statistically significant for both groups.

Chiengthong (2023)¹⁶¹ (N=50) also reported a significant difference in VHI scores at 3 months favoring the laser group following a single Er:YAG laser application compared with sham.¹⁶¹ The change from baseline was significant only for the laser group.

The primary outcome in the trial by Chiengthong (2023)¹⁶¹ was change in Overactive Bladder Symptom Score (OABSS). Trial participants (N=50) had been diagnosed with OAB. The mean OABSS at 3 months was lower in the laser group indicating less severe symptoms. Change from baseline was significant for both groups.

3.3.3.4.2.2 Er:YAG Laser Vs. Hyaluronic Acid Suppositories

Gold (2023)¹⁵⁴ (N=43) did not provide data but reported that VHI improved significantly from baseline to 3 months post-baseline in both the Er:YAG laser and hyaluronic acid suppository groups with a non-significant difference between groups.

The same trial¹⁵⁴ found no statistically significant difference in the percentage of participants reporting recurrent UTIs at 3 months post-baseline.

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3.3.3.5 Long-Term Adverse Event Reporting From Non-Controlled Studies

To supplement AE data reported in RCTs, we extracted data from non-controlled or retrospective studies enrolling at least 20 individuals receiving active treatment and reporting outcomes at least one year after treatment. We identified 15 studies (in 16 papers), which are summarized in Table 13.¹⁶²⁻¹⁷⁷ Fourteen studies were rated critical RoB and one was rated serious RoB using the Risk of Bias in non-Randomized Studies - of Interventions (ROBINS-I) and are discussed briefly; additional information can be found in Appendix Table C.11. Nine studies used CO₂ lasers,^{162, 163, 165-169, 172, 173, 175} five used Er:YAG lasers or neodymium doped YAG lasers (Nd:YAG),^{164, 170, 174, 176, 177} and one used a radiofrequency technique.¹⁷¹ Five studies enrolled breast cancer survivors.^{163, 165-167, 174, 177} Enrollments ranged from 25 participants¹⁷⁶ to 230.¹⁷⁰ Six were from Europe,^{165, 166, 170-172, 174} four from the US,^{162, 163, 167, 169, 175} three from Asia,^{164, 168, 177} and one each from Australia¹⁷³ and South America.¹⁷⁶

Table 13. Overview of included uncontrolled observational studies reporting long-term energy-based treatment harms

Category	Characteristics	CO ₂ Laser (k=9)	Er:YAG Laser (k=5)	Radiofrequency (k=1)	Total (k=15)
Sample Size	≤60	4	2	1	7
	61-99	2	1	0	3
	100-199	3	0	0	3
	200-550	0	2	0	2
Special Populations	History of/high risk for breast cancer	4	0	1	5
Location	Asia	1	2	0	3
	Australia	1	0	0	1
	Europe	3	2	1	6
	North America	4	0	0	4
	South America	0	1	0	1
Funding Source	Industry	3	0	0	3
	Academia	1	1	0	2
	Government	1	0	0	1
	None	4	2	0	6
	NR	0	2	1	3

Abbreviations: CO₂=carbon dioxide; Er:YAG= Erbium-doped yttrium aluminum garnet laser; NR=not reported

At followup ranging from 12 to 24 months, data from 11 individuals¹⁷² to 135 individuals¹⁶⁶ were available. The exception was the retrospective study which included followup data from all 204 participants.¹⁷⁷ Attrition was 20 percent or higher in eight of the 14 studies^{162, 163, 165, 167, 168, 170, 172, 173, 175} with three additional studies not reporting information about loss to followup.^{166, 171, 176} Eight studies reported no AEs^{170-174, 176} or no AEs lasting longer than 1 year.¹⁷⁷ Five reported no serious AEs or no treatment-related AEs but provided no detail about any non-serious events.^{162, 163, 165-168} One reported no study withdrawals due to AEs.¹⁷⁵

3.3.4 Non-Hormonal Interventions: Moisturizers

3.3.4.1 Key Messages

- Vaginal moisturizers may improve vulvovaginal dryness compared with placebo but may result in little to no difference in MBS (low COE). The evidence is very uncertain on the effect of vaginal moisturizers versus placebo on dyspareunia and treatment satisfaction (very low COE).

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- No trials evaluated the effect of vaginal moisturizers on vulvovaginal discomfort/irritation, dysuria, or QoL.
- Vaginal moisturizers probably result in little to no difference in AEs compared with placebo (moderate COE).

3.3.4.2 Overview

Six trials of vaginal moisturizers were included. Four heterogeneous trials were assessed as low or some concerns RoB.^{84, 86, 178, 179} Two trials^{75, 76} were rated as having high RoB and will not be discussed further. Detailed RoB assessments can be found in Appendix Tables C.1 and C.2. Detailed trial characteristics are reported in Appendix Table C.6. Limited information about the high RoB trials is in Table 2 and Appendix Table C.10.

Three trials were small (range 40 to 98 participants); one trial had a moderate sample size (n=200 [moisturizer and placebo arms]).⁸⁶ The average participant age ranged from 46 to 61 years. One trial enrolled breast cancer survivors and had the youngest mean ages (45-46 years)¹⁷⁸ compared to the other trials (57-61 years). Vaginal moisturizers were applied three times per week^{84, 178, 179} or every three days⁸⁶ with placebo gel or lubricants administered at the matching intervals for all trials except one (which compared three times weekly moisturizer plus water-based lubricant as-needed with sexual activity with as-needed lubricant alone¹⁷⁹).

The trials examined the effects of lactic acid-based vaginal gel,¹⁷⁸ hyaluronic acid-based vaginal gel,¹⁷⁹ bioadhesive polycarbophil-based vaginal gel,⁸⁶ and polyacrylic acid vaginal cream,⁸⁴ compared with placebo or lubricant gels. Two trials were multi-arm and investigated other agents compared with placebo: information about the other arms can be found in the Section 3.3.1 for estrogen^{84, 86} and Section 3.3.2 for testosterone.⁸⁴

All four trials were short-term (12 weeks). The four trials each used different outcome metrics, which precluded pooling for meta-analysis. All trials reported vulvovaginal and sexual function outcomes (KQ2), and all reported adverse effects (KQ3). COE ratings for priority outcomes are listed in Table 14. Complete outcomes data are presented in Appendix Table C.22 to C.23.

Trials including moisturizers as comparators to other active agents are reported in other sections of this report. See the Section 3.3.3 for trials of Er:YAG laser versus hyaluronic acid suppositories in women with a history of breast cancer¹⁵⁴ and CO₂ laser versus CO₂ laser plus moisturizer (0.2% hyaluronic acid vaginal gel).¹⁵⁵ See Section 3.3.2 for a trial of aqueous hypromellose-based vaginal gel versus aqueous hypromellose-based vaginal gel plus oxytocin¹³⁰ and a trial evaluating the effect of adding either raloxifene or placebo to a comparison of conjugated equine estrogen or moisturizer.¹³⁸

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Table 14. Summary of COMMA outcomes, findings, and certainty of evidence for vaginal moisturizers

Outcome	Comparator Followup	Study Design: No. Trials (N) Direction of Effect	Findings	Certainty of Evidence	Summary Statement
Vulvovaginal dryness	Placebo 12 weeks	RCT: 4 (418 [†]) ^{84, 86, 178, 179} ↑ 2 trials ↔ 1 trial ? 1 trial	Four trials found mixed effects of moisturizer compared with placebo using three measurement tools. Two trials found a significant benefit using the VAS ¹⁷⁸ or the VRS Dryness Scale. ¹⁷⁹ The other two trials used the FSFI lubrication domain and either reported no significant difference between groups ⁸⁶ or did not provide a statistical comparison of change over time. ⁸⁴	Low ⊕⊕○○ ^{a,c}	Vaginal moisturizer may improve vulvovaginal dryness compared with placebo.
Dyspareunia	Placebo 12 weeks	RCT: 3 (338 [†]) ^{84, 86, 178} ↑ 1 trial ↔ 1 trial ? 1 trial	Three trials found mixed effects of moisturizer compared with placebo using two measurement tools. One trial found a significant benefit using VAS. ¹⁷⁸ The other two trials used the FSFI pain domain and either reported no significant difference between groups ⁸⁶ or did not provide a statistical comparison of change over time. ⁸⁴	Very low ⊕○○○ ^{a,b,c}	The evidence is very uncertain on the effect of vaginal moisturizer on dyspareunia compared with placebo.
Change in MBS	Placebo 12 weeks	RCT: 1 (200 [†]) ⁸⁶ ↔ 1 trial	One trial reported no significant difference between groups in change in severity of MBS. ⁸⁶	Low ⊕⊕○○ ^{a,d}	Vaginal moisturizer may result in little to no difference in change in severity of MBS compared with placebo.
Satisfaction with treatment	Placebo 12 weeks	RCT: 2 (280 [†]) ^{86, 179} ↔ 1 trial ? 1 trial	One trial reported “patients highly satisfied with treatment” (actual results data not available) ¹⁷⁹ and another reported treatment satisfaction was similar between groups. ⁸⁶	Very low ⊕○○○ ^{a,c,d}	The evidence is very uncertain on the effect of vaginal moisturizer on treatment satisfaction compared with placebo.
Adverse effects (any AE)	Placebo 12 weeks	RCT: 4 (418) ^{84, 86, 178, 179} ? 4 trials	Trials reported AEs were similar between groups. All were deemed mild or moderate.	Moderate ⊕⊕⊕○ ^a	Moisturizers probably result in little to no difference in adverse effects compared with placebo.

Abbreviations: AE=adverse effect; COMMA=Core Outcomes in Menopause; FSFI=Female Sexual Function Index; MBS=most bothersome symptom; OIS=optimal effect size; RoB=risk of bias; RCT=randomized controlled trial; VAS=visual analog scale; VRS=Verbal Rating Scale

*Total N includes only polyacrylic acid cream and placebo arms from Fernandes (2014).⁸⁴ See Sections 3.3.1 and 3.3.2 for conjugated estrogens cream and testosterone arm results, respectively.

†Total N includes only non-hormonal moisturizer and placebo arms from Mitchell (2018).⁸⁶ See Section 3.3.1 for conjugated estrogens cream arm results.

Direction of effect

↑: Intervention group had a statistically significantly better outcome than comparison group (e.g., improved symptoms, higher treatment satisfaction)

↔: No statistically significant difference between groups

?: No statistical comparison of change in time between groups provided

Certainty of evidence (COE)

Moderate (⊕⊕⊕○): We are moderately confident in the effect estimate; the true effect is likely to be close to the effect estimate, but there is a possibility that it is substantially different.

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Low (⊕⊕○○): Our confidence in the effect estimate is limited; the true effect may be substantially different from the effect estimate.
Very low (⊕○○○): We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

^aDowngraded one level for study limitations (one or more trials assessed as “some concerns” RoB)

^bDowngraded one level for inconsistency (effect varied across trials)

^cDowngraded one level for study limitations (one or more trials did not provide adequate statistical reporting)

^dDowngraded one level for imprecision (total sample size less than OIS of 400)

3.3.4.3 COMMA Outcomes

3.3.4.3.1 Vulvovaginal Dryness

3.3.4.3.1.1 Moisturizer Vs. Placebo (4 Trials; Total N=418)

Four trials^{84, 86, 178, 179} (N=418) evaluated the effect of vaginal moisturizer versus placebo on vaginal dryness at 12 weeks with mixed results. Nappi (2022)¹⁷⁹ (N=80) was an industry-sponsored trial that enrolled postmenopausal women with vaginal pH \geq 5 and at least one moderate to severe GSM symptom and compared hyaluronic acid-based vaginal gel plus as-needed water-based lubricant to as-needed water-based lubricant alone. They measured vaginal dryness on a 4-point Verbal Rating Score (0=absent, 1=mild, 2=moderate, 3=severe) and reported no significant difference ($P>0.05$) in the proportion of participants with \geq 1 point reduction in dryness severity from baseline to 3 months in both the moisturizer arm (89.8%) and the as-needed water-based lubricant alone group (79.7%). However, a significantly ($P<0.05$) higher proportion of participants in the moisturizer arm improved by \geq 2 points from baseline to 3 months, compared with the placebo group (73.9% vs. 35.3%). Two trials^{84, 86} evaluated dryness with the FSFI lubrication domain (0 (worst) to 6 (best)). Fernandes (2014)⁸⁴ (N=40) enrolled patients from a menopause clinic with any severity GSM symptoms and compared vaginal polyacrylic acid cream to vaginal glycerin and hydroxyethylcellulose (placebo) gel. They found a statistically significant change from baseline to 12 weeks for both vaginal polyacrylic acid cream and for placebo (polyacrylic acid 2.9 to 4.4 and placebo 1.9 to 2.9); they did not provide a statistical test comparing the change over time between treatment arms. Mitchell (2018)⁸⁶ (N=200) enrolled women with at least one moderate to severe GSM symptom and compared polycarbophil gel with hydroxyethylcellulose (placebo) gel. Using the FSFI lubrication domain, they found no significant ($p>0.05$) difference in change from baseline to 12 weeks for the moisturizer and placebo arms (moisturizer 0.9 vs. placebo 1.2). Mitchell (2018)⁸⁶ also reported dryness outcomes on a 4-point severity scale (0=none to 3=severe) only among participants with moderate to severe dryness at baseline (N=154 with week 12 data) and found a non-significant ($P>0.05$) change from baseline to 12 weeks for vaginal moisturizer compared with placebo groups (moisturizer -1.3 vs. placebo -1.4). Lee (2011)¹⁷⁸ (N=98) enrolled postmenopausal women with a history of breast cancer who had vulvovaginal “dryness with pain” scores over 5 on a 10-point VAS (0 [best] to 10 [worst]) at baseline, and compared lactic acid vaginal gel with placebo gel. They found a statistically significant ($P<0.05$) greater reduction in the VAS for dryness with pain from baseline to 12 weeks (lactic acid 8.20 to 4.23 vs. placebo 7.92 to 6.51).

Due to study limitations and inconsistency, we conclude that vaginal moisturizer may result in a reduction in vulvovaginal dryness when compared with placebo treatments (low COE).

3.3.4.3.2 Vulvovaginal Discomfort/Irritation

No trials evaluated the effect of vaginal moisturizer on vulvovaginal discomfort or irritation.

3.3.4.3.3 Dysuria

No trials evaluated the effect of vaginal moisturizer on dysuria.

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3.3.4.3.4 Dyspareunia

3.3.4.3.4.1 Moisturizer Vs. Placebo (3 Trials; Total N=338)

Three trials^{84, 86, 178} (N=338) evaluated the effect of vaginal moisturizer versus placebo on dyspareunia at 12 weeks with mixed results. A fourth trial¹⁷⁹ incompletely reported outcomes from the FSDS-R at 12 weeks, only in supplementary material, which was unobtainable. Two trials^{84, 86} used the FSFI pain domain (0 (worst) to 6 (best)); Fernandes (2014)⁸⁴ (N=40) found a statistically significant change from baseline to 12 weeks for vaginal polyacrylic acid cream but not for placebo (polyacrylic acid 2.6 to 4.3 and placebo 2.1 to 3.1); they did not provide a statistical test comparing the change over time between treatment arms. Mitchell (2018)⁸⁶ (N=200) found no significant ($P>0.05$) difference in change from baseline to 12 weeks for the moisturizer and placebo arms (moisturizer 1.0 vs. placebo 0.9). Mitchell (2018)⁸⁶ also reported pain with penetration outcomes on a 4-point severity scale (0=none to 3=severe) only among participants with moderate to severe pain with penetration at baseline (N=166 with week 12 data) and found a non-significant ($P>0.05$) change from baseline to 12 weeks for vaginal moisturizer compared with placebo groups (moisturizer -1.1 vs. placebo -1.5). Lee (2011)¹⁷⁸ (N=98) used the VAS (0 (best) to 10 (worst)) and found that among breast cancer survivors there was a statistically significant ($P<0.05$) greater reduction in the VAS for dyspareunia from baseline to 12 weeks (lactic acid 8.23 to 5.48 vs. placebo 8.11 to 6.11). Due to study limitations and inconsistency, we conclude that the evidence is very uncertain on the effect of vaginal moisturizer on dyspareunia compared with placebo (very low COE).

3.3.4.3.5 Change in MBS

3.3.4.3.5.1 Moisturizer Vs. Placebo (1 Trial; Total N=200)

One trial⁸⁶ (N=200) evaluated the effect of vaginal moisturizer versus placebo on change in MBS using a 4-point severity scale (0=none to 3=severe). Mitchell (2018)⁸⁶ offered itching, pain, dryness, irritation, or dyspareunia as their MBS options and reported the mean change in severity of the MBS between baseline and 12 weeks. They found no significant ($P>0.05$) difference for vaginal moisturizer compared with placebo gel (-1.2 vs. -1.3). Due to study limitations and imprecision, we conclude that vaginal moisturizer may result in little to no difference in the change in severity of the MBS compared with placebo (low COE).

3.3.4.3.6 QoL (i.e., Distress, Bother, or Interference of Genitourinary Symptoms)

No trials evaluated the effect of vaginal moisturizer on QoL.

3.3.4.3.7 Satisfaction With Treatment

3.3.4.3.7.1 Moisturizer Vs. Placebo (2 Trials; Total N=280)

Two trials^{86, 179} (N=280) evaluated the effect of vaginal moisturizers versus placebo on treatment satisfaction at 12 weeks or 3 months. Mitchell (2018)⁸⁶ (N=200) used a trial-specific, 11-point Likert scale (0=not satisfied to 10=completely satisfied) and reported mean treatment satisfaction was similar between groups (7.7 vs 8.1) without a statistical comparison. They also reported the percentage of participants who reported “meaningful benefit” and found no significant ($P>0.05$) difference between the vaginal moisturizer arm (58%) and the placebo arm (65%). Nappi (2022)¹⁷⁹ (N=80) measured treatment satisfaction with the Patients’ Global Assessment of Overall Satisfaction 4-point scale (0=dissatisfied or very dissatisfied to 3=greatly satisfied) and reported that “overall, patients were highly satisfied with treatment,” with 100 percent of participants in the moisturizer arm “very/greatly satisfied,” at 3 months and no information provided about the placebo arm. Data were only reported in supplementary material, which was

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unobtainable. Due to study limitations and imprecision, we conclude that the evidence is very uncertain on the effect of vaginal moisturizer on treatment satisfaction compared with placebo (very low COE).

3.3.4.3.8 Adverse Effects

Four heterogeneous trials evaluated the potential harms of lactic acid-based vaginal gel,¹⁷⁸ hyaluronic acid-based vaginal gel,¹⁷⁹ vaginal moisturizer,⁸⁶ or polyacrylic acid cream.⁸⁴ We captured when a trial reported any AE/TEAE (k=4), SAEs (k=2), discontinuation due to AE (k=2), or clinically relevant, specific AEs (k=2). One trial⁸⁴ evaluated safety only to state that no AEs were reported in either trial arm. Two of these trials were multi-arm and investigated other agents: information about the other arms can be found in Section 3.3.1 for estrogen^{84, 86} and Section 3.3.2 for testosterone.⁸⁴ Specific counts (when available) and detailed AE reporting can be found in Appendix Table C.23.

3.3.4.3.8.1 Any AE/TEAE

3.3.4.3.8.1.1 Moisturizer Vs. Placebo (4 Trials; Total N=418)

We assessed the 4 trials^{84, 86, 178, 179} (N=418) that reported rates of participants who experienced any AE/TEAE using GRADE and downgraded one level for study limitations. Lee (2011)¹⁷⁸ and Mitchell (2018)⁸⁶ reported a higher rate in the moisturizer arm (38.8%; 53%) than the placebo arm (32.7%; 46%), though neither provided a statistical test of comparison. Nappi (2022)¹⁷⁹ reported that five AEs were observed in four participants; one was considered moderate intensity and the others were considered mild. Fernandes (2014)⁸⁴ evaluated AEs only to state that no AEs were reported in either arm. We conclude that moisturizers probably result in little to no difference in AEs compared with placebo (moderate COE).

3.3.4.3.8.2 Serious AEs

3.3.4.3.8.2.1 Moisturizer Vs. Placebo (2 Trials; Total N=178)

Two trials^{178, 179} (N=178) of moisturizer versus placebo evaluated and reported some form of SAEs. Lee (2011)¹⁷⁸ reported that there were no “major complications,” while Nappi (2022)¹⁷⁹ stated that no severe AE was reported, and no AE was considered related to the study treatment.

3.3.4.3.8.3 Discontinuation Due to AEs

3.3.4.3.8.3.1 Moisturizer Vs. Placebo (2 Trials; Total N=138)

Two trials (N=138) of moisturizer versus placebo reported treatment discontinuation due to AEs. In Lee (2011),¹⁷⁸ two participants in each arm discontinued due to vaginal irritation. Fernandes (2014)⁸⁴ reported that no participants discontinued treatment in either arm.

3.3.4.3.8.4 Specific AEs

3.3.4.3.8.4.1 Moisturizer Vs. Placebo (2 Trials; Total N=298)

Two trials^{86, 178} (N=298) of moisturizer versus placebo reported specific AEs observed over a 12-week treatment period. Vulvovaginal burning, itching, discharge, and (in one trial) UTI were reported in participants using vaginal moisturizers more often than in those using placebo. Mitchell (2018)⁸⁶ reported vaginal candidiasis (3% vs. 2%), vaginal discharge (5% vs. 2%), vaginal odor (1% vs. 5%), vulvovaginal burning (6% vs. 1%), vulvovaginal itching (6% vs. 2%), UTI (7% vs. 4%), and GI signs/symptoms (7% vs. 6%). Authors stated that the rates for specific AEs were not different among the treatment groups. Lee

3. Results, Findings for Key Questions 2 and 3, Non-Hormonal Interventions: Moisturizers

(2011)¹⁷⁸ reported there were no statistically significant ($P>0.05$) differences in adverse effects among breast cancer survivors: irritation/burning ($n=18$ vs. 13), itching ($n=8$ vs. 3), vaginal discharge ($n=5$ vs. 3).

3.3.4.4 Other Outcomes

Sexual function outcomes were mixed across three trials^{84, 86, 179} of postmenopausal women. The mean change in FSFI total score was statistically significantly greater with polyacrylic acid cream compared with lubricant gel.⁸⁴ However, there was no significant difference in the FSFI total score at 12 weeks for women treated with bioadhesive polycarbophil-based vaginal gel compared with a placebo.⁸⁶ No significant difference was found in the mean change in FSDS-R at 12 weeks for women treated with hyaluronic acid-based vaginal gel plus as-needed water-based lubricant compared with as-needed water-based lubricant alone.¹⁷⁹

Three trials^{86, 178, 179} reported objective measures of vaginal atrophy with mixed results. Lee (2011)¹⁷⁸ and Nappi (2022)¹⁷⁹ both found a statistically significant ($P<0.05$) greater reduction in vaginal pH from baseline to 12 weeks/3 months in the groups that received vaginal lactic acid and hyaluronic acid gels, respectively, compared with the groups that received non-acidic placebos. On the other hand, Mitchell (2018)⁸⁶ found no significant ($P>0.05$) difference in pH reduction between polycarbophil gel and hydroxyethylcellulose (placebo) gel. Lee (2011)¹⁷⁸ also reported a statistically significant ($P<0.05$) greater increase in vaginal maturation index in the group that received lactic acid gel compared with the placebo group, whereas Mitchell (2018)⁸⁶ found no significant ($P>0.05$) difference in the increase in superficial cells between the polycarbophil gel and placebo groups.

3.4 Findings for Key Question 4

What is the appropriate followup interval to assess improvement, sustained improvement, or regression of symptoms of GSM in women treated with hormonal, non-hormonal, and energy-based interventions?

3.4.1 Key Messages

- No trials were designed to directly evaluate the appropriate followup interval to assess improvement, sustained improvement, or regression of symptoms of GSM. However, trials of vaginal estrogen, vaginal DHEA, oral ospemifene, and vaginal moisturizers provided some interim data that can be used to estimate time to improvement.
- Most trials of monthly laser applications did not provide symptom outcomes until 12 to 16 weeks after baseline.
- When assessed, GSM symptoms generally began to improve within 1-2 months of initiating treatment with vaginal estrogen, vaginal DHEA, ospemifene, and vaginal moisturizers.
- Limited evidence suggests that vaginal epithelial maturation and pH changes associated with vaginal estrogen begin within 4 weeks and are sustained throughout use (until at least 1 year of followup).

For all intervention types, the most common trial length for efficacy/effectiveness trials was 12 weeks (range 8-52 weeks); very few trials provided 1 year of followup. Many trials of vaginal estrogen, vaginal DHEA, ospemifene, and vaginal moisturizers provided some interim data (commonly at least one mid-point at 4-6 weeks; some trials provided outcomes every 2-4 weeks).

3. Results, Findings for Key Question 4, Key Messages

Generally, hormonal trials that reported genital signs (e.g., changes in vaginal maturation index and pH) began to detect a change by 4 weeks (vaginal estrogen and oral ospemifene) or 4-6 weeks (vaginal DHEA). One trial of vaginal estrogen versus placebo⁹² reported a significant change in vaginal maturation and vaginal pH from baseline to 4, 6, and 12 weeks, with sustained results in an open label extension trial from week 13 to 52.

When reported, symptom improvement for the primary outcome of each trial was generally observed by 2-4 weeks (vaginal estrogen), 4-8 weeks (vaginal DHEA), 8-12 weeks (ospemifene), and 4-6 weeks (vaginal moisturizers). Only 2 trials of vaginal testosterone provided any interim symptom outcomes, with some small changes noted graphically by 4-6 weeks. Trials that identified early benefit often demonstrated further progression of symptom relief by 8 to 12 weeks. None assessed whether the additional benefit was statistically or clinically significant, or whether the level of symptom benefit experienced at 12 weeks represented the maximum expected benefit with longer term use. One trial of vaginal estrogen compared with no treatment for recurrent urinary infection,⁸⁹ found that the Kaplan-Meier curves for proportion of participants without a recurrent infection began to separate at 60 days and reached maximum separation around 150 days (sustained through trial termination at 316 days).

Energy-based interventions were commonly structured to provide three treatments monthly for 3 months. None of the 12 to 16-week trials provided interim outcomes. In one longer trial¹⁵⁶ with primary outcomes reported at 12 months, interim data began to suggest a small change in symptoms graphically at 2 months for both the laser and sham groups, though no statistically significant differences between the groups were found for any symptoms throughout the followup period.

3.5 Findings for Key Question 5

What are the effectiveness, comparative effectiveness, and harms of endometrial surveillance among women who have a uterus and are using hormonal therapy for GSM?

3.5.1 Key Messages

- No trials were designed to directly evaluate the effectiveness, comparative effectiveness, and harms of endometrial surveillance among women who have a uterus and are using hormonal therapy for GSM. However, some trials reported endometrial outcomes using active and/or passive surveillance that can be used to indirectly address surveillance questions.
- Oral ospemifene was associated with thickened endometrial lining and proliferative endometrial histology in more participants than placebo, and with one case of endometrial hyperplasia, using active surveillance at 12 weeks with transvaginal ultrasound and endometrial biopsy,
- In 10 trials up to 36 weeks that used active or passive endometrial surveillance, vaginal estrogen was associated with spontaneous vaginal bleeding and/or bleeding after progesterone challenge in one or more participants in 4 of 5 trials, a nominal increase in endometrial thickness on transvaginal ultrasound in 4 of 6 trials, and proliferative endometrium or hyperplasia in an endometrial polyp on biopsy in 2 of 3 trials. There were no observed cases of endometrial malignancy in these short duration trials.
- Trials of vaginal DHEA, oxytocin, bazedoxifene, raloxifene, and vaginal testosterone reported no difference in endometrial outcomes between treatment and control participants.

3. Results, Findings for Key Question 5, Vaginal Estrogen

3.5.2 Vaginal Estrogen

Nine trials proactively evaluated the effect of vaginal estrogen on endometrial stimulation using endometrial biopsy at 12 weeks (k=1),⁸⁵ transvaginal ultrasound at 8 or 12 weeks (k=6),^{87, 88, 94, 96, 98, 123} or progesterone challenge at 12 weeks (k=2).^{83, 88} Four trials passively assessed for vaginal bleeding among participants receiving vaginal estrogen for 12 (k=3)^{83, 86, 87} or 36 weeks (k=1).⁸⁹ Doses studied included estradiol soft-gel capsules (4 or 10 mcg),⁸⁵ estradiol ring (2 mg),^{83, 88, 89} conjugated estrogen cream (0.625 mg/g; 0.5 g dose nightly,⁹⁴ 1 g nightly for 3 weeks, then 1 week free of treatment,⁸³ 1 g dose three times per week,¹²³ 1 g dose nightly for 2 weeks, then twice weekly,⁹⁸ or 2 g dose three times weekly⁸⁸), estradiol cream (50 or 100 mcg⁸⁷), or estradiol gel (25 mcg⁹⁶).

Active surveillance was performed with scheduled endometrial biopsy on all participants with a uterus (about 55% of participants) at baseline and 12 weeks in 1 large trial (N=574).⁸⁵ Participants received vaginal estradiol (4 or 10 mg soft-gel capsules) or placebo soft-gels. No endometrial hyperplasia or malignancy was seen; no additional details were provided about biopsy results. Transvaginal ultrasound was performed at baseline and 8 or 12 weeks in six trials (N=476): 4 trials that compared vaginal estrogen with placebo,^{94, 96, 98, 123} 1 trial that compared 2 doses of vaginal estrogen,⁸⁷ and 1 trial that compared vaginal estrogen ring to cream.⁸⁸ Average endometrial thickness for participants receiving estrogen increased by 0.08 to 0.5 mm in three trials and decreased by 0.5 to 1 mm in the other two; placebo participant average changes ranged from -0.47 to 0.1. Two older trials^{83, 88} (N=390) assessed endometrial stimulation using progesterone challenge at 12 weeks, and reported vaginal bleeding in 3 to 4 percent of vaginal estrogen ring users and 9 to 21 percent of vaginal estrogen cream users. Notably, vaginal estrogen cream doses in these trials were higher than common current doses: 1 g nightly for three weeks followed by one week free of treatment in Ayton (1996)⁸³ (N=194) and 2 g three times per week in Nachtigall (1995)⁸⁸ (N=196). Subsequent endometrial biopsies identified proliferative endometrium or hyperplasia in an endometrial polyp (n=1) for 4 estradiol ring users and endometrial proliferation for 4 estrogen cream users.

Passive surveillance was performed by inquiring about vaginal bleeding in four vaginal estrogen trials (N=553): 1 trial comparing estrogen to placebo (12 weeks),⁸⁶ 1 trial comparing estrogen to no-treatment (36 weeks),⁸⁹ and 2 comparing estrogen delivery methods or doses (12 weeks).^{83, 87} Three of four trials identified patients receiving vaginal estrogen who experienced vaginal bleeding.

3.5.3 Non-Estrogen Hormones

Two vaginal DHEA trials^{126, 127} reported endometrial biopsy outcomes on participants with a uterus (40% of participants).¹²⁷ In Archer (2015)¹²⁷ (N=255), 18 percent of participants in the DHEA 0.50% group had no tissue or insufficient tissue on biopsy, compared with 7 percent in the placebo and 8 percent in the DHEA 0.25% groups. The remainder of all participants had atrophic biopsy results. One oral DHEA trial¹²⁹ (N=93) reported endometrial lining greater than 4 mm on TVU at 52 weeks in 1 of 26 DHEA participants and 0 of 26 placebo participants.

One oxytocin trial¹³⁰ (N=161) reported no concerns on TVU at 12-weeks.

All included ospemifene trials assessed endometrial outcomes with both TVU and biopsy at baseline and 12 weeks¹³²⁻¹³⁴ or 52 weeks.^{135, 150} TVU measurements for ospemifene participants increased by an average of 0.4 to 1.1 mm; placebo group mean changes ranged from -0.23 to 1.1 mm. In 2 trials (N=1031), 6 percent of ospemifene participants had an endometrial lining ≥ 5 mm at 12 weeks¹³³ or 52 weeks¹³⁵ (compared with $<2\%$ of placebo participants). Endometrial hyperplasia was seen in 1 trial participant across all ospemifene trials,¹³⁵ no endometrial cancer was observed. Three trials (N=1883) provided more detailed endometrial biopsy outcomes at followup. Proliferative endometrial findings (weakly proliferative, active proliferative,

3. Results, Non-Hormonal Interventions Evidence Map, Overview

atypical epithelial proliferation, and proliferative pattern, disordered type) were all found almost exclusively in ospemifene participants (30 total cases across 3 trials^{132, 135, 150}), compared with 1 case of weakly proliferative endometrium in placebo.

One bazedoxifene and one raloxifene trial assessed endometrial outcomes with both transvaginal ultrasound and endometrial biopsy. The raloxifene trial¹³⁹ (N=91) reported no significant difference between intervention and placebo groups for change in endometrial lining thickness from baseline to 6 months, and no hyperplasia, carcinoma, or “clinically significant endometrial proliferation” in either group. The bazedoxifene trial¹³⁷ (N=215) did not report any endometrial results.

Two testosterone trials assessed endometrial outcomes with TVU. One trial¹²³ (N=38) of vaginal testosterone found that mean endometrial thickness did not change significantly from baseline to 12 weeks, and all participants had an endometrial thickness less than 5 mm. One trial¹¹⁵ (N=70) of oral estradiol combined with either transdermal testosterone or placebo found that endometrial thickness increased non-significantly in both groups from baseline to 8 weeks, at which point all participants with a uterus received medroxyprogesterone for 14 days.

3.6 Non-Hormonal Interventions Evidence Map

3.6.1 Key Messages

- The majority of non-hormonal interventions were focused on natural products (i.e., herbal or botanical supplements and vitamins) and were small in sample size.
- About a third of the identified studies were conducted in Iran and focused on sexual symptoms, with a wide variety of herbal or botanical supplements.

3.6.2 Overview

We identified 64 unique studies (63 RCTs and 1 prospective observational study) in 66 publications that investigated 46 unique non-hormonal interventions on symptoms of GSM. We provide summary tables for non-hormonal GSM interventions, with brief narrative descriptions below. We provide an overview of the major characteristics of eligible non-hormonal studies by intervention type in Table 15, and detailed characteristics of included studies in Appendix C. Using standard evidence mapping methods, we did not assess study quality or extract and synthesize outcomes.

All 64 studies provided information on the efficacy of non-hormonal interventions on GSM symptoms (KQ2) and most (k=38) provided information on harms or AEs (KQ3). Most studies enrolled individuals with a single GSM sign, symptom, or score on a symptom specific scale (e.g., vulvovaginal maturation index, vulvovaginal atrophy, sexual dysfunction) rather than a constellation of symptoms or broadly defined GSM.

Studies examined a wide array of non-hormonal interventions and were organized according to the National Center for Complementary and Integrative Health (NCCIH) framework.⁵⁹ Most trials focused on natural products (i.e., herbal or botanical supplements, vitamins, probiotics) (k=45). Fewer examined mind and body practices (k=8; including psychotherapies, acupuncture and Gua Sha therapy [Chinese healing method in which a trained professional uses a smooth-edged tool to stroke skin while applying pressure]), educational interventions (k=5), or non-GSM-specific pharmaceuticals (k=6). Of the natural products and pharmaceuticals, 27 were delivered orally and 23 vaginally. Most studies were small, with only 10 trials enrolling 100 or more participants. Only three trials had sample sizes greater than 200 participants, and

3. Results, Non-Hormonal Interventions Evidence Map, Overview

these investigated psychotherapy and Chinese herbal medicine,¹⁸⁰ *Lactobacillus*,¹⁸¹ and cognitive behavioral therapy and physical exercise.¹⁸² The majority were conducted in Iran (k=24) or other parts of Asia (k=14). The most common non-hormonal intervention trials evaluated the effect of herbal or supplement interventions on sexual function and were conducted in Iran. Table 16 presents a detailed breakdown of interventions and outcomes reported.

Among the 45 studies of natural products, 32 studies examined 21 unique phytoestrogen supplements. Most phytoestrogen supplements were investigated in only one study, though there were multiple studies of soy (k=5), *Pueraria mirifica* (k=4), and fenugreek, licorice, red clover and *Tribulus terrestris* (k=2 each). All phytoestrogen studies were small, roughly half (k=14) had sample sizes ≤ 60 participants, only 2 studies had sample sizes between 100 and 120. The majority of studies included placebo or no-treatment comparison groups, though eight studies (9 publications) compared various phytoestrogen herbal or botanical supplements with vaginal or systemic estrogen. Five studies compared vaginal chamomile,^{107, 108} fenugreek,¹⁰⁶ soy,⁹⁴ *Pueraria mirifica*,¹⁰⁴ and licorice¹⁰² with vaginal conjugated estrogens cream. Two studies compared oral or dietary soy products versus oral estradiol.^{103, 105} One study compared vaginal hop extract versus vaginal estradiol.¹⁸³ All eight studies had sample sizes less than 100 and reported both vulvovaginal and sexual symptoms.

Inconsistency in product formulation, dosing, route, and administration is a perennial challenge for evaluating natural products. Across the 45 studies of natural products, we found few studies testing identical products. For example, though we identified 31 trials testing 20 different phytoestrogens for GSM symptoms, all used different compounds or doses and reported different symptom outcomes, making synthesis impossible.

Studies also used a wide variety of tools to measure outcomes. In total, 64 unique studies used 44 different measures (Appendix Table C.29). The most common tools were the FSFI (k=17), Kupperman Index (k=6), MENQOL (k=5) and Short Form (SF)-36 (k=5). The remaining identified tools were used sparingly, with the vast majority reported in just one (k=27 unique measures) or two (k=11 unique measures) publications. The most commonly reported outcomes included sexual symptoms (k=47), genital or vulvovaginal symptoms (k=32), and urinary symptoms (k=23). Thirty-eight studies reported AEs. Only seven studies of ginseng,¹⁸⁴ soy,^{103, 105} vitamin D/E¹⁸⁵ and *Pueraria mirifica*¹⁸⁶⁻¹⁸⁸ reported outcomes in all three broad categories of interest: urinary symptoms, vulvovaginal or genital symptoms, and sexual symptoms.

3. Results, Non-Hormonal Interventions Evidence Map, Overview

Table 15. Overview of eligible non-hormonal intervention studies

Category	Characteristics	Educational Programs (n=5)	Mind and Body Practices (n=8)	Natural Products (n=45)	Pharmaceutical (n=6)	Total (n=64)
Sample Size	≤60	2	2	16	2	22
	61-99	3	3	24	2	32
	100-199	0	2	3	2	7
	200-499	0	1	2	0	3
Route of Administration	Oral	0	0	22	5	27
	Vaginal	0	0	22	1	23
	Other	5	7	1	0	13
Special Populations	Breast or gynecologic cancer	3	3	2	1	9
Country	Africa	0	1	0	0	1
	Asia (other)	0	2	9	1	12
	Asia (Iran)	2	1	21	0	24
	Australia	1	0	0	0	1
	Europe	0	3	6	0	9
	North America	2	0	2	5	9
	South America	0	1	7	0	8
Outcomes Reported*	Genital or vulvovaginal symptoms	2	1	27	2	32
	Urinary symptoms	1	5	13	4	23
	Sexual symptoms	4	6	34	3	47
	Psychological symptoms	3	4	3	1	11
	QoL	3	6	7	3	19
	Adverse effects	1	2	31	5	39

Abbreviations: AE=adverse effect; COMMA=Core Outcomes in Menopause; GSM=genitourinary syndrome of menopause; QoL=quality of life

*Outcome categories (COMMA outcomes noted) include: **Genital or vulvovaginal symptoms:** vaginal/vulvar irritation (COMMA), vaginal soreness, vaginal pain, vulvovaginal dryness/lubrication (COMMA); **Urinary symptoms:** dysuria (COMMA), recurrent urinary tract infections, urinary frequency, urinary urgency, nocturia, urinary urge incontinence, overactive bladder; **Sexual symptoms:** dyspareunia (COMMA), orgasmic dysfunction, low libido, decreased arousal, sexual desire, sexual function, bleeding associated with sexual activity; **Psychological symptoms:** depression, anxiety, and partner satisfaction; **Quality of life:** distress, bother or interference of GSM symptoms (COMMA); **Adverse effects (COMMA):** any reported AE or safety outcomes (breast cancer, breast cancer recurrence or progression, breast tenderness, cardiovascular risk)

3. Results, Non-Hormonal Interventions Evidence Map, Overview

Table 16. Interventions and outcomes reported in non-hormonal intervention studies

Intervention Category	Intervention Sub-Category	# Trials	Intervention of Interest	Vulvovaginal Signs/Symptoms	Urinary Symptoms	Sexual Symptoms	Psychological Symptoms	QoL	Adverse Effects
Educational Programs (k=5)	Sexual (k=3)	3	Sexual education ^{189, 190, 191}	-	-	2	2	1	1
	Lifestyle (k=2)	2	Lifestyle interventions ^{192, 193}	2	1	2	1	2	-
Natural Products (k=45)	Phytoestrogens (k=32)	1	Alcea ¹⁹⁴	1	-	1	-	-	1
		1	Black seed oil ¹⁹⁵	-	1	1	-	1	1
		1	Chamomile ^{107, 108}	-	-	1	-	-	1
		1	Curcumin ¹⁹⁶	-	-	1	1	-	1
		1	Fennel ^{197, 198}	1	-	1	-	-	1
		2	Fenugreek ^{106, 199}	2	-	2	-	-	1
		1	Genistein ²⁰⁰	1	-	-	-	-	-
		1	Ginseng ¹⁸⁴	1	1	1	1	-	-
		1	Hop extract ¹⁸³	-	-	1	-	-	1
		2	Licorice ^{102, 201}	2	-	2	-	-	1
		3	Mixed herbal ²⁰²⁻²⁰⁴	-	1	1	-	2	3
		1	Nettle ²⁰⁵	1	-	1	-	-	-
		1	Palm pollen ²⁰⁶	-	-	1	-	-	-
		4	Pueraria mirifica ^{104, 186-188}	4	3	4	-	-	4
		2	Red clover ^{207, 208}	1	-	2	-	-	-
		1	Sea buckthorn ²⁰⁹	1	-	-	-	-	1
		5	Soy ^{94, 103, 105, 210, 211}	5	2	4	-	-	4
		1	Squill oil ²¹²	-	-	1	-	-	-
		2	Tribulus Terrestris ^{213, 214}	-	-	2	-	-	1
	Others (k=6)	1	EstroG-100 ²¹⁵	1	-	-	1	-	1
		2	Lactobacillus ^{181, 216}	1	1	1	-	-	2
		3	Mixed herbal ^{180, 217, 218}	1	-	3	-	1	3
	Vitamins (k=7)	3	Vitamin D ²¹⁹⁻²²¹	1	2	1	-	2	2
		2	Vitamin E ^{109, 110}	1	1	1	-	-	1
		2	Vitamin D/E ^{185, 222}	2	1	1	-	-	-
Mind and Body Practices (k=8)	Physical (k=4)	1	Acupuncture ²²³	-	1	-	1	-	-
		1	Gua sha therapy ²²⁴	-	1	1	-	1	1
		1	Nerve stimulation ²²⁵	-	1	-	-	1	-
		1	Yoga/pelvic floor muscle training ²²⁶	1	-	1	-	1	-
	Psychological (k=4)	2	Cognitive behavioral therapy ^{182, 227}	-	1	2	2	2	-
		1	Mindfulness-based Stress Reduction ²²⁸	-	-	1	-	1	-
Pharmaceutical (k=6)	Pharmaceutical (k=6)	1	Mindfulness/aromatherapy ²²⁹	-	-	1	1	-	1
		1	Antibiotics ²³⁰	-	1	-	-	-	1
		1	Aprepitant ²³¹	-	1	-	-	-	1

3. Results, Non-Hormonal Interventions Evidence Map, Overview

Intervention Category	Intervention Sub-Category	# Trials	Intervention of Interest	Vulvovaginal Signs/Symptoms	Urinary Symptoms	Sexual Symptoms	Psychological Symptoms	QoL	Adverse Effects
		1	Citalopram ²³²	1	1	-	-	1	1
		1	Gabapentin ²³³	1	-	1	1	-	1
		1	Lidocaine ²³⁴	-	-	1	-	1	-
		1	Vibegron ²³⁵	-	1	-	-	1	1

Abbreviations: QoL=quality of life

4. Discussion

4.1 Overview

This systematic review provides an overview and evaluation of the evidence for screening, treatment, and monitoring of genitourinary syndrome of menopause (GSM). We found that vaginal estrogen, vaginal dehydroepiandrosterone (DHEA), oral ospemifene, and vaginal moisturizers may all improve at least some GSM symptoms in mostly short-term followup. Participants who received a lubricating cream or gel as a control treatment also often improved. No treatment significantly improved vaginal discomfort/irritation or dysuria. The evidence does not demonstrate efficacy of vaginal or systemic testosterone, vaginal oxytocin, oral raloxifene or bazedoxifene, or energy-based therapies for any GSM symptoms.

Harms reporting for most interventions was limited, in part, by studies with small sample sizes and short duration not being sufficiently powered to evaluate infrequent but serious harms. Less serious, infrequent adverse effects varied by treatment. For example, vaginal estrogen was associated with vaginal bleeding, discharge, and breast tenderness; vaginal DHEA was associated with increased facial hair, voice changes, and headaches; oral ospemifene was associated with hot flushes and vaginal candidiasis; and carbon dioxide (CO₂) laser was associated with vaginal bleeding, pain, and discharge. We did identify and report on specific Food and Drug Administration (FDA) indications, warnings and contraindications that can also be used to inform clinical decision making. For example, ospemifene is noted to be relatively contraindicated in women with coagulation disorders or prior cardiovascular events (and most studies excluded these women). Additionally, testosterone is not approved for women for any indication.

With the exception of vaginal DHEA, ospemifene, and some estrogen trials, the majority of studies that identified beneficial treatment effects were small (< 100 women). Most trials were short-term (commonly 12 weeks), which leaves important knowledge gaps for longer-term management of GSM symptoms, which tend to persist and potentially worsen with time since menopause. Importantly, despite the breadth of the evidence, the heterogeneous GSM literature contained few studies that evaluated identical combinations of populations, interventions, comparators, and outcomes. Numerous methodological issues with analyses and outcome reporting led to evidence downgrading, with ratings as low or very low certainty for most conclusions.

Strengths of our report include: a comprehensive search of randomized controlled trials (RCTs) and prospective observational studies with a concurrent control group investigating U.S.-available hormonal, non-hormonal, and energy-based interventions for GSM; rigorous assessment of methodologic quality for studies of moisturizers, hormonal interventions, and energy-based interventions; a high-level mapping of the evidence for non-hormonal interventions; and synthesis of long-term observational studies assessing energy-based treatment harms; and suggestions for future research based on our findings. Our findings are intended to help clinicians, patients, and other stakeholders to make informed decisions about GSM screening and treatment.

We found evidence spanning 40 years (1983-2023) across 172 studies of varied interventions to treat symptoms of GSM. One hundred seven of the publications (66 RCTs [24 secondary analyses], 15 uncontrolled studies, and 1 prospective observational study) evaluated estrogen (k=38) and non-estrogen (k=36) hormonal interventions, moisturizers (k=4), or energy-based (k=34) interventions and were assessed for methodologic quality. Sixty-seven percent (k=68)

4. Discussion

were rated low or some concerns risk of bias (RoB) (high or moderate quality). The low or some concerns RoB studies reported mixed results on the effects of hormonal, moisturizer, and energy-based interventions to treat various GSM symptoms (discussed below in Section 4.3). The high RoB trials (k=19) were primarily studies of vaginal estrogen and energy-based treatments (k=16), with comparable study characteristics to the low or some concerns RoB trials: about half were placebo controlled, nearly 40 percent were industry-funded, 3 included participants with cancer. The most common reason for a high RoB rating was missing outcome data, which was rarely a concern among low or some concerns RoB trials.

Sixty-six of the 172 publications reported on 63 RCTs and 1 observational study of non-hormonal interventions. We provide an evidence map with an overview of study characteristics for the heterogeneous non-hormonal literature, which describes 46 unique interventions (natural products, k=45; mind/body practices, k=8; educational interventions, k=5; and non-hormonal pharmaceuticals, k=6). This map serves as a starting point for clinicians, researchers, and professional groups interested in exploring the evidence for complementary and alternative therapies for GSM.

We intentionally focused on studies with at least 8-weeks of followup and on RCTs or prospective observational studies with a concurrent comparison group that included at least 20 participants per study arm. We did not include studies of systemic estrogen, which is used primarily to treat vasomotor symptoms of menopause and has been previously reviewed extensively. To focus on interventions most relevant for U.S.-based clinicians and patients, we did not include interventions unavailable or discontinued in the United States. Studies reported on dozens of patient, clinician, and laboratory outcomes; our report focuses on 8 patient-centered outcomes identified by the Core Outcomes in Menopause (COMMA) review⁴⁴ as most important to patients and clinicians, including (1) pain with sex, (2) vulvovaginal dryness, (3) vulvovaginal discomfort/irritation, (4) dysuria, (5) change in most bothersome symptom (MBS), (6) distress, bother, or interference of genitourinary symptoms (i.e., quality of life), (7) satisfaction with treatment, and (8) side effects of treatment. Additional outcomes identified in our protocol and summarized descriptively in the report include non-pain aspects of sexual function, recurrent urinary infections, urinary incontinence, and signs of vulvovaginal atrophy. We also searched for, but did not find, evidence related to screening for GSM. We report limited evidence that indirectly relates to optimal monitoring time intervals and the potential benefits and harms of endometrial surveillance for hormonal interventions.

4.2 Broader Context

The diversity and volume of the included literature reflect the evolving GSM nomenclature as well as the ongoing deliberation in the field about the definition of GSM as a syndrome (versus a collection of one or more symptoms),^{36-38, 236} the number and type of symptoms and/or physical signs required to make a diagnosis of GSM, and the causal relationship between menopause and GSM symptoms. Relatively few studies focused on patients with sexual (k=6) or urinary (k=3) symptoms only, while the majority included patients with vulvovaginal or some combination of symptoms. Only 21 percent of included studies required a prior clinical diagnosis related to GSM or vulvovaginal atrophy (or associated symptoms) for participant inclusion, with an additional 13 percent verifying eligibility via physical exam or questionnaire. Two-thirds of studies relied on self-reported GSM symptoms, perhaps more reflective of clinical practice, with inconsistent inclusion requirements for an elevated vaginal pH or vaginal atrophy on epithelial maturation evaluation. The broad definition of GSM applied to this review increased the scope of

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applicable studies and may be consistent with how GSM is defined by clinicians in practice. However, it likely also increased heterogeneity of studies and limited strength of evidence for synthesis of findings.

The large number of non-hormonal therapies included in our evidence map (46 unique interventions) may reflect a broader interest in complementary and alternative therapies. Enthusiasm for hormonal menopausal therapies has waxed and waned historically, with increased interest described recently in the lay press.²³⁷

4.3 Strengths and Limitations of the Evidence Base

The main strength of this evidence base is the breadth of U.S.-available interventions that have been tested for a wide array of GSM symptoms over the past 40 years. We identified higher quality (e.g., low or some concerns RoB) evidence examining the use of multiple formulations of vaginal estrogen, 6 different non-estrogen hormonal therapies, vaginal moisturizers, and 3 different energy-based therapies. Forty-five percent of included studies were industry-sponsored, and 15 percent did not report the source of funding (42% of high RoB trials were industry-sponsored). We identified limitations of the low or some concerns ROB studies that underwent full data extraction and of the non-hormonal intervention studies related to populations studied, interventions and comparators evaluated, and outcomes reported, as described below. We also noted a lack of evidence related to screening for GSM, and only indirect evidence related to appropriate followup intervals and endometrial surveillance.

Populations. Overall, the literature focused on postmenopausal predominantly white women. Though GSM symptoms tend to be more prevalent with increasing age, most studies enrolled women shortly after menopause, in their 50s and early 60s. Most women had moderate to severe baseline symptoms. Women were actively recruited, screened for study eligibility, and monitored for treatment adherence. Therefore, the applicability of evidence to an older population, racial/ethnic minorities, those with less severe symptoms or potentially less treatment adherent, is limited. Racial and ethnic differences in the experience of menopausal symptoms include potential differences in the prioritization or comfort discussing GSM symptoms.²³⁸⁻²⁴⁰

Treatments with the potential for serious systemic adverse effects (such as venous thromboembolism) were generally not tested in higher risk populations, such as those with a past history or risk factors for those outcomes, or in older patients. Obese women, who are at higher risk for endometrial cancer and venous thromboembolism, were excluded from many studies. When developing and finalizing the scope of this review, our key informants and technical expert panel indicated interest in GSM treatment for diverse patient populations, including those from non-white racial and ethnic backgrounds, transgender patients, women who underwent surgical menopause, and women with a history of breast cancer. However, over half of studies did not report racial or ethnic backgrounds of included study participants. All remaining studies included at least 80 percent white participants and over a quarter of total studies included at least 90 percent white participants. Less than half of studies reported inclusion of women with a hysterectomy, while a quarter excluded women with past hysterectomy; the remainder were unclear. Studies inconsistently reported whether past hysterectomy included removal of the ovaries (inducing surgical menopause) or uterus alone (reducing the risk of endometrial hyperplasia), and only one-third of studies reported the proportion of participants per study arm without a uterus. Studies did not commonly report on differences in outcomes for participants with surgical menopause compared with natural menopause. We found no studies in transgender populations, or among postpartum or lactating women, who may experience GSM symptoms due

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to a hypoestrogenic state. Over half of studies excluded women with a history of cancer or at high risk for cancer, while only 6 studies specifically recruited active or treated cancer patients (2 energy-based,^{153, 154} 1 vaginal DHEA,¹²⁴ 1 vaginal moisturizer,¹⁷⁸ 1 vaginal testosterone compared with placebo,¹²⁵ and 1 vaginal testosterone compared with vaginal estrogen⁹⁷). Most studies were small, with median n=47 participants per treatment arm. Less than one-third of studies included over 100 participants per arm (only 6 studies had n=200-380 participants per arm). Trials of herbal and botanical supplements were almost all small, with nearly 90 percent of studies under 100 people. Finally, many studies, especially those testing energy-based interventions, recruited women from specialty care, rather than primary care patient populations, and it was often unclear how many treatments women had previously tried for their symptoms.

Interventions. There was broad variability in dosing, formulations, and routes of delivery for study interventions. Most treatments were delivered vaginally, with the rest administered orally or transdermally. Even within intervention categories, variation in treatment dosing and route of delivery contributed to heterogeneity that largely precluded meta-analysis. For example, among the non-estrogen hormonal interventions, there were studies of vaginal and oral DHEA, and oral, transdermal, and vaginal testosterone. Several interventions were evaluated in combination with concurrent treatment with either estrogen or as-needed vaginal lubricant. Each of these treatment differences limited our ability to synthesize studies and draw conclusions with a higher COE. Vaginal moisturizers are a heterogeneous group of substances intended to replace or mimic vaginal secretions typical of a premenopausal state or alter the vaginal pH to better support a typical premenopausal vaginal flora. Though dozens of formulations of vaginal moisturizers are commercially available, we found only 4 with published studies that met inclusion criteria for review (many other moisturizer publications were excluded due to ineligible study population, lack of control arm, or inadequate length of followup). Finally, trials examining herbal and botanical supplements studied a broad variety of formulations and combination therapies that made synthesis challenging.

Comparators. The description of interventions used for control arms was highly variable and sometimes missing or incomplete. Many studies reported providing a “matched” placebo tablet, capsule, gel, or cream; others did not define the nature of the control or the composition of the placebo treatment. Many studies reported symptom improvement in participants who received lubricating vaginal placebo creams or gels. For this reason, studies with an oral placebo tablet, such as ospemifene trials, or no-treatment control groups, may have been more likely to demonstrate a difference between intervention and control groups. For a condition that is often treated symptomatically with vaginal lubricants, “placebo” creams and gels may represent an effective therapy, and the content of those creams or gels may be relevant for understanding the relative efficacy of the intervention under investigation.

Outcomes. In consultation with partners, Key Informants, and Technical Expert Panel (TEP) members, we focused on studies with patient-centered outcomes. Patient-centered outcomes are most relevant for clinicians and patients seeking symptom relief, and multiple studies have found that presence and severity of physical exam findings do not directly correlate with self-reported GSM symptoms.¹¹⁻¹³ However, patient-centered outcomes are inherently subjective and the validity of many study-specific or visual analogue measures used remains unknown. GSM is defined broadly to include a multitude of vulvovaginal, sexual, and urinary symptoms, and there are no outcome measures that holistically assess GSM severity. Studies included a large number of outcomes assessed using a diverse array of measurement tools. Though the COMMA review has defined a set of core outcomes,⁴⁴ they have yet to identify

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validated or preferred measures for assessing each outcome. Our ability to synthesize findings through meta-analysis was limited by the heterogeneity of measurement and reporting of outcomes. Among the measures frequently used, several use categorical/ordinal scales, which makes it difficult to interpret a change in scores, and few have an established threshold for minimal clinically important (noticeable) differences (MCID). Even when MCIDs are established for a particular population, symptom severity, intervention type and followup duration thresholds may vary across these domains. For this reason, we derived our Grading of Recommendations Assessment, Development and Evaluation (GRADE) certainty of evidence (COE) using a “noncontextualized” approach based on statistical measures of significance rather than a partially or fully contextualized approach that includes effect size magnitude or clinically meaningful changes. One of the most commonly used outcomes in GSM studies, MBS severity, was recommended by the FDA as a co-primary endpoint for vaginal estrogen studies in 2003.²⁴¹ However, we found that this outcome was reported in different ways throughout the literature: some studies included women with any one of several GSM symptoms as their MBS, and assessed change after treatment, while other studies limited inclusion criteria for participants or outcome assessment to one or two specific symptoms. Though studies within each intervention type generally used a common set of outcome measures, non-hormonal studies (described in the evidence map) used far more heterogeneous tools: 64 unique trials used 44 different outcome measures; 38 measures were used in only 1 or 2 publications. Additionally, though GSM treatments are often prescribed or recommended long-term, only three studies (all non-estrogen hormonal interventions) had a treatment duration of 1 year, while one additional study of CO₂ laser included 12 months of followup. The remaining studies all followed participants for less than a year, with most providing just 12 weeks of followup. We evaluated only studies with at least 8 weeks of followup (eliminating 64 publications with shorter followup), but outcomes were still assessed at different timepoints in different studies, which made comparison and synthesis more difficult. Finally, we identified variation and important limitations in data analyses and presentation of findings. Appropriate analyses should include how the change from baseline to followup in an outcome measure for the participants in the intervention arm compares with the change from baseline to followup in that outcome measure for the participants in the comparator arm (difference of the difference). However, many studies reported only change from baseline to followup in the intervention arm (lacking control) or only reported a comparison of the intervention and comparator arms at followup (a single time-point does not account for potential baseline differences). Such reporting can bias assessment of treatment effectiveness. Finally, many studies did not provide any measures of statistical significance or confidence intervals around the point estimates of effect. Such methods represent incomplete or inaccurate reporting in the individual studies, especially for readers with inadequate time or experience to construct the calculations themselves. This was particularly noticeable in harms reporting; definitions and reporting of harms/adverse effects also varied widely.

4.4 Strengths and Limitations of the Review Process

Our review process had several strengths. We applied a comprehensive and sensitive search filter in 3 large databases (MEDLINE, Embase, and CINAHL) in addition to searching reference lists of relevant systematic reviews. In every step of the review after abstract triage, at least two independent reviewers were involved. Discrepancies were discussed and resolved within the research team.

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Our review process was also subject to several limitations. We limited our review to studies published in English (introducing potential language bias) and those evaluating interventions available in the US (limiting applicability to clinicians and patients outside the US). This restriction resulted in excluding studies of estriol (the 16-hydroxylated metabolite of estradiol),²⁴² promestriene (a synthetic estrogen),²⁴³ and tibolone (which has estrogenic, progestogenic, and androgenic activity),²⁴⁴ all of which are available in many countries outside the US and have contributed to the evidence base for prior systematic reviews.^{48, 245, 246} Recent literature suggests that clinicians consider tailoring local estrogen and hormonal therapy based on specific effects and potential adverse effects of individual formulations.²⁴⁷ We also limited systemic estrogen studies to those comparing a GSM-specific treatment to systemic estrogen (rather than studies comparing routes/doses of systemic estrogen or systemic estrogen vs. placebo), which may have caused us to miss some studies that evaluated GSM symptoms as secondary outcomes (and symptoms for other indications as primary outcomes). We did not separate out the high-risk subgroups of interest (e.g., breast cancer survivors) in our analysis or GRADE. We highlighted which studies included these populations of interest, but GRADE assessments were organized by intervention, not population. We focused on intervention studies, but additional insight into some patient-centered outcomes could be supplemented with observational studies.

We made several decisions to focus the scope of this review, after discussion with operational partners and TEP members. We excluded certain interventions and prepared an evidence map of others. These decisions limit our conclusions in several ways. For example, we cannot comment on effectiveness or harms of excluded interventions, such as estriol, or of non-hormonal complementary and alternative therapies.

After consultation with operational partners and TEP members, we did not extract and synthesize outcomes from high RoB trials and instead focused on trials most likely to give reliable estimates about benefits and harms. This may have affected some conclusions about vaginal estrogen, but is unlikely to have changed our conclusions about energy-based interventions. One example for vaginal estrogen is a large (N=550) high RoB trial⁶⁵ that reported that vaginal estrogen, compared with placebo, resulted in a statistically significant improvement in dyspareunia. Low certainty evidence from seven low or some concerns RoB trials indicated that vaginal estrogen may result in little to no difference for dyspareunia, so it is possible that the addition of outcomes from lower quality trials would have altered this conclusion. However, we believe that our final group of included/analyzed vaginal estrogen studies represent those most clinically relevant and methodologically rigorous. With respect to high RoB trials of energy-based interventions, all six trials evaluated different comparisons. Though we did not formally extract outcomes from these trials, an overview does not demonstrate a statistically significant benefit for GSM symptoms. Inclusion of outcomes from these high RoB energy-based trials would have provided additional categories of comparison (such as ultrasound versus sham and radiofrequency versus vaginal estrogen), but would be unlikely to alter our overall conclusions about energy-based interventions.

4.5 Implications for Clinical Practice

The findings detailed in this systematic review summarize and evaluate the existing literature about GSM screening and treatment.

For Key Question (KQ) 1 (screening for GSM), we found no RCTs or prospective observational studies with a concurrent control group that evaluated the potential effectiveness

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and harms of screening for GSM. Though screening (or case-finding) is generally thought to be low-risk, it may have trade-offs to consider, including the medicalization of a natural process,⁴ the costs of treatment (psychological and monetary), and the potential side-effects of treatment. That said, many women report being bothered by GSM symptoms but not discussing them with their clinicians;^{28, 29} it is possible that asking women about the presence of symptoms may lead to symptom improvement for some women using a relatively low-risk, low-cost local treatment.

For KQ2 and KQ3, (efficacy, comparative effectiveness, and harms of interventions to treat GSM symptoms), vaginal estrogen, vaginal DHEA, ospemifene, and vaginal moisturizers may all improve at least some GSM symptoms. However, evidence does not clearly demonstrate the efficacy of vaginal oxytocin, vaginal or systemic testosterone, oral raloxifene or bazedoxifene, or energy-based therapies such as CO₂ or Erbium-doped yttrium aluminum garnet (Er:YAG) laser, for any GSM symptoms. Harms reporting for most interventions was limited in part by studies not being sufficiently powered to evaluate infrequent but serious harms though most studies did not report frequent serious harms. As noted earlier, populations and symptom severity enrolled in these studies may not fully reflect patients seen in many clinical settings, especially those in primary care. Clinicians may choose to tailor treatment based on side effects, personal risk factors (e.g., cancer history), insurance coverage or cost, and patient preference for route or type of therapy and availability of treatments. Evidence is consistent with current practice to try low-cost over-the-counter vaginal lubricants and moisturizers first for most GSM symptoms. A broad review of efficacy and harms of non-hormonal treatments other than moisturizers, particularly herbal and botanical supplements, was hindered by study limitations.

For KQ4 (timing of evaluations) we found no studies that directly addressed appropriate followup intervals, but limited evidence suggests that symptoms began improving within 1-2 months for effective treatments and continued to improve through 12 weeks (average length of study followup). Frequent evaluation and the selected timing in trials may not be practical for many patients and clinicians. Few studies evaluated outcomes beyond 6 months thus providing little empiric evidence to guide clinicians for prolonged therapy.

For KQ5 (endometrial surveillance) we found no studies that directly addressed the effectiveness and harms of endometrial surveillance in clinical practice with respect to patient centered outcomes. In more than half of trials that used active or passive surveillance to assess endometrial safety, vaginal estrogen was associated with cases of vaginal bleeding, a nominal increase in endometrial thickness, proliferative endometrium, and one case of endometrial hyperplasia in a polyp. Importantly, no studies performed transvaginal ultrasound or endometrial biopsy in women receiving vaginal estrogen for more than 12 weeks. Ospemifene was associated with thickened endometrial lining, proliferative endometrial histology, and one case of endometrial hyperplasia in studies up to 1 year. Limited evidence suggests that vaginal DHEA, vaginal oxytocin, oral bazedoxifene and raloxifene, and vaginal testosterone are not associated with clinically relevant endometrial stimulation in primarily short-term and 3 year-long studies. Notably, all the trials that used transvaginal ultrasound or endometrial biopsy for active endometrial surveillance also excluded patients with any baseline abnormalities on ultrasound or biopsy. However, it is not standard clinical practice to perform a screening transvaginal ultrasound or endometrial biopsy to rule out endometrial abnormalities prior to initiating hormonal GSM treatments, so it is unclear how these trial findings would generalize to an unscreened clinical population. There is little evidence to guide clinicians on endometrial surveillance in clinical practice.

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4.6 Implications for Future Research

A fundamental question for future research is whether common genitourinary symptoms after menopause represent a unified syndrome that can be cohesively diagnosed, studied, and managed. Women treated clinically for individual symptoms such as postmenopausal vulvovaginal dryness or dyspareunia may be different from those who receive a diagnosis of GSM for a clinical trial. Additionally, some genitourinary symptoms in older women are likely related to aging, not postmenopausal hormonal changes, and many postmenopausal women with urinary incontinence or dyspareunia may have experienced these symptoms prior to menopause. Clarifying the diagnostic criteria for GSM has important implications for labeling normal physiologic aging as a disease, and for the associated potential benefits and harms of healthcare interventions. Additional research is needed to inform the identification and management of GSM in clinical practice. Several professional organizations recommend screening all postmenopausal women for GSM,^{30, 32, 40} though there is no standard protocol for how to screen and we found no studies that directly assessed the potential benefits and harms of screening (KQ1).

Future research should directly address the treatment of GSM among subpopulations of interest, especially women with a history of breast cancer, women who have received or are receiving breast or urogenital cancer treatment, and women at high risk for cancer. Evaluating interventions among older and more racially and ethnically diverse women would also enhance our understanding of treatment effectiveness and harms. Long-term followup for efficacy, tolerability, and safety represents a critical gap needed to guide treatment longer than one year. Future studies could improve the reporting of adverse effects by reporting reasons for study drop out, assessing whether there is a statistical difference in adverse effect (AE) severity and frequency between treatment arms, and assessing tissue-level changes in those with subjective AEs.

With the breadth of interventions studied, several treatment comparisons were notably missing. For example, we found no studies directly comparing the effectiveness of vaginal estrogen with vaginal moisturizers, vaginal DHEA, or ospemifene, and no studies of hybrid lasers or radiofrequency versus sham treatment. For energy-based treatments, future studies should evaluate the combination of laser treatments with other interventions (such as moisturizer), and study different dosing protocols and schedules. We identified 8 studies of various phytoestrogens compared with vaginal estrogen (see non-hormonal evidence map). A future synthesis comparing the effectiveness and harms of phytoestrogens to estrogens could be useful.

4.7 Conclusions

Despite the breadth of the evidence of hormonal, non-hormonal and energy-based interventions for GSM, few studies evaluated identical combinations of interventions, comparators, and outcomes and there were often important limitations in study design and outcome reporting, leading to low or very low COE for most conclusions. In general, vaginal estrogen, vaginal DHEA, oral ospemifene, and vaginal moisturizers may all improve at least some GSM symptoms, though the effects versus placebo appear to be generally modest. However, the evidence does not currently support the efficacy of CO₂ laser, Er:YAG laser, vaginal or systemic testosterone, vaginal oxytocin, or oral raloxifene or bazedoxifene for any GSM symptoms. There was not a strong signal for frequent serious adverse effects in short-term,

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relatively small studies, but lack of long-term data on endometrial safety of hormonal interventions represents a critical gap. Evidence supports current practice to try low-cost over-the-counter vaginal moisturizers and lubricants first for most GSM symptoms. Future studies would be strengthened by a standard definition and uniform diagnostic criteria for GSM, a common set of validated outcome measures and reporting standards, and attention to clinically relevant patient populations and intervention comparisons.

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Abbreviations and Acronyms

AE	Adverse effect
AHRQ	Agency for Healthcare Research and Quality
AI	Aortic insufficiency
ASFQ	Abbreviated Sexual Function Questionnaire
AUB	Abnormal uterine bleeding
BAI	Beck Anxiety Inventory
BDI-II	Beck Depression Inventory
BFLUTS	Bristol Female Lower Urinary Tract Symptoms Questionnaire
BMI	Body mass index
BSI-18	Brief Symptom Inventory-18
BZA	Bazedoxifene
CAD	Coronary artery disease
CARES	Cancer Rehabilitation Evaluation System
CAUTI	Catheter-associated urinary tract infection
CE	Conjugated estrogens
CEC	Conjugated estrogens cream
CEE	Conjugated equine estrogen
CI	Confidence interval
CMA	Comprehensive menopausal assessment
CO ₂	Carbon dioxide
COMMA	Core Outcomes in Menopause
CTCAE	Common Terminology Criteria of Adverse Events
CVA	Cerebrovascular accident
DAISY	DistillerSR's Artificial Intelligence System
DIVA	Day-to-Day Impact of Vaginal Aging
Er:YAG	Erbium-doped yttrium aluminum garnet laser
EtOH	Ethanol
DHEA	Dehydroepiandrosterone
DM	Diabetes mellitus
DVT	Deep venous thromboembolism
EBT	Energy-based treatment
EP	Estrogens and progestogens
EPC	Evidence-based Practice Center
FACT-B	Functional Assessment of Cancer Therapy—Breast
FACT-ES	Functional Assessment of Cancer Treatment—Endocrine Symptoms
FIEI	Female Intervention Efficacy Index
FSDS	Female Sexual Distress Scale
FSFI	Female Sexual Function Index
FSH	Follicle-stimulating hormone

FSSQ	Functional Social Support Questionnaire
g	Gram
GAD-7	Generalized Anxiety Disorder
GCS	Greene climacteric scale
GI	Gastrointestinal
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GSM	genitourinary syndrome of menopause
GU	Genitourinary
Gyn	Gynecological
HADS	Hospital Anxiety and Depression Scale
HKSJ	Hartung, Knapp, Sidik, and Jonkman
h/o	History of
hr	Hour
HRT	Hormone replacement therapy
HTN	Hypertension
hx	History
ICIQ-OAB	International Consultation on Incontinence Questionnaire-Overactive Bladder
ICIQ-SF	International Consultation on Incontinence Questionnaire-Short Form
ICIQ-UI	International Consultation on Incontinence Questionnaire-Urinary Incontinence
ID	Identification
IIQ-7	Incontinence Impact Questionnaire
IQR	Interquartile range
ISSWSH	International Society for the Study of Women's Sexual Health
IU	International Unit
IUD	Intrauterine device
ITT	Intention to treat
IVT	Intravaginal testosterone
k	Number of trials
KI	Kupperman Index
KQ	Key Question
LUTS	Lower urinary tract symptoms
LSM	Least square means
MBS	Most bothersome symptom
mcg	Microgram
MENQOL	Menopause-Specific Quality of Life
mg	Milligram
MI	Myocardial infarction
MPA	Medroxyprogesterone acetate
mL	Milliliter
mm	Millimeter
MRS	Menopause Rating Scale

MSBR	Mindfulness-based Stress Reduction therapy
MsFLASH	Menopause Strategies: Finding Lasting Answers for Symptoms and Health
MSIQ	Menopausal Sexual Interest Questionnaire
MS-TSQ	Menopause Symptoms Treatment Satisfaction Questionnaire
MUI	Mixed urinary incontinence
n	Subset of sample size
N	Total sample size
N/A	Not applicable
NCCIH	National Center for Complementary and Integrative Health
NR	Not reported
nRCT	Non-RCT
NRS	Numeric Rating Scale
NS	Not significant
OAB	Overactive bladder
OABSS	Overactive Bladder Symptom Score
OIS	Optimal information size
PCORI®	Patient-Centered Outcomes Research Institute
PFMT	Pelvic floor muscle training
PGWB	Psychological General Well-Being Index
PHQ-8	Patient Health Questionnaire
PICOTS	Population, Intervention, Comparator, Outcomes, Timing, and Study design/setting
QLACS	Quality of Life in Adult Cancer Survivors
QoL	Quality of life
QS-F	Scale for Quality of Sexual Function
QUID	Questionnaire for Urinary Incontinence Diagnosis
RCT	Randomized controlled trial
RD	Risk difference
RoB	Risk of bias
RR	Risk ratio
SAQ	Sexual Activity Questionnaire
SD	Standard deviation
SE	Standard error
SEM	Standard error of mean
SERM	Selective estrogen receptor modulator
SF-36	Short Form Health Survey (36-item)
SF-Q	Sexual Function Questionnaire
SMD	Standardized mean differences
s/p	Status post
SQ-F	Sexual Quotient—female version
SR	Systematic Review
SSS	Sabbatsberg Sexual Self-Rating Scale

SUI	Stress urinary incontinence
sx	Symptom
TEAE	Treatment emergent adverse effect
TIA	Transient ischemic attack
TOO	Task Order Officer
TVS	Transvaginal sonography
TVU	Transvaginal ultrasound
UDI-6	Urinary Distress Inventory
UK	United Kingdom
US	United States
UTI	Urinary tract infection
UTN	Universal Trial Number
UUDI	Urge Urogenital Distress Inventory
VAS	Visual Analogue Scale
VEL	Vaginal erbium laser
VHI	Vaginal Health Index
VMI	Vaginal Maturation Index
VMV	Vaginal Maturation Value
VPAQ	Vulvar Pain Assessment Questionnaire
VRS	Verbal Rating Scale
vs	Versus
VSI	Vaginal Symptom Index
VSQ	Vulvovaginal Symptom Questionnaire
VTE	Venous thromboembolism
VVA	Vulvovaginal atrophy
WMD	Weighted mean differences
ZUF-8	Zurich Satisfaction Questionnaire

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Appendix A. Methods

Search Strategy

Search Details and Sources

The search strategy was designed and conducted by an experienced medical librarian with input from the investigators. We applied the following limits or filters to the database searches:

- Language. Only included publications written in English due to resource constraints.
- Publication status. Only included peer-reviewed published studies.
- Humans or organisms. Only included studies of human subjects, not animals.
- Study design. The search was limited to randomized controlled trials (RCTs) and systematic reviews (SRs) of RCTs for KQ2 and KQ4; prospective observational studies with concurrent comparison group were also allowed for KQ1, KQ3, and KQ5. After review of the breadth of initially included studies, study design was further limited to trials with at least 20 individuals randomized per arm to identify the literature with the highest likelihood of having statistical power to detect an effect from our interventions of interest. We also excluded SRs, since none found covered sufficient studies/categories to reasonably replace individual studies. Instead, we used the SR reference lists to identify any missed primary studies.

We conducted a comprehensive literature search in January/February 2023. We searched the following databases:

- Ovid MEDLINE(R) ALL <1946 to January 30, 2023> Date searched: January 30, 2023
- Embase <1974 to February 01, 2023> Date searched: February 1, 2023
- CINAHL Plus with Full Text

Database Search Strategies

Database: Ovid MEDLINE(R) ALL <1946 to January 30, 2023>

- 1 climacteric/ or menopause/ or menopause, premature/ or postmenopause/ or primary ovarian insufficiency/ or (climacteric or estrogen-deficien* or hypoestrogeni* or menopaus* or postmenopaus* or post-menopaus* or primary ovarian insufficiency).ti,ab.
- 2 ((genitourinary or genito-urinary) adj3 (symptom* or syndrome)).ti,ab.
- 3 female urogenital diseases/ or vaginal diseases/ or vaginal discharge/ or vaginitis/ or atrophic vaginitis/ or vulvovaginitis/ or vulvitis/ or vulvodynia/ or (urogenital or vaginal atrophy or vaginal burning or vaginal discharge or vaginal dryness or vaginal itch* or vagina* pain* or vaginitis or vulvitis or vulvovaginitis or vulvovaginal atrophy).ti,ab. or (inflammation adj3 (vagin* or vulva*)).ti,ab.
- 4 Dysuria/ or lower urinary tract symptoms/ or nocturia/ or urinary bladder, overactive/ or Urethral Diseases/ or Urethritis/ or urinary incontinence/ or urinary incontinence, urge/ or (dysuria or urinary symptom* or nocturia or overactive bladder or urethral caruncle or urethral prolapse or urethritis or incontinence or recurrent urinary tract infection*).ti,ab.
- 5 dyspareunia/ or pelvic pain/ or sexual dysfunction, physiological/ or (dyspareunia or sexual dysfunction or pelvic pain).ti,ab.
- 6 or/2-5

- 7 1 and
- 8 exp Estrogens/ or Androgens/ or Estrogen replacement therapy/ or Testosterone/ or Dehydroepiandrosterone/ or Progesterone/ or exp Selective Estrogen Receptor Modulators/ or (estrogen* or oestrogen* or estradiol or oestradiol or bioidentical hormon* therap* or compound* hormon* therap* or androgens or ospemifene or phytoestrogens or prasterone or progesterone or selective estrogen receptor modulators or vaginal testosterone or intravaginal dehydroepiandrosterone or vaginal dehydroepiandrosterone or intravaginal DHEA or vaginal DHEA).ti,ab.
- 9 Lasers, Gas/tu or Laser Therapy/ or (carbon dioxide laser or CO2 laser or erbium aluminum laser or erbium laser or Er:YAG laser or laser therap* or radiofrequency).ti,ab.
- 10 Acupuncture Point/ or Acupuncture Therapy/ or drugs, chinese herbal/ or Yoga/ or (acupuncture or herbal supplement* or pelvic floor physical therap* or pelvic floor therap* or pelvic floor training or yoga).ti,ab.
- 11 Lubricants/ or hyaluronic acid/ or "vaginal creams, foams, and jellies"/ or Oxytocin/ or Probiotics/ or ((vagina* or intravagin*) adj2 (cream* or dilator* or foam* or gel* or hyaluronic acid or insert or jelly or jellies or lubricant* or moisturizer* or oxytocin or probiotic* or vitamin D or vitamin E)).ti,ab.
- 12 ((nonhormon* or non-hormon*) adj2 (therap* or treatment*)).ti,ab.
- 13 or/8-12
- 14 6 and 13
- 15 7 or 14
- 16 comment/ or editorial/ or letter/ or exp congress/ or clinical conference/ or consensus development conference/ or "Review"/
- 17 (canine or canines or cow or cows or dog or dogs or mouse or mice or rabbit or rabbits or rat or rats).ti,ab.
- 18 Penile Erection/ or Erectile Dysfunction/ or Prostatic Neoplasms/ or (erectile dysfunction or penile or prostate or prostatic).ti.
- 19 or/16-18
- 20 15 not 19
- 21 limit 20 to english language

Database: Embase <1974 to February 01, 2023>

- 1 climacterium/ or early menopause/ or menopause/ or postmenopause/ or premature ovarian failure/ or (climacteri* or estrogen-deficien* or hypoestrogeni* or menopaus* or postmenopaus* or post-menopaus* or premature ovarian failure or primary ovarian insufficiency).ti,ab.
- 2 ((genitourinary or genito-urinary) adj3 (symptom* or syndrome)).ti,ab.
- 3 atrophic vaginitis/ or urogenital tract disease/ or vaginitis/ or vagina atrophy/ or vagina disease/ or "vagina discharge (disease)"/ or vaginal dryness/ or vagina pain/ or vulvovaginitis/ or vulvitis/ or vulvodynia/ or (urogenital symptoms or vaginal atrophy or vaginal burning or vaginal discharge or vaginal dryness or vaginal itch* or vagina* pain* or vaginitis or vulvitis or vulvovaginitis or vulvovaginal atrophy or (inflammation adj3 (vagin* or vulva*))).ti,ab.
- 4 dysuria/ or lower urinary tract symptom/ or nocturia/ or overactive bladder/ or urethra disease/ or urethritis/ or urine incontinence/ or urge incontinence/ or (dysuria or urinary symptom* or nocturia or overactive bladder or urethral caruncle or urethral prolapse or urethritis or urge incontinence or recurrent urinary tract infection*).ti,ab.

- 5 dyspareunia/ or female sexual dysfunction/ or pelvic pain/ or (dyspareunia or sexual dysfunction or pelvic pain).ti,ab.
- 6 or/2-5
- 7 androgen therapy/ or estrogen therapy/ or phytoestrogen/dt, va, po or prasterone/dt, va, po or progesterone/dt, th or selective estrogen receptor modulator/dt or testosterone/dt, th or (androgen* or bioidentical hormon* therap* or compound* hormon* therap* or estrogen* or oestrogen* or estradiol or oestradiol or intravaginal dehydroepiandrosterone or vaginal dehydroepiandrosterone or intravaginal DHEA or vaginal DHEA or ospemifene or phytoestrogen therap* or prasterone or progesterone therap* or selective estrogen receptor modulator or vaginal testosterone).ti,ab.
- 8 carbon dioxide laser/ or erbium YAG laser/ or gas laser/ or laser therapy/ or radiofrequency therapy/ or (carbon dioxide laser or CO2 laser or erbium aluminum laser or erbium laser or Er:YAG laser or laser therap* or radiofrequency).ti,ab.
- 9 acupuncture/ or acupuncture point/ or herbal medicine/ or yoga/ or (acupuncture or herbal supplement* or pelvic floor physical therap* or pelvic floor therap* or pelvic floor training or yoga).ti,ab.
- 10 agents used intravaginally/ or hyaluronic acid/dt, va or lubricating agent/dt, va or oxytocin/dt, va or probiotic agent/dt, va or vitamin D/dt, va or ((vagina* or intravagin*) adj2 (cream* or dilator* or foam* or gel* or hyaluronic acid or insert or jelly or jellies or lubricant* or moisturizer* or oxytocin or probiotic* or vitamin D or vitamin E)).ti,ab.
- 11 ((nonhormon* or non-hormon*) adj2 (therap* or treatment*)).ti,ab.
- 12 or/7-11
- 13 1 and 6
- 14 6 and 12
- 15 13 or 14
- 16 exp animal experiment/ or exp animal model/ or exp experimental animal/ or (cow or cows or canine or canines or dog or dogs or mouse or mice or rabbit or rabbits or rat or rats).ti,ab.
- 17 erectile dysfunction/ or penis erection/ or exp prostate tumor/ or (erectile dysfunction or penile or prostate or prostatic).ti.
- 18 16 or 17
- 19 15 not 18
- 20 limit 19 to (english language and embase)
- 21 limit 20 to (books or chapter or conference abstract or conference paper or "conference review" or editorial or letter or note or "preprint (unpublished, non-peer reviewed)" or "review")
- 22 20 not 21

Database: CINAHL Plus With Full Text <Searched February 01, 2023>

Interface – EBSCOhost Research Databases

- 1 ((MH "Climacteric") OR (MH "Menopause") OR (MH "Menopause, Premature") OR (MH "Postmenopause")) OR ((climacteric or estrogen-deficien* or hypoestrogeni* or menopaus* or postmenopaus* or post-menopaus* or primary ovarian insufficiency or induced menopause or surgical menopause))
- 2 (MH "Genitourinary Syndrome of Menopause") OR ((genitourinary or genito-urinary) N3 (symptom* or syndrome))

3 MH "Female Urogenital Diseases") OR (MH "Vaginal Diseases") OR (MH "Vaginal Discharge") OR (MH "Vaginitis") OR (MH "Vulvodynia") OR (MH "Vulvovaginitis") OR (MH "Vulvitis") OR (MH "Dysuria") OR ((MH "Overactive Bladder") OR (MH "Urge Incontinence") OR (MH "Urethral Diseases") OR (MH "Urinary Tract Infections") OR (MH "Urinary Incontinence") OR (MH "Urethritis") OR (MH "Dyspareunia") OR (MH "Pelvic Pain") OR (MH "Sexual Dysfunction, Female") OR ((dysuria or urinary symptom* or nocturia or overactive bladder or urethral caruncle or urethral prolapse or urethritis or urge incontinence or recurrent urinary tract infection* OR dyspareunia or sexual dysfunction or pelvic pain OR urogenital or vaginal atrophy or vaginal burning or vaginal discharge or vaginal dryness or vaginal itch* or vagina* pain* or vaginitis or vulvitis or vulvovaginitis or vulvovaginal atrophy)) OR ((inflammation N3 (vagin* or vulva*)))

4 2 OR 3

5 1 AND 4

6 ((MH "Androgens") OR (MH "Estrogens") OR (MH "Selective Estrogen Receptor Modulators+") OR (MH "Dehydroepiandrosterone") OR (MH "Estradiol") OR (MH "Estriol") OR (MH "Phytoestrogens") OR (MH "Progesterone") OR (MH "Testosterone") OR (MH "Radiofrequency Therapy") OR (MH "Laser Therapy")) OR ((MH "Selective Estrogen Receptor Modulators+") OR (MH "Dehydroepiandrosterone") OR ((MH "Vaginal Creams, Foams and Jellies") OR (MH "Hyaluronic Acid") OR (MH "Oxytocin") OR (MH "Probiotics") OR (MH "Lubricants")) OR ((MH "Acupuncture") OR (MH "Acupuncture Points") OR (MH "Drugs, Chinese Herbal") OR (MH "Yoga")) OR ((bioidentical hormon* therap* or compound* hormon* therap* or estrogen* or oestrogen* or estradiol or oestradiol or phytoestrogen* or progesterone or androgens or intravaginal dehydroepiandrosterone or vaginal dehydroepiandrosterone or intravaginal DHEA or vaginal DHEA or ospemifene or prasterone or selective estrogen receptor modulators or vaginal testosterone)) OR ((carbon dioxide laser or CO2 laser or erbium aluminum laser or erbium laser or Er:YAG laser or laser therap* or radiofrequency) OR (acupuncture or herbal supplement* or pelvic floor physical therap* or pelvic floor therap* or pelvic floor training or yoga)) OR ((vagina* or intravagin*) N2 (cream* or dilator* or foam* or gel* or hyaluronic acid or insert or jelly or jellies or lubricant* or moisturizer* or oxytocin or probiotic* or vitamin D or vitamin E)) OR ((nonhormon* or non-hormon*) N2 (therap* or treatment*)))

7 6 AND 4

8 5 OR 7

9 (MM "Books") OR (MH "Book Reviews") OR (MH "Newsletters") OR (MH "Theses and Dissertations") OR (MH "News") OR (MH "Teaching Materials") OR (MH "Pamphlets") OR (ZT "book") or (ZT "book chapter") or (ZT "book review") or (ZT "ceu") or (ZT "commentary") or (ZT "conference paper") or (ZT "conference proceeding") or (ZT "dissertation") or (ZT "doctoral dissertation") or (ZT "editorial") or (ZT "letter") or (ZT "letter to the editor") or (ZT "newspaper") or (ZT "opinion") or (ZT "pamphlet") or (ZT "proceedings")

10 8 NOT 9

Limiters - English Language; Peer Reviewed; Research Article; Exclude MEDLINE records;
Sex: Female; Expanders - Apply equivalent subjects; Search modes - Boolean/Phrase

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Appendix C. Evidence Tables

Risk of Bias Assessments

Table C.1. Risk of bias assessments of randomized controlled trials with RoB-2

Trial Name or Author Year	Bias From Randomization Process	Bias From Deviation From Intended Interventions (Assignment)	Bias From Deviation From Intended Interventions (Adherence)	Bias From Missing Outcome Data	Bias in Measurement of Outcome	Bias in Selection of Reported Result	Overall Risk of Bias (Low, Some Concerns, High)
Abedi, 2020 ¹	Low	Some concerns	Low	Low	Low	Low	Some concerns
Aguiar, 2020 ²	Some concerns	Some concerns	High	High	High	Low	High
Antoniou, 1997 ³	Some concerns	Some concerns	High	Low	Low	Low	High
Archer, 2019 ⁴	Low	Low	Low	Low	Low	Low	Low
Archer, 2018 ⁵	Some concerns	Low	Low	Some concerns	Low	Low	Some concerns
Archer, 2015 ⁶	Low	Low	Low	Low	Low	Low	Low
Ayton, 1996 ⁷	Low	Low	Low	Low	Low	Low	Low
Bachmann, 2010 ⁸	Some concerns	Low	Low	Low	Low	Low	Some concerns
Bachmann, 2010 ⁹	Some concerns	Low	Low	Low	Low	Low	Some concerns
Bachmann, 2009 ¹⁰	Some concerns	Low	Low	Low	Low	Low	Some concerns
Bachmann, 2008 ¹¹	Low	Low	Low	High	Low	Low	High
Bachmann, 1997 ¹²	High	Some concerns	Low	Low	Low	Some concerns	High
Barton, 2018 ¹³	Low	Some concerns	Low	Low	Low	Low	Some concerns
Chaikittisilpa, 2019 ¹⁴	Low	Some concerns	Low	Low	Low	Low	Some concerns
Chiengthong, 2023 ¹⁵	Low	Low	Low	Low	Low	Low	Low
Chompootaweep, 1998 ¹⁶	Some concerns	High	Low	Some concerns	Low	Some concerns	High
Constantine, 2017 ¹⁷	Low	Some concerns	Low	Low	Low	Low	Some concerns

Trial Name or Author Year	Bias From Randomization Process	Bias From Deviation From Intended Interventions (Assignment)	Bias From Deviation From Intended Interventions (Adherence)	Bias From Missing Outcome Data	Bias in Measurement of Outcome	Bias in Selection of Reported Result	Overall Risk of Bias (Low, Some Concerns, High)
Constantine, 2017 ¹⁸	Low	Low	Low	Low	Low	Low	Low
Constantine, 2015 ¹⁹	Some concerns	Low	Low	Low	Low	Low	Some concerns
Constantine, 2019 ²⁰	Low	Low	Low	Low	Low	Low	Low
Davis, 2018 ²¹	Low	Low	Low	Low	Low	Low	Low
De Seta, 2021 ²²	Low	Low	Some concerns	Low	High	Low	High
Derzko, 2020 ²³	Low	Low	Low	High	Low	Some concerns	High
Diem, 2018 ²⁴	Low	Low	Low	Low	Low	Low	Low
Dow, 1983 ²⁵	Low	High	High	High	Low	Some concerns	High
Eftekhar, 2020 ²⁶	Low	Low	Low	Low	Low	Low	Low
Eftekhar, 2021 ²⁷	Low	Some concerns	Low	Low	Low	Low	Some concerns
Eriksen, 1999 ²⁸	Some concerns	Low	Low	Low	Low	Low	Some concerns
Fernandes, 2014 ²⁹	Low	Low	Low	Low	Low	Low	Low
Fernandes, 2018 ³⁰	Low	Low	Some concerns	Low	Low	Low	Some concerns
Fernandes, 2023 ³¹	Some concerns	Low	Some concerns	High	High	High	High
Fianu Jonasson, 2020 ³²	Low	Low	Low	Low	Low	Low	Low
Fidecicchi, 2023 ³³	Some concerns	Some concerns	Low	Low	Some concerns	Low	Some concerns
Freedman, 2009 ³⁴	Some concerns	Low	Low	Low	Low	Low	Some concerns
Gibson, 2020 ³⁵	Low	Low	Low	Low	Low	Low	Low
Goetsch, 2023 ³⁶	Low	Some concerns	Low	Low	Low	Some concerns	Some concerns
Gold, 2023 ³⁷	Low	Low	Low	Low	Some concerns	Low	Some concerns
Goldstein, 2019 ³⁸	Low	Low	Low	Low	Low	Low	Low
Goldstein, 2014 ³⁹	Low	Low	Low	Low	Low	Low	Low
Hickey, 2023 ⁴⁰	Low	Low	Low	High	Low	Low	High
Hidalgo, 2005 ⁴¹	Low	Low	Low	Low	Low	Low	Low

Trial Name or Author Year	Bias From Randomization Process	Bias From Deviation From Intended Interventions (Assignment)	Bias From Deviation From Intended Interventions (Adherence)	Bias From Missing Outcome Data	Bias in Measurement of Outcome	Bias in Selection of Reported Result	Overall Risk of Bias (Low, Some Concerns, High)
Jiang, 2016 ⁴²	Low	Some concerns	Low	High	Low	Low	High
Jokar, 2016 ⁴³	High	Some concerns	Some concerns	Low	Low	Some concerns	High
Kagan, 2010 ⁴⁴	Low	Low	Low	Low	Low	Low	Low
Kalogirou, 1996 ⁴⁵	Some concerns	High	Low	Low	Low	Some concerns	High
Kessel, 2003 ⁴⁶	Low	Some concerns	Some concerns	Some concerns	Low	Low	Some concerns
Kim, 2017 ⁴⁷	Low	Low	Some concerns	High	Low	Low	High
Kingsberg, 2016 ⁴⁸	Low	Low	Low	Some concerns	Low	Some concerns	Some concerns
Kroll, 2018 ⁴⁹	Some concerns	Low	Low	High	Low	Low	High
Labrie, 2011 ⁵⁰	Some concerns	Low	Low	Low	Low	Low	Some concerns
Labrie, 2018 ⁵¹	Low	Low	Low	Low	Low	Low	Low
Labrie, 2009 ⁵²	Some concerns	Low	Low	Low	Low	Low	Some concerns
Labrie, 2009 ⁵³	Some concerns	Low	Low	Low	Low	Low	Some concerns
Labrie, 2010 ⁵⁴	Some concerns	Low	Low	Low	Low	Low	Some concerns
Labrie, 2014 ⁵⁵	Some concerns	Low	Low	Low	Low	Low	Some concerns
Labrie, 2015 ⁵⁶	Low	Low	Low	Low	Low	Low	Low
Lee, 2011 ⁵⁷	Some concerns	Some concerns	Some concerns	Some concerns	Low	Some concerns	Some concerns
Li, 2021 ⁵⁸	Low	Low	Low	Low	Low	Low	Low
Melisko, 2017 ⁵⁹	Low	Low	Low	Low	Low	Low	Low
Mension, 2023 ⁶⁰	Low	High	Low	Some concerns	Low	Low	High
Mitchell, 2019 ⁶¹	Low	Low	Low	Low	Low	Some concerns	Some concerns
Mitchell, 2018 ⁶²	Low	Low	Low	Low	Low	Low	Low
Nachtigall, 1995 ⁶³	Some concerns	Low	Some concerns	Low	Low	Low	Some concerns
Nappi, 2022 ⁶⁴	Some concerns	Low	Some concerns	Low	Low	Low	Some concerns
Nelken, 2011 ⁶⁵	Low	Some concerns	Low	Low	Low	Some concerns	Some concerns
Page, 2022 ⁶⁶	Low	Low	Low	Low	Low	Low	Low
Palacios, 2022 ⁶⁷	Some concerns	Some concerns	High	Low	Low	Low	High
Panjari, 2009 ⁶⁸	Low	Low	Low	Low	Low	Low	Low

Trial Name or Author Year	Bias From Randomization Process	Bias From Deviation From Intended Interventions (Assignment)	Bias From Deviation From Intended Interventions (Adherence)	Bias From Missing Outcome Data	Bias in Measurement of Outcome	Bias in Selection of Reported Result	Overall Risk of Bias (Low, Some Concerns, High)
Panjari, 2009 ⁶⁹	Low	Low	Low	Low	Low	Low	Low
Panyawogudom, 2023 ⁷⁰	Low	Low	High	Low	Low	Low	High
Paraiso, 2020 ⁷¹	Some concerns	Low	Low	Low	Low	Low	Low
Parsons, 2003 ⁷²	Low	Some concerns	Low	Some concerns	Low	Low	Some concerns
Penteado, 2008 ⁷³	Some concerns	Some concerns	Low	Low	Low	Low	Some concerns
Pinkerton, 2003 ⁷⁴	Low	Low	Low	Low	Low	Low	Low
Politano, 2019 ⁷⁵	Some concerns	Some concerns	High	High	Some concerns	Low	High
Portman, 2013 ⁷⁶	Some concerns	Low	Low	Low	Low	Low	Some concerns
Portman, 2014 ⁷⁷	Some concerns	Low	Low	Low	Low	Low	Some concerns
Raghunandan, 2010 ⁷⁸	Some concerns	Low	Some concerns	Low	Low	Some concerns	Some concerns
Ruanphoo, 2020 ⁷⁹	Some concerns	Some concerns	Low	Low	Low	Low	Some concerns
Salvatore, 2021 ⁸⁰	Low	Some concerns	Low	Low	Low	Low	Some concerns
Sarmiento, 2023 ⁸¹	Low	Low	High	Low	High	Low	High
Seyyedi, 2016 ⁸²	Low	Some concerns	Low	High	Low	Low	High
Seyyedi, 2016 ⁸³	Some concerns	Some concerns	Low	High	Low	Low	High
Simon, 2019 ⁸⁴	Low	Low	Low	Low	Low	Some concerns	Some concerns
Simon, 2013 ⁸⁵	Some concerns	Low	Low	Low	Low	Low	Some concerns
Simon, 2008 ⁸⁶	Low	Low	Low	High	Low	Low	High
Tanmahasamut, 2020 ⁸⁷	Low	Some concerns	Low	Low	Some concerns	Low	Some concerns
Tseng, 2009 ⁸⁸	Some concerns	Some concerns	Low	Low	Low	Some concerns	Some concerns
Tungmunsakulchai, 2015 ⁸⁹	Low	Low	Low	Low	Low	Low	Low
Zohrabi, 2020 ⁹⁰	Low	Some concerns	Low	Low	Low	Low	Some concerns

Table C.2. Risk of bias assessments of non-randomized comparison studies with ROBINS-I

Study Name or Author Year	Bias Due to Confounding*†	Selection Bias	Bias in Classification of Interventions	Bias Due to Departures From Intended Interventions (Assignment)	Bias Due to Departures From Intended Interventions (Adherence)	Bias Due to Measurement of Outcomes	Bias Due to Missing Data	Bias in the Selection of Reported Results	Overall Risk of Bias† (Low, Moderate, Serious, Critical, No Information)
Alvisi, 2022 ⁹¹	Low	Low	Low	Low	Low	Moderate	Low	Low	Moderate
Behnia-Willison, 2017 ⁹²	Critical	-	-	-	-	-	-	-	Critical
Eder, 2019 ⁹³	Critical	-	-	-	-	-	-	-	Critical
Gambacciani, 2017 ⁹⁴	Critical	-	-	-	-	-	-	-	Critical
Gambacciani, 2018 ⁹⁵	Critical	-	-	-	-	-	-	-	Critical
Gaspa, 2017 ⁹⁶	Critical	-	-	-	-	-	-	-	Critical
Li, 2021 ⁹⁷	Critical	-	-	-	-	-	-	-	Critical
Lin, 2022 ⁹⁸	Critical	-	-	-	-	-	-	-	Critical
Okui, 2023 ⁹⁹	Low	Low	Low	Low	Moderate	Moderate	Low	Low	Serious
Quick, 2021 ¹⁰⁰	Critical	-	-	-	-	-	-	-	Critical
Quick, 2022 ¹⁰¹	Critical	-	-	-	-	-	-	-	Critical
Samuels, 2019 ¹⁰²	Critical	-	-	-	-	-	-	-	Critical
Siliquini, 2017 ¹⁰³	Critical	-	-	-	-	-	-	-	Critical
Siliquini, 2021 ¹⁰⁴	Critical	-	-	-	-	-	-	-	Critical
Sokol, 2017 ¹⁰⁵	Critical	-	-	-	-	-	-	-	Critical
Veron, 2021 ¹⁰⁶	Critical	-	-	-	-	-	-	-	Critical
Vicariotto, 2017 ¹⁰⁷	Critical	-	-	-	-	-	-	-	Critical

*Publications rated critical in Domain 1 did not undergo full ROBINS-I assessment as indicated by “-” in the remaining cells for these publications.

†Low=low, except for concerns about uncontrolled confounding.

Summary of Key Findings for COMMA Effectiveness Outcomes

Table C.3. Certainty of evidence statements for COMMA outcomes

Intervention Vs. Comparator	COE Intervention Vs. Comparator Effect on DRYNESS	COE Intervention Vs. Comparator Effect on DISCOMFORT/ IRRITATION	COE Intervention Vs. Comparator Effect on DYSURIA	COE Intervention Vs. Comparator Effect on DYSPAREUNIA	COE Intervention Vs. Comparator Effect on CHANGE IN MBS	COE Intervention Vs. Comparator Effect on QUALITY OF LIFE	COE Intervention Vs. Comparator Effect on TREATMENT SATISFACTION	COE Intervention Vs. Comparator Effect on ADVERSE EFFECTS
	# Trials (N): Direction of Effect	# Trials (N): Direction of Effect	# Trials (N): Direction of Effect	# Trials (N): Direction of Effect	# Trials (N): Direction of Effect	# Trials (N): Direction of Effect	# Trials (N): Direction of Effect	# Trials (N): Direction of Effect
Vaginal estrogen vs. Placebo	Low ⊕⊕○○ May improve <u>7 (2072):</u> ↑ 2 trials ↔ 1 trial ↑↔ 2 trials ? 2 trials	Very low ⊕○○○ Uncertain <u>4 (1777):</u> ↑ 1 trial ↔ 1 trial ↑↔ 1 trial ↓↔ 1 trial	Low ⊕⊕○○ May result in little to no difference <u>1 (488):</u> ↔ 1 trial	Low ⊕⊕○○ May result in little to no difference <u>7 (2072):</u> ↑ 2 trials ↔ 2 trials ↑↔ 1 trial ? 2 trials	Low ⊕⊕○○ May improve <u>4 (1003):</u> ↑ 2 trials ↔ 1 trial ? 1 trial	Moderate ⊕⊕⊕○ Probably results in little to no difference <u>1 (195):</u> ↔ 1 trial	Low ⊕⊕○○ May result in higher <u>1 (195):</u> ↑ 1 trial	Low ⊕⊕○○ May result in little to no difference <u>5 (2070):</u> ↔ 1 trial ? 4 trials
Vaginal estrogen vs. No treatment	Low ⊕⊕○○ May improve <u>1 (108):</u> ↑ 1 trial	Low ⊕⊕○○ May result in little to no difference <u>1 (108):</u> ↔ 1 trial	Low ⊕⊕○○ May result in little to no difference <u>1 (108):</u> ↔ 1 trial	Low ⊕⊕○○ May improve <u>1 (108):</u> ↑ 1 trial	NR	NR	NR	Not assessed
Vaginal estrogen ring vs. Vaginal estrogen cream	Low ⊕⊕○○ May result in little to no difference <u>2 (390):</u> ↔ 2 trials	Very low ⊕○○○ Uncertain <u>1 (196):</u> ↔ 1 trial	Low ⊕⊕○○ May result in little to no difference <u>1 (194):</u> ↔ 1 trial	Low ⊕⊕○○ May result in little to no difference <u>2 (390):</u> ↔ 2 trials	NR	NR	Moderate ⊕⊕⊕○ Probably results in higher <u>2 (390):</u> ↑ 2 trials	Not assessed

Intervention Vs. Comparator	COE Intervention Vs. Comparator Effect on DRYNESS	COE Intervention Vs. Comparator Effect on DISCOMFORT/ IRRITATION	COE Intervention Vs. Comparator Effect on DYSURIA	COE Intervention Vs. Comparator Effect on DYSPAREUNIA	COE Intervention Vs. Comparator Effect on CHANGE IN MBS	COE Intervention Vs. Comparator Effect on QUALITY OF LIFE	COE Intervention Vs. Comparator Effect on TREATMENT SATISFACTION	COE Intervention Vs. Comparator Effect on ADVERSE EFFECTS
	# Trials (N): Direction of Effect	# Trials (N): Direction of Effect	# Trials (N): Direction of Effect	# Trials (N): Direction of Effect	# Trials (N): Direction of Effect	# Trials (N): Direction of Effect	# Trials (N): Direction of Effect	# Trials (N): Direction of Effect
Vaginal DHEA vs. Placebo	Low ⊕⊕○○ May improve <u>4 (1472):</u> ↑ 4 trials	Very low ⊕○○○ Uncertain <u>1 (16):</u> ↑↔ 1 trial	NR	Low ⊕⊕○○ May improve <u>4 (1472):</u> ↑ 4 trials	Very low ⊕○○○ Uncertain <u>2 (659):</u> ↑ 1 trial ↔ 1 trial	Low ⊕⊕○○ May improve <u>1 (216):</u> ↑↔ 1 trial	NR	Low ⊕⊕○○ May result in more <u>3 (1256):</u> ↔ 1 trial ? 2 trials
Oral DHEA vs. Placebo	NR	NR	NR	NR	NR	Very low ⊕○○○ Uncertain <u>1 (93):</u> ↔ 1 trial	NR	Very low ⊕○○○ Uncertain <u>1 (93):</u> ? 1 trial
Vaginal oxytocin vs. Placebo	Very low ⊕○○○ Uncertain <u>2 (243):</u> ↑ 1 trial ↔ 1 trial	Very low ⊕○○○ Uncertain <u>1 (86):</u> ↑ 1 trial	NR	Very low ⊕○○○ Uncertain <u>2 (243):</u> ↑ 1 trial ↔ 1 trial	Moderate ⊕⊕⊕○ Probably results in little to no difference <u>1 (157):</u> ↔ 1 trial	NR	NR	Low ⊕⊕○○ May result in little to no difference <u>1 (157):</u> ? 1 trial
Oral ospemifene vs. Placebo	Low ⊕⊕○○ May improve <u>3 (1771):</u> ↑ 2 trials ↔ 1 trial	High ⊕⊕⊕⊕ Results in little to no difference <u>1 (627):</u> ↔ 1 trial	NR	Low ⊕⊕○○ May improve <u>3 (2062):</u> ↑ 2 trials ↑↔ 1 trial	NR	NR	High ⊕⊕⊕⊕ Results in higher <u>1 (419):</u> ↑ 1 trial	Low ⊕⊕○○ May result in little to no difference <u>4 (2372):</u> ? 4 trials

Intervention Vs. Comparator	COE Intervention Vs. Comparator Effect on DRYNESS	COE Intervention Vs. Comparator Effect on DISCOMFORT/ IRRITATION	COE Intervention Vs. Comparator Effect on DYSURIA	COE Intervention Vs. Comparator Effect on DYSPAREUNIA	COE Intervention Vs. Comparator Effect on CHANGE IN MBS	COE Intervention Vs. Comparator Effect on QUALITY OF LIFE	COE Intervention Vs. Comparator Effect on TREATMENT SATISFACTION	COE Intervention Vs. Comparator Effect on ADVERSE EFFECTS
	# Trials (N): Direction of Effect	# Trials (N): Direction of Effect	# Trials (N): Direction of Effect	# Trials (N): Direction of Effect	# Trials (N): Direction of Effect	# Trials (N): Direction of Effect	# Trials (N): Direction of Effect	# Trials (N): Direction of Effect
Oral raloxifene and/or bazedoxifene vs. Placebo	Low ⊕⊕○○ May result in little to no difference <u>2 (274):</u> ↔ 2 trials	Low ⊕⊕○○ May result in little to no difference <u>2 (274):</u> ↔ 2 trials	Low ⊕⊕○○ May result in little to no difference <u>2 (274):</u> ↔ 2 trials	Low ⊕⊕○○ May result in little to no difference <u>2 (274):</u> ↔ 2 trials	NR	Low ⊕⊕○○ May improve less <u>1 (215):</u> ↓ 1 trial	Very low ⊕○○○ Uncertain <u>2 (393):</u> ↔ 1 trial ? 1 trial	Not assessed
Vaginal testosterone vs. Placebo	Very low ⊕○○○ Uncertain <u>2 (84):</u> ↔ 1 trial ? 1 trial	NR	NR	Very low ⊕○○○ Uncertain <u>2 (84):</u> ↔ 1 trial ? 1 trial	NR	NR	NR	Very low ⊕○○○. Uncertain <u>1 (40):</u> ? 1 trial
Systemic testosterone plus systemic estrogen vs. Systemic estrogen alone	Low ⊕⊕○○ May result in little to no difference <u>2 (130):</u> ↔ 1 trial ? 1 trial	NR	NR	Low ⊕⊕○○ May result in little to no difference <u>1 (70):</u> ↔ 1 trial	NR	NR	NR	Very low ⊕○○○ Uncertain <u>2 (140):</u> ↔ 1 trial ? 1 trial

Intervention Vs. Comparator	COE Intervention Vs. Comparator Effect on DRYNESS	COE Intervention Vs. Comparator Effect on DISCOMFORT/ IRRITATION	COE Intervention Vs. Comparator Effect on DYSURIA	COE Intervention Vs. Comparator Effect on DYSPAREUNIA	COE Intervention Vs. Comparator Effect on CHANGE IN MBS	COE Intervention Vs. Comparator Effect on QUALITY OF LIFE	COE Intervention Vs. Comparator Effect on TREATMENT SATISFACTION	COE Intervention Vs. Comparator Effect on ADVERSE EFFECTS
	# Trials (N): Direction of Effect	# Trials (N): Direction of Effect	# Trials (N): Direction of Effect	# Trials (N): Direction of Effect	# Trials (N): Direction of Effect	# Trials (N): Direction of Effect	# Trials (N): Direction of Effect	# Trials (N): Direction of Effect
Vaginal moisturizer vs. Placebo	Low ⊕⊕○○ May improve <u>4 (418):</u> ↑ 2 trials ↔ 1 trial ? 1 trial	NR	NR	Very low ⊕○○○ Uncertain <u>3 (338):</u> ↑ 1 trial ↔ 1 trial ? 1 trial	Low ⊕⊕○○ May result in little to no difference <u>1 (200):</u> ↔ 1 trial	NR	Very low ⊕○○○ Uncertain <u>2 (280):</u> ↔ 1 trial ? 1 trial	Moderate ⊕⊕⊕○ Probably results in little to no difference <u>4 (418)</u> ? 4 trials
CO ₂ laser vs. Sham laser	Very low ⊕○○○ Uncertain <u>4 (293):</u> ↑ 1 trial ↔ 1 trial ? 2 trials	Very low ⊕○○○ Uncertain <u>3 (205):</u> ↑ 1 trial ↔ 1 trial ? 1 trial	Low ⊕⊕○○ May result in little to no difference <u>3 (205):</u> ↔ 2 trials ? 1 trial	Very low ⊕○○○ Uncertain <u>3 (205):</u> ↑ 1 trial ↔ 1 trial ? 1 trial	Low ⊕⊕○○ May result in little to no difference <u>1 (60):</u> ↔ 1 trial	Low ⊕⊕○○ May result in little to no difference <u>3 (205):</u> ↔ 2 trials ? 1 trial	Very low ⊕○○○ Uncertain <u>2 (148):</u> ? 2 trials	Very low ⊕○○○ Uncertain <u>4 (293):</u> ↑ 4 trials
CO ₂ laser vs. Vaginal conjugated estrogen cream	Low ⊕⊕○○ May result in little to no difference <u>2 (119):</u> ↔ 1 trial ? 1 trial	Low ⊕⊕○○ May result in little to no difference <u>1 (69):</u> ↔ 1 trial	Low ⊕⊕○○ May result in little to no difference <u>1 (69):</u> ↔ 1 trial	Low ⊕⊕○○ May result in little to no difference <u>2 (119):</u> ↔ 1 trial ? 1 trial	NR	Low ⊕⊕○○ May result in little to no difference <u>1 (69):</u> ↔ 1 trial	Very low ⊕○○○ Uncertain <u>1 (69):</u> ? 1 trial	Very low ⊕○○○ Uncertain <u>2 (119):</u> ? 2 trials

Intervention Vs. Comparator	COE Intervention Vs. Comparator Effect on DRYNESS <u># Trials (N):</u> Direction of Effect	COE Intervention Vs. Comparator Effect on DISCOMFORT/ IRRITATION <u># Trials (N):</u> Direction of Effect	COE Intervention Vs. Comparator Effect on DYSURIA <u># Trials (N):</u> Direction of Effect	COE Intervention Vs. Comparator Effect on DYSPAREUNIA <u># Trials (N):</u> Direction of Effect	COE Intervention Vs. Comparator Effect on CHANGE IN MBS <u># Trials (N):</u> Direction of Effect	COE Intervention Vs. Comparator Effect on QUALITY OF LIFE <u># Trials (N):</u> Direction of Effect	COE Intervention Vs. Comparator Effect on TREATMENT SATISFACTION <u># Trials (N):</u> Direction of Effect	COE Intervention Vs. Comparator Effect on ADVERSE EFFECTS <u># Trials (N):</u> Direction of Effect
CO ₂ laser vs. CO ₂ laser plus hyaluronic acid gel	Very low ⊕○○○ Uncertain <u>1 (50):</u> ↔ 1 trial	Very low ⊕○○○ Uncertain <u>1 (50):</u> ↔ 1 trial	Very low ⊕○○○ Uncertain <u>1 (50):</u> ↔ 1 trial	Very low ⊕○○○ Uncertain <u>1 (50):</u> ↔ 1 trial	NR	Very low ⊕○○○ Uncertain <u>1 (50):</u> ↔ 1 trial	NR	Very low ⊕○○○ Uncertain <u>1 (50):</u> ? 1 trial
CO ₂ laser vs. Radio-frequency, placebo	NR	NR	NR	Very low ⊕○○○ Uncertain <u>1 (246):</u> ? 1 trial	NR	Very low ⊕○○○ Uncertain <u>1 (246):</u> ? 1 trial	NR	Not assessed
Er:YAG laser vs. Sham laser	NR	NR	NR	NR	NR	Low ⊕⊕○○ May result in little to no difference <u>1 (50):</u> ↔ 1 trial	NR	Very low ⊕○○○ Uncertain <u>1 (50):</u> ? 1 trial
Er:YAG laser vs. Hyaluronic acid suppositories	Very low ⊕○○○ Uncertain <u>1 (43):</u> ? 1 trial	NR	NR	Very low ⊕○○○ Uncertain <u>1 (43):</u> ? 1 trial	NR	Very low ⊕○○○ Uncertain <u>1 (43):</u> ? 1 trial	Very low ⊕○○○ Uncertain <u>1 (43):</u> ? 1 trial	Very low ⊕○○○ Uncertain <u>1 (43):</u> ? 1 trial
Er:YAG laser vs. Er:YAG hyperstack	NR	NR	NR	Very low ⊕○○○ Uncertain <u>1 (68):</u> ↑ 1 trial	NR	NR	NR	Not assessed

Abbreviations: AE=adverse event; CEC=conjugated estrogen cream; CO₂=carbon dioxide; COE=certainty of evidence; COMMA=Core Outcomes in Menopause; DHEA=dehydroepiandrosterone; Er:YAG=Erbium-doped yttrium aluminum garnet laser; HA=hyaluronic acid; MBS=most bothersome symptom; QoL=quality of life

*Quasi-randomized study design (all other trials are RCTs)

Direction of effect

↑: Intervention group had a statistically significantly better outcome than comparison group (e.g., improved symptoms, higher treatment satisfaction)

↓: Intervention group had a statistically significantly worse outcome than comparison group (e.g., worsened symptoms, lower treatment satisfaction)

↔: No statistically significant difference between groups

↑↔ or ↓↔: Mixed statistical significance of intervention group effect versus comparison group effect within multi-arm trials (e.g., one intervention dose/schedule had a statistically significantly better outcome than comparison group but there was no statistically significant difference between another intervention dose/schedule and comparison group)

?: No statistical comparison of change in time between groups provided

Certainty of evidence (COE)

High certainty (⊕⊕⊕⊕): We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty (⊕⊕⊕○): We are moderately confident in the effect estimate; the true effect is likely to be close to the effect estimate, but there is a possibility that it is substantially different.

Low certainty (⊕⊕○○): Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

Very low certainty (⊕○○○): We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

Characteristics of Included Studies Rated Low or Some Concerns ROB

Table C.4. Characteristics of included trials of estrogen hormonal interventions rated low or some concerns ROB

Intervention Vs. Comparator	Author, Year Trial ID # of Publications Funding Location (# of Sites)	RoB Total N Length of Follow-Up	Major Inclusion/Exclusion Criteria	Intervention(s) (Route; Form; Dose; Frequency) N Age (Years) Race (n, %)	Comparator(s) (Route; Form; Dose; Frequency) N Age (Years) Race (n, %)	Primary Outcome Other Outcomes Reported (Measures Used)
Vaginal Estrogen vs. Placebo	Archer, 2018 ⁵ NR 1 publication Industry NR (Multi-site, NR)	Some concerns N=573 12 weeks	Mod-severe vaginal dryness (MBS) FSH>40 or ≥40 years with intact uterus with 1 yr of amenorrhea VMI≤5%; pH>5 Excluded: porphyria; untreated HTN; abnormal pap at screening; hx or risk of VTE	Estradiol (vaginal; cream; 0.003%; 1x/day for 2 wks, then 2x/wk) N=287 59.5 (6.7) White (236, 86.5%); Black (42, 14.7%); Asian (6, 2.1%); American Indian/Alaska Native (4, 1.4%)	Placebo (vaginal; cream; N/A; 1x/day for 2 wks, then 2x/wk) N=286 59.8 (6.1) White (241, 84%); Black (43, 15%); Asian (2, 0.7%); American Indian/Alaska Native (2, 0.7%)	VVA signs and vaginal dryness Vulvovaginal dryness (4-point severity scale) Dysuria (4-point severity scale) Dyspareunia (4-point severity scale) Adverse effects

Intervention Vs. Comparator	Author, Year Trial ID # of Publications Funding Location (# of Sites)	RoB Total N Length of Follow-Up	Major Inclusion/Exclusion Criteria	Intervention(s) (Route; Form; Dose; Frequency) N Age (Years) Race (n, %)	Comparator(s) (Route; Form; Dose; Frequency) N Age (Years) Race (n, %)	Primary Outcome Other Outcomes Reported (Measures Used)
	Bachmann, 2009 ¹⁰ NR 1 publication Industry Canada, US (multicenter, NR)	Some concerns N=423 12 weeks	At least 1 mod-severe VVA symptom (vaginal dryness, itching, burning, or dyspareunia) VMI≤5%; pH>5 Excluded: prior hysterectomy; >2 HTN medications	Conjugated Estrogens (vaginal; cream; 0.3 mg; 1x/day 21/7) N=143 57.7 (5.8) White (134, 93.7%) Conjugated Estrogens (vaginal; cream; 0.3 mg; 2x/wk) N=140 57.5 (5.5) White (127, 90.7%)	Placebo (vaginal; cream; N/A; 1x/day 21/7) N=72 58.0 (5.8) White (63, 87.5%) Placebo (vaginal; cream; N/A; 2x/wk) N=68 58.7 (5.8) White (66, 97.1%)	Changes from baseline in VMI, vaginal pH, and MBS severity at week 12 Change in MBS (4-point severity scale) Adverse effects

Intervention Vs. Comparator	Author, Year Trial ID # of Publications Funding Location (# of Sites)	RoB Total N Length of Follow-Up	Major Inclusion/Exclusion Criteria	Intervention(s) (Route; Form; Dose; Frequency) N Age (Years) Race (n, %)	Comparator(s) (Route; Form; Dose; Frequency) N Age (Years) Race (n, %)	Primary Outcome Other Outcomes Reported (Measures Used)
	Constantine, 2017 ¹⁸ NCT02253173 6 publications ^{17, 18, 20, 48, 84, 108} Industry US, Canada (89)	Low ¹⁸ , Some concerns ⁸⁴ N=765 12 weeks	Mod-severe dyspareunia VMI≤5%; pH>5 Sexually active with penetration BMI≤38 >40% prior hysterectomy Excluded: endometrial hyperplasia or cancer; undiagnosed vaginal bleeding; liver or kidney disorder; VTE; CVA; TIA; DM; HTN; MI or ischemic heart disease, malignancy or endocrine disease; heavy smokers, alcohol or drug abuse	Estradiol (vaginal; soft-gel capsule; 4 mcg; 1x/day for 2 wks, then 2x/wk) N=191 NR White (162, 87.1%); Black (20, 10.8%); Asian (3, 1.6%) Estradiol (vaginal; soft-gel capsule; 10 mcg; 1x/day for 2 wks, then 2x/wk) N=191 58.6 (6.3) White (165, 87.8%); Black (21, 11.2%); Asian (2, 1.1%)	Placebo (vaginal; soft-gel capsule; N/A; 1x/day for 2 wks, then 2x/wk) N=192 59.4 (6.0) White (160, 85.6%); Black (21, 11.2%); Asian (1, 0.5%)	Dyspareunia and VVA Vulvovaginal dryness (VVA-Self Assessment Questionnaire) Vulvovaginal irritation (VVA-Self Assessment Questionnaire) Dyspareunia (4-point severity scale) Sexual function (FSFI) Adverse effects
	Fernandes, 2014 ^{29*} UTN identifier U1111-11255434 2 publications ^{29, 30} Foundation Brazil (1)	Low N=40* 12 weeks	Attending a menopause clinic, with vulvovaginal dryness, irritation/itching, or dyspareunia; BMI 18.5-30 Excluded: surgical menopause or hysterectomy, h/o VTE, MI, breast or endometrial cancer, severe HTN, DM, liver failure	Conjugated estrogens (vaginal; cream; 0.625 mg; 3x/wk) N=20 56.4 (4.8) White (70%); Nonwhite (30%)	Placebo (vaginal; lubricant with glycerin gel; N/A; 3x/wk) N=20 57.7 (4.7) White (65%); Nonwhite (35%)	Change in FSFI score Vulvovaginal dryness (FSFI lubrication) Dyspareunia (FSFI pain) Sexual function (FSFI total) Adverse effects

Intervention Vs. Comparator	Author, Year Trial ID # of Publications Funding Location (# of Sites)	RoB Total N Length of Follow-Up	Major Inclusion/Exclusion Criteria	Intervention(s) (Route; Form; Dose; Frequency) N Age (Years) Race (n, %)	Comparator(s) (Route; Form; Dose; Frequency) N Age (Years) Race (n, %)	Primary Outcome Other Outcomes Reported (Measures Used)
	Freedman, 2009 ³⁴ NCT00361569 1 publication Industry US (88)	Some concerns N=305 12 weeks	At least 1 mod-severe VVA symptom (vaginal dryness, soreness, irritation/itching, dyspareunia, or bleeding after intercourse) VMI≤5%; pH>5 Natural or surgical menopause Mean 156 months since menses Normal mammogram, normal endometrial biopsy Excluded: any contraindication to estrogens; triglycerides >350; uncontrolled HTN or DM; current vaginal infection	Synthetic Conjugated Estrogens-A (vaginal; cream [1 or 2 g]; 0.625 mg/g; 1x/day for 1 wk, then 2x/wk) N=150 60.0 (6.5) African American (10, 7.4%); Asian (1, 0.7%), White (112, 83.0%), Hispanic (11, 8.1%), Other (1, 0.7%)	Placebo (vaginal; cream [1 or 2 g]; N/A; 1x/day for 1 wk, then 2x/wk) N=155 59.9 (6.8) African American (5, 3.6%); Asian (1, 0.7%); White (126, 90.0%); Hispanic (7, 5.0%); Other (1, 0.7%)	Change in severity of the MBS Change in MBS (4-point severity scale) Adverse effects
	Lima, 2013 ^{109†} 093/10 1 publication None Brazil (NR)	Some concerns N=60 [†] 12 weeks	Experiencing VVA symptoms (vulvovaginal dryness, burning, and dyspareunia) FSH>40, no superficial cells, endometrial thickness <4.0 mm ≥2 year since last menses Excluded: prior hysterectomy; breast cancer; hot flashes; any contraindication to study drugs/procedure	Conjugated estrogens (vaginal; cream [1 g]/0.625 mg; 1x/day) N=30 56 (SD NR) NR	Placebo (vaginal; gel; N/A; 1x/day) N=30 57 (SD NR) NR	Change in dryness, dyspareunia Vulvovaginal dryness (4-point severity scale) Dyspareunia (4-point severity scale) Genital signs (VMV) Adverse effects

Intervention Vs. Comparator	Author, Year Trial ID # of Publications Funding Location (# of Sites)	RoB Total N Length of Follow-Up	Major Inclusion/Exclusion Criteria	Intervention(s) (Route; Form; Dose; Frequency) N Age (Years) Race (n, %)	Comparator(s) (Route; Form; Dose; Frequency) N Age (Years) Race (n, %)	Primary Outcome Other Outcomes Reported (Measures Used)
	Mitchell, 2018 ^{62†} NCT02516202 4 publications ^{24, 35, 61, 62} Government US (2)	Low N=200 [‡] 12 weeks	At least 1 mod-severe VVA symptom (dryness, dyspareunia, or irritation/itching) ≥2 years since last menses No VMI/pH Excluded: endometrial hyperplasia or cancer; h/o breast cancer; undiagnosed vaginal bleeding; severe liver disease; VTE; CVA, TIA, MI or ischemic heart disease; lichen sclerosis or planus	Estradiol (vaginal; tablet; 10 mcg; 1x/day for 2 wks, then 2x/wk) + Placebo (vaginal; gel; N/A; every 3 days) N=102 61 (4) White (87, 85%); African American (7, 7%); Other/unknown (8, 8%)	Dual Placebo (vaginal; gel; N/A; every 3 days + vaginal; tablet; N/A; 1x/day for 2 wks, then 2x/wk) N=100 61 (4) White (90, 90%); African American (2, 2%); Other/unknown (8, 8%)	Change in severity of the MBS Vulvovaginal dryness/lubrication (FSFI lubrication) Vulvovaginal irritation (4-point severity scale) Dyspareunia (FSFI pain) Sexual function (FSFI) Change in MBS (4-point severity scale) Distress, bother or interference of GU symptoms (MENQOL and DIVA) Psychological symptoms (PHQ-8 and GAD-7) Treatment satisfaction (study-specific Likert scale) Adverse effects
	Raghunandan, 2010 ⁷⁸ NR 1 publication NR India (1)	Some concerns N=50 [¶] 12 weeks	Symptoms of urogenital or sexual dysfunction disorders (vaginal dryness, irritation/itching, dyspareunia) Normal mammogram and pap Excluded: any known contraindication to HRT	Estrogen (vaginal; cream [1 g]; 0.625 mg; 1x/day for 2 wks, then 2x/wk) N=25 52.2 (7.5) NR	Placebo (vaginal; gel [1 g]; N/A; 1x/day for 2 wks, then 2x/wk) N=25 51.6 (5.7) NR	Urogenital and sexuality scores Sexual function (study adapted sexuality score)
	Tanmahasamut, 2020 ⁸⁷ TCTR20170322001 1 publication Academia Thailand (1)	Some concerns N=80 8 weeks	VVA symptoms (vaginal dryness, irritation, soreness, discharge, or dyspareunia) Endometrial thickness ≤5 mm by TVU (if uterus intact) Surgical menopause possible Excluded: breast cancer; CVD; liver disease; undiagnosed vaginal bleeding; liver or kidney disorder; VTE; any contraindication to use of estrogen	Estradiol (vaginal; gel; 25 mcg; 1x day for 1-2 wks, then 2x/wk) N=40 54.9 (9.8) NR	Placebo (vaginal; gel; N/A; 1x day for 1-2 wks, then 2x/wk) N=40 56.4 (4.5) NR	Mean change from baseline to week 8 in VMI Change in MBS (4-point severity scale) Adverse effects

Intervention Vs. Comparator	Author, Year Trial ID # of Publications Funding Location (# of Sites)	RoB Total N Length of Follow-Up	Major Inclusion/Exclusion Criteria	Intervention(s) (Route; Form; Dose; Frequency) N Age (Years) Race (n, %)	Comparator(s) (Route; Form; Dose; Frequency) N Age (Years) Race (n, %)	Primary Outcome Other Outcomes Reported (Measures Used)
Vaginal Estrogen vs. No Treatment	Eriksen, 1999 ²⁸ NR 1 publication Industry Norway (15)	Some concerns N=108 36 weeks	≥2 years since last menses or surgical (bilateral oophorectomy) ≥3 UTIs in last 12 months Excluded: h/o UTI pre-menopause; urologic or gynecologic abnormalities; vaginal bleeding; hepatic or kidney disease; prior hysterectomy	Estradiol (vaginal; ring; 2 mg; 1x/day) N=53 67 (10) White (53, 100%)	No treatment N=55 69 (8) White (55, 100%)	Symptomatic UTI Vaginal dryness (4-point severity scale) Vulvovaginal itching (4-point severity scale) Dysuria (4-point severity scale) Urge incontinence (4-point severity scale) Dyspareunia (4-point severity scale) Adverse effects
Vaginal Estrogen vs. Vaginal Testosterone	Melisko, 2017 ⁵⁹ NCT00698035 1 publication Industry US (1)	Low N=76 12 weeks	All participants have stage I-III HR+ breast cancer on an aromatase inhibitor and vulvovaginal dryness, dyspareunia, or decreased libido Excluded: gynecologic cancer, vaginal or vulvar radiation	Estradiol (vaginal; ring; 7.5 mcg; 1x/day) N=40 56 (SD NR) White: 36 (% NR) Asian: 0 (% NR) Hispanic: 3 (% NR)	Testosterone (vaginal; cream [0.5 g]; 1%; 1x/day for 2 wks, then 3x/wk) N=36 57 (SD NR) White: 33 (% NR) Asian: 1 (% NR) Hispanic: 2 (% NR)	Safety of IVT or vaginal estrogen ring Sexual function (CARES) Genital signs (Gyn exam)
Vaginal Estrogen Delivery Method Comparison	Ayton, 1996 ⁷ NR 1 publication Industry Australia (NR)	Low N=195 12 weeks	VVA symptoms (vaginal dryness, dyspareunia, dysuria and/or urgency) and signs Excluded: prior hysterectomy or bilateral oophorectomy; hormone-dependent neoplasia; vaginal bleeding; sex hormone treatment within 3 months; grade II-III vaginal prolapse; VTE; liver disease	Estradiol (vaginal; ring; 2 mg; 1x/day) N=130 59.3 (7.3) White (129, % NR); Other (2, % NR)	Conjugated estrogens (vaginal; cream [1 g]; 0.625 mg; 1x/day for 3 wks, then 0x/day for 1 wk, then repeat) N=65 59.9 (7.3) White (63, % NR)	Vaginal mucosal maturation, endometrial response to progestogen challenge test Vulvovaginal dryness/lubrication (study-specific) Dysuria (4-point severity scale) Dyspareunia (4-point severity scale) Treatment satisfaction (study-specific)

Intervention Vs. Comparator	Author, Year Trial ID # of Publications Funding Location (# of Sites)	RoB Total N Length of Follow-Up	Major Inclusion/Exclusion Criteria	Intervention(s) (Route; Form; Dose; Frequency) N Age (Years) Race (n, %)	Comparator(s) (Route; Form; Dose; Frequency) N Age (Years) Race (n, %)	Primary Outcome Other Outcomes Reported (Measures Used)
	Nachtigall, 1995 ⁶³ NR 1 publication NR NR	Some concerns N=196 15 weeks	VVA signs and symptoms (vaginal dryness, dyspareunia, dysuria, urgency, vaginal burning, or tightness) Natural or surgical menopause FSH>40; endometrial echo <5 mm Normal mammogram Excluded: contraindication to study drugs/technique	Estradiol (vaginal; ring; 7.5 mcg/24 hr; 1x/day for 12 wks, then none) N=129 NR NR	Conjugated estrogens (vaginal; cream; 2 g; 3x/wk for 12 wks, then none) N=67 NR NR	Urogenital atrophy Dyspareunia (FSFI pain) Treatment satisfaction (Study- specific questionnaire) Adverse effects
Vaginal Estrogen Dose Comparison	Goetsch, 2023 ³⁶ NCT03240081 1 publication Foundation US (1)	Some concerns N=50 12 weeks	Mod-severe dyspareunia Natural or surgical menopause Heterosexual partnership >2 years Excluded: dyspareunia pre- menopause; chronic vulvar or pelvic pain; h/o estrogen- sensitive cancer; h/o uncorrected erectile dysfunction in partner	Estradiol (vaginal; cream; 50 mcg; 1x/day) N=25 59.2 (6.2) White (24, 96%); Asian (0); More than one race (1, 4%)	Estradiol (vaginal; cream; 100 mcg; 1x/day) N=25 60.2 (7.5) White 24 (96%) Asian: 1 (4%) More than one race: 0 (0%)	Dyspareunia Vulvovaginal irritation (VPAQ) Urinary symptoms (UDI-6) Adverse effects
Vaginal Estrogen vs. OAB Pharmaceuticals	Nelken, 2011 ⁶⁵ NR 1 publication Industry US (1)	Some concerns N=59 12 weeks	≥10 voids in a 24-hr period ≥12 months since last menses or FSH>25 for women with prior hysterectomy Excluded: postvoid residual >50 mL; MUI w/ SUI as predominant symptom; SUI; pelvic organ prolapse; uncontrolled DM; contraindication to either study medication	Estradiol (vaginal; ring; 7.5 mcg/24 hr; 1x/day) N=28 57.7 (4.2) NR	Oxybutynin (oral; NR; 5 mg; 2x/day) N=31 59.0 (6.8) NR	Change from baseline in the number of daily voiding episodes Urinary symptoms (voiding frequency) Adverse effects

Intervention Vs. Comparator	Author, Year Trial ID # of Publications Funding Location (# of Sites)	RoB Total N Length of Follow-Up	Major Inclusion/Exclusion Criteria	Intervention(s) (Route; Form; Dose; Frequency) N Age (Years) Race (n, %)	Comparator(s) (Route; Form; Dose; Frequency) N Age (Years) Race (n, %)	Primary Outcome Other Outcomes Reported (Measures Used)
	Tseng, 2009 ⁸⁸ NR 1 publication NR Taiwan (NR)	Some concerns N=80 12 weeks	≥12 months since last menses or FSH>30-40 for women with prior hysterectomy OAB Excluded: advanced pelvic organ prolapse; severe constipation; elevated post-void residual; neurological deficit; contraindication to tolterodine or estrogen; breast cancer; undiagnosed vaginal bleeding	Tolterodine (oral; NR; 2 mg; 2x/day) + Conjugated estrogens (vaginal; cream; 0.625 mg; 2x/wk) N=40 66.2 (6.8) NR	Tolterodine (oral; NR; 2 mg; 2x/day) N=40 64.5 (7.4) NR	NR Urinary symptoms (UDI-6 and IIQ-7) Adverse effects

Abbreviations: DM=diabetes mellitus; FSFI=Female Sexual Function Index; FSH=follicle-stimulating hormone; g=gram; h/o=history of; hr=hour; HRT=hormone replacement therapy; ID=identification; IIQ-7=Incontinence Impact Questionnaire; KQ=Key Question; mcg=microgram; mg=milligram; MUI=mixed urinary incontinence; N/A=not applicable; NR=not reported; OAB=overactive bladder; RoB=risk of bias; SD=standard deviation; SUI=stress urinary incontinence; UDI-6=Urinary Distress Inventory; UTI=urinary tract infection; VPAQ=Vulvar Pain Assessment Questionnaire; VTE=venous thromboembolism

*Multi-arm trial, only conjugated estrogens and placebo arms from Fernandes (2014)²⁹ described here. See Table C.5 for testosterone arm and Table C.6 for polyacrylic acid arm.

†Multi-arm trial, only conjugated estrogens and placebo arms from Lima (2013)¹⁰⁹ described here. See Table C.28 for isoflavone arm.

‡Multi-arm trial, only estradiol and placebo arms from Mitchell (2018)⁶² described here. See Table C.6 for moisturizer arm.

¶Multi-arm trial, only estrogen and placebo arms from Raghunandan (2010)⁷⁸ described here. See Table C.5 for estrogen + testosterone arm.

Table C.5. Characteristics of included trials of non-estrogen hormonal interventions rated low or some concerns ROB

Intervention Vs. Comparator	Author, Year Trial ID # of Publications Funding Location (# of Sites)	RoB Total N Length of Follow-Up	Major Inclusion/Exclusion Criteria	Intervention(s) (Route; Form; Dose; Frequency) N Age (Years) Race (n, %)	Comparator(s) (Route; Form; Dose; Frequency) N Age (Years) Race (n, %)	Primary Outcome Other Outcomes Reported (Measures Used)
Vaginal DHEA vs. Placebo	Archer, 2015 ⁶ NCT01256684 1 publication Industry Canada (9), US (24)	Low N=255 12 weeks	At least mod-severe dyspareunia at baseline Dyspareunia is MBS FSH>40; VMI<5%; pH>5 Normal mammogram, Pap, and baseline endometrial biopsy 51% surgical menopause Mean 14.5 yrs since menses Excluded: any history of cancer, unprovoked VTE, uncontrolled DM, HTN, depression	DHEA (vaginal; ovule; 0.25% [3.25 mg]; 1x/day) N=87 59.4 (SD NR) White: 81 (94) Black or African American: 4 (5) Asian: 0 (0) Other: 1 (1) DHEA (vaginal; ovule; 0.5% [6.5 mg]; 1x/day) N=87 57.5 (SD NR) White: 83 (95) Black or African American: 3 (3) Asian: 1 (1) Other: 0 (0)	Placebo (vaginal; ovule; N/A; 1x/day) N=81 58.8 (SD NR) White: 69 (86) Black or African American: 9 (11) Asian: 1 (1) Other: 1 (1)	Change from baseline to week 12 in MBS severity (Dyspareunia) Vulvovaginal dryness (4-point severity scale) Dyspareunia (4-point severity scale) Genital signs (VMI and pH) Adverse effects

Intervention Vs. Comparator	Author, Year Trial ID # of Publications Funding Location (# of Sites)	RoB Total N Length of Follow-Up	Major Inclusion/Exclusion Criteria	Intervention(s) (Route; Form; Dose; Frequency) N Age (Years) Race (n, %)	Comparator(s) (Route; Form; Dose; Frequency) N Age (Years) Race (n, %)	Primary Outcome Other Outcomes Reported (Measures Used)
	Barton, 2018 ¹³ NCT01376349 1 publication Government US, Canada (82)	Some concerns N=443 12 weeks	At least mod-severe dyspareunia or dryness at baseline All participants have a history of breast (97%) or gyn (3%) cancer; no active cancer 30-37% surgical menopause 15-16% on Tamoxifen 55-56% on Aromatase Inhibitor	DHEA (vaginal; gel [0.4 mL]; 3.25 mg; 1x/day) N=147 56.8 (6.7) White: 142 (97) Black or African American: 3 (2) Asian: 0 Unknown: 2 (1) DHEA (vaginal; gel [0.4 mL]; 6.5 mg; 1x/day) N=149 57.3 (8.2) White: 142 (95) Black or African American: 5 (4) Asian: 0 (0) Unknown: 2 (1)	Placebo (vaginal; gel; N/A; 1x/day) N=147 58 (7.3) White: 137 (93) Black or African American: 7 (5) Asian: 1 (1) Unknown: 2 (1)	Change from baseline in MBS (dryness or dyspareunia) Vulvovaginal dryness (FSFI lubrication) Dyspareunia (FSFI pain) Sexual function (FSFI total) Change in MBS (4-point severity scale) Adverse effects

Intervention Vs. Comparator	Author, Year Trial ID # of Publications Funding Location (# of Sites)	RoB Total N Length of Follow-Up	Major Inclusion/Exclusion Criteria	Intervention(s) (Route; Form; Dose; Frequency) N Age (Years) Race (n, %)	Comparator(s) (Route; Form; Dose; Frequency) N Age (Years) Race (n, %)	Primary Outcome Other Outcomes Reported (Measures Used)
	Labrie, 2009 ⁵² NR 5 publications ^{50, 52-55} Industry Canada (multicenter, NR)	Some concerns N=216 12 weeks	At least mod-severe dyspareunia, dryness, or irritation/itching FSH>40; VMI<5%; pH>5 Normal mammogram, Pap, and baseline endometrial biopsy BMI 18-35 Excluded: any history of cancer, VTE, uncontrolled DM or migraine	DHEA (vaginal; ovule; 0.25% [3.25 mg]; 1x/day) N=53 57 (42-72) NR DHEA (vaginal; ovule; 0.5% [6.5 mg]; 1x/day) N=56 58 (50-74) NR DHEA (vaginal; ovule; 1.0% [13 mg]; 1x/day) N=54 59 (46-69) NR	Placebo (vaginal; ovule; N/A; 1x/day) N=53 58 (49-70) NR	Determine the minimal dose of DHEA that produces maximal effect on the vaginal mucosa Vulvovaginal dryness (4-point severity scale; MENQOL dryness) Dyspareunia (4-point severity scale) Sexual function (ASFAQ; MENQOL sexual domain) Change in MBS (4-point severity scale) Distress, bother, or interference of GU symptoms (MENQOL total) Psychological symptoms (PGWB) Genital signs (VMI and pH) Adverse effects
	Labrie, 2018 ⁵¹ NCT02013544 2 publications ^{51, 56} Industry US (24), Canada (14)	Low N=558 12 weeks	At least mod-severe dyspareunia at baseline Dyspareunia is MBS FSH>40; VMI<5%; pH>5 Normal mammogram, Pap, and baseline endometrial biopsy 36% surgical menopause 13.9 mean yrs since menses Excluded: any history of cancer, unprovoked VTE, uncontrolled depression	DHEA (vaginal; ovule; 0.5% [6.5 mg]; 1x/day) N=376 59.6 (SD NR) White: 338 (90) Black or African American: 28 (7) Asian: 4 (1) American Indian or Alaska Native: 1 (0) Native Hawaiian or Other Pacific Islander: 1 (0) White, Black, or African: 2 (1)	Placebo (vaginal; ovule; N/A; 1x/day) N=182 59.6 (SD NR) White: 163 (91) Black or African American: 13 (7) Asian: 2 (1) American Indian or Alaska Native: 0 (0) Native Hawaiian or Other Pacific Islander: 0 (0) White, Black, or African: 2 (1)	Changes from baseline to week 12 in the percentages of parabasal and superficial cells, vaginal pH, and severity of dyspareunia (MBS) Vulvovaginal dryness (4-point severity scale; FSFI lubrication) Dyspareunia (4-point severity scale; FSFI pain) Sexual function (FSFI total) Genital signs (VMI and pH) Adverse effects

Intervention Vs. Comparator	Author, Year Trial ID # of Publications Funding Location (# of Sites)	RoB Total N Length of Follow-Up	Major Inclusion/Exclusion Criteria	Intervention(s) (Route; Form; Dose; Frequency) N Age (Years) Race (n, %)	Comparator(s) (Route; Form; Dose; Frequency) N Age (Years) Race (n, %)	Primary Outcome Other Outcomes Reported (Measures Used)
Oral DHEA vs. Placebo	Panjari, 2009 ⁶⁹ NR 2 publications ^{69, 110} NR Australia (1)	Low N=93 52 weeks	Normal mammogram, Pap, endometrial thickness<4 mm on TVU at baseline BMI 18-34 Mean 6.6-7.2 yrs since menopause Excluded: surgical menopause, history of gyn/breast cancer, mod-severe acne, hirsutism, or androgenic alopecia, severe depression	DHEA (oral; capsule; 50 mg; 1x/day) N=47 55.1 (4.5) NR	Placebo (oral; capsule; N/A; 1x/day) N=46 53.9 (4.7) NR	Sexual function Sexual function (SSS) Psychological symptoms (PGWB) Distress, bother, or interference of GU symptoms (MENQOL total) Adverse effects
	Fianu Jonasson, 2020 ³² EudraCT number: 2016- 000158-36 1 publication Industry Sweden (3)	Low N=161 12 weeks	At least one mod-severe VVA symptom VMI<5%; pH>5; endometrial thickness<4 mm Normal Pap smear required for women with intact uterus BMI ≤32 kg/m ²	Oxytocin (vaginal; gel [1 x 1 mL]; 400 IU; 1x/day) N=81 58.0 (3.9) NR	Placebo (vaginal; gel [1 x 1 mL]; N/A; 1x/day) N=80 58.7 (3.1) NR	MBS severity Vulvovaginal dryness (4-point severity scale) Dyspareunia (4-point severity scale) Change in MBS (4-point severity scale) Genital signs (vaginal cytology) Adverse effects
Oxytocin Gel vs. Placebo Gel	Zohrabi, 2020 ⁹⁰ IRCT20160602028220N2 2 publications ^{1, 90} Academia Iran (2)	Some concerns N=96 8 weeks	Self-reported VVA symptoms at baseline FSH>40; vaginal atrophy confirmed with VMI and pH Mean 4.13/3.78 yrs since menopause BMI ≤30 kg/m ² Excluded: vaginal infection, h/o smoking, vaginal bleeding or spotting, breast disease, use of HRT, use of vaginal lubricant within 15 days of treatment	Oxytocin (vaginal; gel; 2 g; 1x/day) N=48 54.2 (3.3) NR	Placebo (vaginal; gel; N/A; 1x/day) N=48 54.1 (3.7) NR	Vaginal atrophy (i.e., number of superficial cells and parabasal cells) and sexual function Vulvovaginal dryness (FSFI lubrication) Vulvovaginal discomfort or irritation (study checklist) Dyspareunia (FSFI pain, study checklist) Sexual function (FSFI total) Genital signs (VMI) Adverse effects

Intervention Vs. Comparator	Author, Year Trial ID # of Publications Funding Location (# of Sites)	RoB Total N Length of Follow-Up	Major Inclusion/Exclusion Criteria	Intervention(s) (Route; Form; Dose; Frequency) N Age (Years) Race (n, %)	Comparator(s) (Route; Form; Dose; Frequency) N Age (Years) Race (n, %)	Primary Outcome Other Outcomes Reported (Measures Used)
Ospemifene (oral) vs. Placebo	Archer, 2019 ⁴ NCT02638337 2 publications ^{4, 38} Industry US (68)	Low N=631 12 weeks	At least moderate-severe vulvovaginal dryness Dryness is MBS Follicle-stimulating hormone>40; VMI<5%; pH>5 Excluded: cancer in the past 10 yrs, h/o VTE, CVA, CAD, excess EtOH, BMI>38	Ospemifene (oral; tablet; 60 mg; 1x/day) N=316 59.7 (6.6) White: 273 (87) Black: 38 (12) American Indian or Alaska Native: 0 (0) Asian: 1 (0.3) Other: 1 (0.3)	Placebo (oral, tablet; N/A; 1x/day) N=315 59.8 (7.2) White: 266 (85) Black: 32 (10) American Indian or Alaska Native: 7 (2) Asian: 3 (1) Other: 6 (2)	Changes from baseline to week 12 in the percentages of parabasal and superficial cells, vaginal pH, and severity of vaginal dryness (MBS) Vulvovaginal dryness (FSFI lubrication domain; 4-point severity scale) Vulvovaginal discomfort or irritation (4-point severity scale) Dyspareunia (FSFI pain domain; 4-point severity scale) Sexual function (FSFI total) Genital Signs (VMI & pH) Treatment Satisfaction Adverse effects
	Bachmann, 2010 ⁸ NCT01585558 2 publications ^{8, 85} Industry US (76)	Some concerns N=826 12 weeks	At least 1 moderate-severe VVA symptom FSH>40; VMI<5%; pH>5 Normal breast exam, mammogram, Pap, endometrial biopsy, and transvaginal ultrasound Excluded: cancer in the past 10 yrs; h/o VTE; uncontrolled HTN; excess EtOH; BMI>37	Ospemifene (oral; tablet; 30 mg; 1x/day) N=282 58.4 (6.3) NR Ospemifene (oral; tablet; 60 mg; 1x/day) N=276 58.6 (6.3) NR	Placebo (oral, tablet; N/A; 1x/day) N=268 58.9 (6.1) NR	Changes from baseline to week 12 in the percentage of superficial and parabasal cells, vaginal pH, and severity of MBS (vaginal dryness or dyspareunia) Dryness (4-point severity scale) Dyspareunia (4-point severity scale) Adverse effects

Intervention Vs. Comparator	Author, Year Trial ID # of Publications Funding Location (# of Sites)	RoB Total N Length of Follow-Up	Major Inclusion/Exclusion Criteria	Intervention(s) (Route; Form; Dose; Frequency) N Age (Years) Race (n, %)	Comparator(s) (Route; Form; Dose; Frequency) N Age (Years) Race (n, %)	Primary Outcome Other Outcomes Reported (Measures Used)
	Goldstein, 2014 ³⁹ NCT00566982 1 publication Industry Europe (23)	Low N=426 1 year	No symptoms required VMI<5%; pH>5 Normal breast exam, mammogram, baseline endometrial biopsy Excluded: hysterectomy	Ospemifene (oral; tablet; 60 mg; 1x/day) N=363 61.7 (6.2) White: 361 (99) Black: 1 (0.3) Asian: 1 (0.3)	Placebo (oral, tablet; N/A; 1x/day) N=63 62.9 (6.5) White: 63 (100) Black: 0 (0) Asian: 0 (0)	12-month safety, particularly endometrial Genital Signs (VMI & pH) Adverse effects
	Constantine, 2015 ¹⁹ 3 publications ^{19, 76, 77} Industry US (110)	Some concerns N=919 12 weeks Dyspareunia stratum ⁷⁶ : N=605 Dryness stratum ¹¹¹ : N=314	One larger study with two parallel strata ^{76, 77} Prior diagnosis of VVA Mod-severe dryness or dyspareunia Dyspareunia is MBS ⁷⁶ Dryness is MBS ⁷⁷ VMI<5%; pH>5 Excluded: BMI>37	Ospemifene (oral; tablet; 60 mg; 1x/day) N=463 58.7 (6.6) White: 409 (88) Black: 28 (6) Other: 26 (6)	Placebo (oral, tablet; N/A; 1x/day) N=456 58.5 (6.4) White: 396 (87) Black: 35 (8) Other: 25 (6)	Change from baseline to week 12 in MBS severity (dyspareunia or vaginal dryness); FSFI total and domain scores Dryness (FSFI lubrication domain; 4-point severity scale) Dyspareunia (FSFI pain domain; 4-point severity scale) Sexual function (FSFI total) Genital signs (VMI & pH) Adverse effects
Bazedoxifene (oral) +/- Conjugated Estrogen Eream vs. Placebo	Kagan, 2010 ⁴⁴ SMART-3 2 publications ^{9, 44} Industry US (66)	Some concerns N=652 12 weeks	At least 1 moderate-severe VVA symptom (vaginal dryness, irritation/itching, or dyspareunia) VMI<5%; pH≥5; FSH>40 BMI≤34 kg/m ² Normal endometrial biopsy Excluded: h/o endometrial hyperplasia; estrogen- dependent neoplasia; undiagnosed vaginal bleeding; chronic renal or hepatic disease; VTE; CVA; MI; malignancy within 5 yrs (except for skin) or h/o breast cancer, melanoma, or gynecological cancer	BZA (oral; tablet; 20 mg; 1x/day) N=110 56.4 (4.5) White: 103 (94) Black: 4 (3) Other: 3 (3)	Placebo (oral; tablet; N/A; 1x/day) N=105 56.1 (4.2) White: 96 (91) Black: 2 (2) Other: 7 (7)	Change from baseline to week 12 in proportion of superficial and parabasal cells, vaginal pH, and MBS severity Distress, bother, or interference of GU symptoms (MENQOL total) Treatment satisfaction (MS- TSQ) Adverse effects

Intervention Vs. Comparator	Author, Year Trial ID # of Publications Funding Location (# of Sites)	RoB Total N Length of Follow-Up	Major Inclusion/Exclusion Criteria	Intervention(s) (Route; Form; Dose; Frequency) N Age (Years) Race (n, %)	Comparator(s) (Route; Form; Dose; Frequency) N Age (Years) Race (n, %)	Primary Outcome Other Outcomes Reported (Measures Used)
Raloxifene (oral) + Vaginal Estrogen or Moisturizer vs. Placebo (oral) + Vaginal Estrogen or Moisturizer	Parsons, 2003 ⁷² NR 2 publications ^{46, 72} NR US (16)	Some concerns N=187 3 months	At least 2 signs of VVA Natural menopause only No menses for ≥ 2 years Excluded: treated with estrogen within the previous 3 months or non-estrogen/OTC remedies within previous 2 months; abnormal cervical cytology; suspected or confirmed breast malignancy; prior hysterectomy, bilateral oophorectomy, or endometrial ablation procedure; disorder of the vulva	Raloxifene (oral; tablet; 60 mg; 1x/day) + Moisturizer (vaginal; cream; N/A; 1x/day for 2 wks, then 2x/wk) N=47 59.6 (6.3) White: 41 (87) Black: 1 (2) Asian: 2 (4) Hispanic: 3 (6) Other: 0 (0) Raloxifene (oral; tablet; 60 mg; 1x/day) + Conjugated estrogens (vaginal; cream; 0.5 g; 1x/day for 2 wks, then 2x/wk) N=46 59.7 (8.0) White: 45 (98) Black: 1 (2) Asian: 0 (0) Hispanic: 0 (0) Other: 0 (0)	Placebo (oral; tablet; N/A; 1x/day) + Moisturizer (vaginal; cream; N/A; 1x/day for 2 wks, then 2x/wk) N=46 58.3 (6.9) White: 42 (91) Black: 4 (9) Asian: 0 (0) Hispanic: 0 (0) Other: 0 (0) Placebo (oral; tablet; N/A; 1x/day)+ Conjugated estrogens (vaginal; cream; 0.5 g; 1x/day for 2 wks, then 2x/wk) N=48 59.9 (7.4) White (41, 85.4%); Black (2, 4.2%); Asian (1, 2.1%); Hispanic (3, 6.3%); Other (1, 2.1%)	Improvement of signs and symptoms of vaginal atrophy Vulvovaginal dryness (4-point severity scale; SAQ) Vulvovaginal discomfort or irritation (4-point severity scale) Dysuria (4-point severity scale) Dyspareunia (4-point severity scale; SAQ) Sexual function (SAQ) Genital Signs (4-point scale, VMV) Treatment satisfaction

Intervention Vs. Comparator	Author, Year Trial ID # of Publications Funding Location (# of Sites)	RoB Total N Length of Follow-Up	Major Inclusion/Exclusion Criteria	Intervention(s) (Route; Form; Dose; Frequency) N Age (Years) Race (n, %)	Comparator(s) (Route; Form; Dose; Frequency) N Age (Years) Race (n, %)	Primary Outcome Other Outcomes Reported (Measures Used)
Raloxifene (oral) + Vaginal Estrogen vs. Placebo (oral) + Vaginal Estrogen	Pinkerton, 2003 ⁷⁴ NR 1 publication Industry US (10)	Low N=91 6 months	At least 2 signs of VVA Natural menopause only No menses for ≥ 2 years Endometrial thickness <5 mm Excluded: treated with raloxifene, systemic or vaginal estrogen or any other Rx/OTC remedy within 3 months of entry; abnormal Pap smear or mammogram; h/o breast or endometrial cancer; prior hysterectomy, bilateral oophorectomy, or endometrial ablation procedure	Raloxifene (oral; tablet; 60 mg; 1x/day) + Estradiol (vaginal; ring; 7.5 mcg; 1x/day) N=46 58 (SD NR) White: 85% Hispanic: 8% Asian: 4% African American: 3%	Placebo (oral; tablet; N/A; 1x/day) + Estradiol (vaginal; ring; 7.5 mcg; 1x/day) N=45 58 (SD NR) White: 85% Hispanic: 8% Asian: 4% African American: 3%	Not identified Vulvovaginal dryness (4-point severity scale) Vulvovaginal discomfort or irritation (4-point severity scale) Dysuria (4-point scale) Dyspareunia (4-point scale) Adverse effects
Vaginal Testosterone vs. Control (placebo or KY jelly)	Davis, 2018 ²¹ ACTRN12615000083594 1 publication Foundation Australia (NR)	Low N=44 26 weeks	All participants have invasive breast cancer, taking an aromatase inhibitor and report symptoms (vulvovaginal dryness, soreness, irritation/burning, or dyspareunia); pH <5 Excluded: moderate-severe acne, hirsutism, androgenic alopecia, major medical illness, past other cancer, excess EtOH Mean AI duration of use 2 yrs	Testosterone (vaginal; cream [1 g]; 300 mcg; 1x/day for 2 wks, then 3x/wk) N=22 57.7 (7.9) NR	Placebo (vaginal; cream; N/A; 1x/day for 2 wks, then 3x/wk) N=22 55.1 (9.7) NR	Change from baseline in the satisfaction domain of the FSFI at 26 weeks Vulvovaginal dryness (4 point scale; FSFI lubrication) Dyspareunia (4-point scale; FSFI pain) Irritation/burning (4-point scale) Sexual function (FSFI total) Genital signs (pH, vaginal epithelial maturation)
	Fernandes, 2014 ^{29*} UTNU1111-11255434 2 publications ^{29, 112} Foundation Brazil (1)	Low N=40* 12 weeks	Attending a menopause clinic, with vulvovaginal dryness, irritation/itching, or dyspareunia; BMI 18.5-30 Excluded: surgical menopause or hysterectomy, h/o VTE, MI, breast or endometrial cancer, severe HTN, DM, liver failure	Testosterone (vaginal; cream [1 g]; 300 mcg; 3x/wk) N=20 56.2 (5.3) White: 80% Nonwhite: 20%	Placebo (vaginal; gel; 3 g; 3x/wk) N=20 57.7 (4.7) White: 65% Nonwhite: 35%	Change in FSFI score Vulvovaginal dryness (FSFI lubrication) Dyspareunia (FSFI pain) Sexual function (FSFI total) Adverse effects

Intervention Vs. Comparator	Author, Year Trial ID # of Publications Funding Location (# of Sites)	RoB Total N Length of Follow-Up	Major Inclusion/Exclusion Criteria	Intervention(s) (Route; Form; Dose; Frequency) N Age (Years) Race (n, %)	Comparator(s) (Route; Form; Dose; Frequency) N Age (Years) Race (n, %)	Primary Outcome Other Outcomes Reported (Measures Used)
Vaginal Testosterone vs. Vaginal Estrogen	Melisko, 2017 ⁵⁹ NCT00698035 1 publication Industry US (1)	Low N=76 12 weeks	All participants have stage I-III HR+ breast cancer on an aromatase inhibitor and vulvovaginal dryness, dyspareunia, or decreased libido Excluded: gynecologic cancer, vaginal or vulvar radiation	Testosterone (vaginal; cream [0.5 g]; 1%; 1x/day for 2 wks, then 3x/wk) N=36 57 (SD NR) White: 33 (% NR) Asian: 1 (% NR) Hispanic: 2 (% NR)	Estradiol (vaginal; ring; 7.5 mcg; 1x/day) N=40 56 (SD NR) White: 36 (% NR) Asian: 0 (% NR) Hispanic: 3 (% NR)	Safety of IVT or vaginal estrogen ring Sexual function (CARES) Genital signs (Gyn exam) Adverse effects
Vaginal Testosterone + Vaginal Estrogen vs. Vaginal Estrogen Alone vs. Control	Raghunandan, 2010 ^{78†} NR 1 publication NR India (1)	Some concerns N=75 12 weeks	Symptoms of urogenital or sexual dysfunction disorders (vaginal dryness, irritation/itching, dyspareunia) Normal mammogram and pap Excluded: any known contraindication to HRT	Testosterone (vaginal; cream [0.5 g]; 2%); 1x/day) + Estrogen (vaginal; cream [1 g]; 0.625) N=25 51.4 (4.8) NR	Placebo (vaginal; gel [1 g]; N/A; 1x/day for 2 wks, then 2x/wk) N=25 51.6 (5.7) NR	Urogenital and sexuality scores Sexual function (study adapted sexuality score) Adverse effects
Systemic Testosterone + Systemic Estrogen vs. Systemic Estrogen Alone	Chaikittisilpa, 2019 ¹⁴ TCRT20180423001 1 publication Academia Thailand (1)	Some concerns N=70 8 weeks	Sexually active women attending a menopause clinic Baseline FSFI<26.5 Excluded: past hormonal therapy, h/o AUB, VTE, CVA, CAD, liver disease or cancer Mean 5-6 yrs since menopause 80-86% "natural" menopause	Estradiol valerate (oral; tablet; 1 mg; 1x/day) + Testosterone (transdermal; gel; 50 mg; 1x/day) N=35 53.5 (3.3) NR	Estradiol valerate (oral; tablet; 1 mg; 1x/day) + Placebo (transdermal; gel; N/A; 1x/day) N=35 53.0 (9.0) NR	FSFI score Sexual function (FSFI total) Adverse effects

Intervention Vs. Comparator	Author, Year Trial ID # of Publications Funding Location (# of Sites)	RoB Total N Length of Follow-Up	Major Inclusion/Exclusion Criteria	Intervention(s) (Route; Form; Dose; Frequency) N Age (Years) Race (n, %)	Comparator(s) (Route; Form; Dose; Frequency) N Age (Years) Race (n, %)	Primary Outcome Other Outcomes Reported (Measures Used)
	Penteado, 2008 ⁷³ NR 1 publication Industry Brazil (1)	Some concerns N=60 12 months	Sexual complaints after menopause Mean 5.6 yrs since menopause	Testosterone (oral; capsule; 2.0 mg; 1x/day) + Conjugated estrogens (oral; tablet; 0.625 mg; 1x/day) + MPA (oral; tablet; 2.5 mg; 1x/day) N=31 52.4 (4.2) NR	Placebo (oral; capsule; N/A; 1x/day) + Conjugated estrogens (oral; tablet; 0.625 mg; 1x/day)) + MPA (oral; tablet; 2.5 mg; 1x/day) N=29 51.8 (3.6) NR	Sexual energy and orgasm Vulvovaginal dryness (% prevalence) Sexual function (study adapted or specific measures)
	Tungmunsakulchai, 2015 ⁸⁹ NCT01724658 1 publication Academia Thailand (1)	Low N=70 8 weeks	Sexually active women attending a menopause clinic Baseline FSFI<26.5 Excluded: severe vasomotor sx; h/o VTE, CVA, CAD, cancer, liver disease, psychiatric disorder	Estrogen valerate (oral; NR; 1 mg; 2x/wk) + Testosterone (oral; NR; 40 mg; 2x/wk) N=35 53.8 (3.6) NR	Estrogen valerate (oral; NR; 1 mg; 2x/wk) + Placebo (oral; NR; N/A; 2x/wk) N=35 52.7 (4.1) NR	FSFI score Vulvovaginal dryness (FSFI lubrication) Dyspareunia (FSFI pain) Sexual function (FSFI total) Adverse effects

Abbreviations: ASFQ=Abbreviated Sexual Function Questionnaire; BMI=body mass index; BZA=bazedoxifene; CAD=coronary artery disease; CVA=cerebrovascular accident; DHEA=dehydroepiandrosterone; DM=diabetes mellitus; EtOH=ethanol; FSFI=Female Sexual Function Index; FSH=follicle-stimulating hormone; g=gram; GSM=genitourinary syndrome of menopause; GU=genitourinary; gyn=gynecological; h/o=history of; HRT=hormone replacement therapy; HTN=hypertension; ID=identification; IU=international unit; kg=kilogram; KQ=Key Question; MBS=most bothersome symptom; mcg=microgram; mg=milligram; MENQOL=Menopause-Specific Quality of Life; MI=myocardial infarction; mL=milliliter; mm=millimeter; MPA=medroxyprogesterone acetate; MS-TSQ=Menopause Symptoms Treatment Satisfaction Questionnaire; N/A=not applicable; NR=not reported; OTC=over the counter; PGWB=Psychological General Well-Being Index; RoB=risk of bias; Rx=prescription; SAQ=Sexual Activity Questionnaire; SD=standard deviation; SSS=Sabbatsberg Sexual Self-Rating Scale; START=Selective estrogen Menopause And Response to Therapy; TVU=transvaginal ultrasound; US=United States; VMI=Vaginal Maturation Index; VMV=vaginal maturation value; VTE=venous thromboembolism; VVA=vulvovaginal atrophy; wk=week; yr=year

*Multi-arm trial, only testosterone and placebo arms from Fernandes (2014)²⁹ described here. See Table C.4 for conjugated estrogens arm and Table C.6 for polyacrylic acid arm.

†Multi-arm trial, only testosterone + estrogen and placebo arms from Raghunandan (2010)⁷⁸ described here. See Table C.4 for estrogen arm.

Table C.6. Characteristics of included trials of non-hormonal moisturizers rated low or some concerns ROB

Intervention Vs. Comparator	Author, Year Trial ID # of Publications Funding Location (# of Sites)	RoB Total N Length of Follow-Up	Major Inclusion/Exclusion Criteria	Intervention(s) (Route; Form; Dose; Frequency) N Age (Years) Race (n, %)	Comparator(s) (Route; Form; Dose; Frequency) N Age (Years) Race (n, %)	Primary Outcome Other Outcomes Reported (Measures Used)
Polyacrylic Acid Cream (Vagidrat) vs. KY Jelly	Fernandes, 2014 ^{29*} U1111-11255434 2 publications ^{29, 30} Foundation Brazil (1)	Low N=40* 12 weeks	Attending a menopause clinic, with vulvovaginal dryness, irritation/itching, or dyspareunia; BMI 18.5-30 Excluded: surgical menopause or hysterectomy, h/o VTE, MI, breast or endometrial cancer, severe HTN, DM, liver failure	Polyacrylic acid (vaginal; cream; 3 g; 3x/week) N=20 57.0 (5.4) White (95)	Placebo (vaginal; lubricant with glycerin gel; N/A; 3x/wk) N=20 57.7 (4.7) White (65%); Nonwhite (35%)	Change in FSFI score Vulvovaginal dryness (FSFI lubrication) Dyspareunia (FSFI pain) Sexual function (FSFI total)
Lactic Acid Gel (pH-balanced) vs. Placebo Gel	Lee, 2011 ⁵⁷ NCT00607295 1 publication Academia South Korea (1)	Some concerns N=98 12 weeks	Experiencing vulvovaginal dryness with VAS pain >5.0 Breast cancer survivors Menopause for ≥12 months Excluded: natural menopause; severe medical disease or complication; other cancers; h/o hysterectomy or oophorectomy	Lactic acid (vaginal; gel; 2 mL; 3x/wk) N=49 45.9 (NR) NR	Placebo (vaginal; gel; N/A; 3x/wk) N=49 45.0 (NR) NR	Change of VAS from baseline during treatment for vaginal symptoms (dryness and dyspareunia) Dryness (VAS) Dyspareunia (VAS)
Vaginal Moisturizing Gel (Replens) vs. Placebo Hydroxyethyl-cellulose Gel	Mitchell, 2018 ^{62†} NCT02516202 4 publications ^{24, 35, 61, 62} Government United States (2)	Low N=200† 12 weeks	At least 1 mod-severe VVA symptom (dryness, dyspareunia, or irritation/itching) ≥2 years since last menses No VMI/pH Excluded: endometrial hyperplasia or cancer; h/o breast cancer; undiagnosed vaginal bleeding; severe liver disease; VTE; CVA, TIA, MI or ischemic heart disease; lichen sclerosis or planus	Glycerin and polycarbophil (vaginal; gel; NR; every 3 days) + Placebo (vaginal; tablet; N/A; 1x/day for 2 wks, then 2x/wk) N=100 61 (4) White (90)	Dual Placebo (vaginal; gel; N/A; every 3 days + vaginal; tablet; N/A; 1x/day for 2 wks, then 2x/wk) N=100 61 (4) White (90, 90%); African American (2, 2%); Other/unknown (8, 8%)	Decrease in severity of MBS Dryness (FSFI lubrication) Dyspareunia (FSFI pain) Sexual function (FSFI total) Change in MBS (4-point severity scale) Treatment satisfaction (10-point Likert scale)

Intervention Vs. Comparator	Author, Year Trial ID # of Publications Funding Location (# of Sites)	RoB Total N Length of Follow-Up	Major Inclusion/Exclusion Criteria	Intervention(s) (Route; Form; Dose; Frequency) N Age (Years) Race (n, %)	Comparator(s) (Route; Form; Dose; Frequency) N Age (Years) Race (n, %)	Primary Outcome Other Outcomes Reported (Measures Used)
Hyaluronic Acid-based Gel + As-needed Water-based Lubricant vs. As-needed Water-based Lubricant	Nappi, 2022 ⁶⁴ NCT04355403 1 publication Industry Slovakia (2)	Some concerns N=80 12 weeks	At least 1 mod-severe VVA symptom (dyspareunia, vulvovaginal irritation/itching, dysuria, vaginal dryness) FSH>40; pH≥5; VHI≤15 Excluded: vulvovaginal lichen; embolic disorders; h/o malignant tumors; hypersensitivity to intervention; sexually inactive	Hyaluronic acid (vaginal; gel; 0.2% hyaluronic acid in 4g; every 3 days) N=46 56.7 (6.1) NR	Placebo (vaginal; gel; N/A; every 3 days) N=34 60.1 (8.3) NR	Proportion of subjects having a reduction ≥1 point in the VRS dryness Score from baseline to 3 months Dryness (VRS) Dyspareunia (FSFI pain) Sexual function (FSDS-R) Treatment satisfaction (4-point scale)

Abbreviations: CVA=cerebrovascular accident; DM=diabetes mellitus; FSDS-R=Female Sexual Distress Scale-Revised; FSH=follicle-stimulating hormone; FSFI=Female Sexual Function Index; g=gram; h/o=history of; HTN=hypertension; MI=myocardial infarction; RoB=risk of bias; SD=standard deviation; TIA=transient ischemic attack; VAS=visual analog scale; VHI=vaginal health index; VMI=vaginal maturation index; VRS=verbal rating scale; VTE=venous thromboembolism; VVA=vulvovaginal atrophy; wk=week

*Multi-arm trial, only polyacrylic and placebo arms from Fernandes (2014)²⁹ described here. See Table C.4 for estrogen arm and Table C.5 for testosterone arm.

†Multi-arm trial, only moisturizer and placebo arms from Mitchell (2018)⁶² described here. See Table C.4 for estrogen arm.

Table C.7. Characteristics of included trials of energy-based interventions rated low or some concerns ROB

Intervention Vs. Comparator	Author, Year Trial ID # of Publications Funding Location (# of Sites)	RoB Total N Length of Follow-Up	Major Inclusion/Exclusion Criteria	Intervention(s) (# of Applications; Frequency; Site) N Age (Years) Race (n, %)	Comparator(s) (# of Applications; Frequency; Site) N Age (Years) Race (n, %)	Primary Outcome
CO₂ Laser vs. Sham Laser	Page, 2022 ⁶⁶ NCT04021966 1 publication None Belgium (1)	Low N=60 3 months*	Mod-severe dryness, itching, burning dyspareunia, dysuria (MBS score (score ≥2 on 0-3 scale) verified by study team Excluded: previous vaginal laser therapy	Fractional microablative CO₂ laser (3; every 4 wks; vagina) N=30 57.4 (7.1) NR	Sham laser (3; every 4 wks; vagina) N=30 56.2 (6.3) NR	Change in MBS severity

Intervention Vs. Comparator	Author, Year Trial ID # of Publications Funding Location (# of Sites)	RoB Total N Length of Follow-Up	Major Inclusion/Exclusion Criteria	Intervention(s) (# of Applications; Frequency; Site) N Age (Years) Race (n, %)	Comparator(s) (# of Applications; Frequency; Site) N Age (Years) Race (n, %)	Primary Outcome
	Li, 2021 ⁵⁸ ACTRN1261600-1403426 1 publication NR Australia (1)	Low N=85 12 months	Age ≥18 years; amenorrheic ≥12 mo; at least 1 symptom (dyspareunia, burning, itching, dryness) severe enough to present for further treatment; no vaginal estrogen for ≥6 mo before inclusion Included women s/p hysterectomy Excluded: prior vaginal energy-based treatment	Fractional microablative CO₂ laser (3; every 4-8 wks; vagina) N=43 55 (7) White (98%)	Sham laser (3; every 4-8 wks; vagina) N=42 58 (8) White (95%)	Change in symptom severity assessed with VAS and VSQ
	Salvatore, 2021 ⁸⁰ NCT03754205 1 publication None Greece (1), Italy (1)	Some concerns N=60 4 months	Clinically diagnosed GSM; dyspareunia and dryness were 3 MBSs Excluded: vulvodynia, vulvovaginitis, vulvovaginal pathology; dryness or dyspareunia for reasons other than GSM; prior vaginal energy-based treatment; use of non-hormonal (3 mo) or hormonal (6 mo) therapies prior to screening; history of gynecological or breast cancer	Fractional microablative CO₂ laser (3; every 1 mo; Vaginal canal, introitus, and labial minora) N=30 57.0 (6.8) NR	Sham laser (3; every 1 mo; Vaginal canal, introitus, and labial minora) N=30 58.4 (6.0) NR	Changes in dryness and dyspareunia intensity
	Ruanphoo, 2020 ⁷⁹ TCTR2016062-7002 1 publication None Thailand (1)	Some concerns N=88 3 months	Age >50 years; last menstruation ≥12 mo ago; any mod-severe vaginal atrophy symptom Excluded: hormonal therapy in past 6 mo; moisturizer or lubricant use in past 30 days; genital hiatus diameter <2 cm	Fractional microablative CO₂ laser (3; every 4 wks; vagina) N=44 61.7 (8.0) NR	Sham laser (3; every 4 wks; vagina) N=44 59.8 (7.5) NR	VHI score

Intervention Vs. Comparator	Author, Year Trial ID # of Publications Funding Location (# of Sites)	RoB Total N Length of Follow-Up	Major Inclusion/Exclusion Criteria	Intervention(s) (# of Applications; Frequency; Site) N Age (Years) Race (n, %)	Comparator(s) (# of Applications; Frequency; Site) N Age (Years) Race (n, %)	Primary Outcome
CO₂ Laser vs. Vaginal Congugated Estrogen Cream	Eftekhari, 2020 ²⁶ IRCT20160916-029835N3 1 publication NR Iran (1)	Low N=50 6 months	Age 45-65 years; sexually active; symptoms of VVA (dryness, irritation, soreness, or dyspareunia) Excluded: smoker; use of topical or hormone replacement therapy (past 6 mo) or vaginal lubricant (past 30 days); psychiatric disorders; undiagnosed vaginal bleeding; hormonal imbalance; serious disease or chronic condition that could interfere with study compliance	CO₂ laser (3; every 1 mo; vagina) N=25 57.0 (6.4) NR	Congugated estrogens (vaginal; cream; 0.625 mg; 3x/week for 3 mo) N=25 54.6 (8.2) NR	Change in FSFI
	Paraiso, 2020 ⁷¹ NCT02691936 1 publication Foundation US (6)	Low N=69 6 months	Bothersome vaginal dryness (≥ 7 on 10 cm scale); last menstruation ≥ 12 mo ago Excluded: contraindication to vaginal estrogen; history of gynecological cancer (including vaginal and cervical) or pelvic or vaginal radiation; h/o thrombophlebitis, heart failure or MI in past 12 mo; pelvic surgery in past 6 mo; vaginal estrogen (any form) in past month; moisturizers, lubricants, or homeopathic preparations in past 2 weeks; any chronic condition that could interfere with compliance	Fractional microablative CO₂ laser (3; every 6 wks; vagina, introitus, vestibule) N=34 61.0 (8.0) White (91%); Black (3%); Hispanic (1%); Asian (6%)	Conjugated estrogens (vaginal; cream; 0.5 g; 1x/day for 2 wks, then 2x/wk) N=35 60.0 (7.0) White (94%); Black (3%); Hispanic (3%); Asian (0%)	Subjective improvement of vaginal dryness

Intervention Vs. Comparator	Author, Year Trial ID # of Publications Funding Location (# of Sites)	RoB Total N Length of Follow-Up	Major Inclusion/Exclusion Criteria	Intervention(s) (# of Applications; Frequency; Site) N Age (Years) Race (n, %)	Comparator(s) (# of Applications; Frequency; Site) N Age (Years) Race (n, %)	Primary Outcome
CO₂ Laser vs. CO₂ Laser + Hyaluronic Acid Gel	Alvisi, 2022 ⁹¹ NR 1 publication None Italy (1)	Moderate (ROBINS-I) N=50 3 months	VVA; VHI <15; last menstruation ≥12 mo ago; recent negative cervical smear test Excluded: previous use of energy-based devices; hormonal therapy (systemic or local) or ospemifene in past 6 mo; contraindication to estrogen therapies; vaginal bleeding of unknown origin	Non-ablative CO₂ laser (3; every 4-6 wks; Vaginal, vulvar) N=25 60.6 (8.5) NR	Non-ablative CO₂ laser (3; every 4-6 wks; Vaginal, vulvar) + Hyaluronic Acid (vaginal; gel; 0.2%; 1x/day for 21 days, then 3x/wk) N=25 57.2 (8.5) NR	Vaginal and vulvar health (VHI and VuHI)
CO₂ Laser vs. Radiofrequency, Placebo	Eftekhari, 2021 ²⁷ IRCT201907080-44143N1 1 publication Academia Iran (1)	Some concerns N=246 3 months	History of UI; sexually active, sexual problems due to VVA; last menstruation ≥12 months ago; presence of VVA symptoms; sexual dysfunction Excluded: hematuria; pregnancy; childbirth in past year; abnormal vaginal bleeding, damage to vaginal tissue; history of damage to spinal nerves; radial hysterectomy with neuropathy; epilepsy; autoimmune disease, >50g urine leakage per hour	Fractional CO₂ laser Physio Vag Device (3; every 4 wks; NR) N=82 56.3 (7.2) NR	Radiofrequency Physio Vag Device (3; every 4-6 wks; Intravaginal and extravaginal) N=82 57.7 (7.3) NR Placebo (not specified) N=82 54.8 (11.5) NR	Not identified
Er:YAG Laser vs Sham	Chiengthong, 2023 CTR20181218002 1 publication ¹⁵ Foundation Thailand (1)	Some concerns N=50 3 months	Parous; diagnosed with OAB and with ≥1 vaginal atrophy symptom; no previous hormonal or other medical treatment Excluded: stress or mixed urinary incontinence; previous OAB treatment; history of interstitial cystitis; postvoid residual urine >200mL; previous pelvic radiation or malignant disease	Er:YAG laser MCL31 Dermablade; Asclepion Laser Technologies (1 application; once; Vagina, introitus) N=25 64.2 (6.8) NR	Sham laser (1 application; once; Vagina, introitus) N=25 65.6 (7.7) NR	Improvement in OAB symptoms

Intervention Vs. Comparator	Author, Year Trial ID # of Publications Funding Location (# of Sites)	RoB Total N Length of Follow-Up	Major Inclusion/Exclusion Criteria	Intervention(s) (# of Applications; Frequency; Site) N Age (Years) Race (n, %)	Comparator(s) (# of Applications; Frequency; Site) N Age (Years) Race (n, %)	Primary Outcome
Er:YAG Laser vs. Er:YAG Laser (hyperstack)	Fidecicchi, 2023 ³³ NR 1 publication None Italy (1)	Some concerns N=68 6 months	History of treated breast cancer; superficial dyspareunia; sexually active; hormonal profile diagnostic for menopause (FSH >40U/L; estradiol <25pg/mL); negative Pap smear Excluded: scars, lesions, or infection of GU tract (active or past 30 days); use of lubricants, local preparations, hormones, or other treatments for menopausal symptoms in past 3 mo; abnormal uterine bleeding; use of photosensitizing drugs or history of photosensitivity disorders; condition that could interfere with protocol	Er:YAG laser (2; every 1 mo; Vagina) N=22 54 (48–58) NR	Hyaluronic acid (vaginal; suppositories; dose NR; 1x/day for 10 days, then 3x/wk) N=21 56 (49–58) NR	Superficial dyspareunia
Er:YAG Laser vs. Hyaluronic Acid Suppositories	Gold, 2023 ³⁷ NCT03816735 1 publication Industry Austria (1)	Some concerns N=43 3 months	History of breast cancer; completed locoregional therapy; reported at least 1 of: dryness, burning or irritation, lack of lubrication during sexual intercourse/sexual discomfort or pain, symptoms of urgency and dysuria, recurrent UTI Excluded: current or past genitourinary malignancy; abnormal Pap smear; abnormal uterine bleeding; use of photosensitive medication	Er:YAG laser VEL Renovalase (3; every 30 days; Vagina, vestibule, introitus) N=34 59.1 (6.5) NR	Er:YAG with hyperstack VEL Renovalase (3; every 30 days; Vagina, vestibule, introitus) N=34 59.5 (7.6) NR	VHI at 3 months

Abbreviations: cm=centimeter; CO₂=carbon dioxide; Er-YAG=Erbium-doped yttrium aluminum garnet laser; FSFI=Female Sexual Function Index; FSH=follicle stimulating hormone; GU=genitourinary; GSM=genitourinary syndrome of menopause; h/o=history of; MBS=most bothersome symptom; MI=myocardial infarction; mL=milliliter; mo=month; NR=not reported; OAB=overactive bladder; ROB=risk of bias; s/p=status post; UI=urinary infection; UTI=urinary tract infection; VAS=Visual Analogue Scale; VEL=vaginal erbium laser; VHI=Vaginal Health Index; VuHI=vulvovaginal health index; VSQ=Vulvovaginal Symptom Questionnaire; VVA=vulvovaginal atrophy; wk=week

*18 months cross-over trial; primary outcome assessed at 3 months after 3rd session of laser or sham

Characteristics of Included Studies Rated High ROB

Table C.8. Characteristics of included trials of estrogen hormonal interventions rated high ROB

Author, Year PMID Country (Sites) Funding	Population	Intervention Sample Size Dose, Timing, Duration Route	Comparison 1 Sample Size Dose, Timing, Duration Route	Comparison 2 Sample Size Dose, Timing, Duration Route	Outcomes Reported	Measures Used
Palacios, 2022 ⁶⁷ 34813408 Spain (1) Novo Nordisk Health Care AG; Instituto Palacios, Madrid, Spain	Postmenopausal women with at least one moderate-to- severe VVA symptom	Estradiol N=60 10 mcg 12 weeks Vaginal tablet	Promestriene N=60 10 mg/g, 12 weeks Vaginal cream	N/A	Genital or vulvovaginal signs, safety outcomes, treatment satisfaction	Gynecological/pelvic/vaginal examination, study-specific or author written checklist or questionnaire, VHI, VMI
Kroll, 2018 ⁴⁹ 28926514 NR (Multicenter; total # NR) Allergan	Postmenopausal women with VVA who reported their most bothersome symptom as dyspareunia	Estradiol N=277 15mg estradiol; 0.5 g cream, 12 weeks Vaginal cream	Placebo N=273 0.5 g cream, 12 weeks Vaginal cream	N/A	Dysuria, genital or vulvovaginal signs, vulvovaginal symptoms, sexual symptoms, dyspareunia	Gynecological/pelvic/vaginal examination, MBS, study- specific or author written checklist or questionnaire
Jiang, 2016 ⁴² 26757270 China (Multicenter; total # NR) Astellas Pharma Inc.	Postmenopausal women with overactive bladder	Promestriene + solifenacin succinate N=52 5 mg, 12 weeks Vaginal capsule	Solifenacin succinate N=52 5 mg, 12 weeks Vaginal tablet	N/A	Urinary symptoms (urinary frequency, urinary urgency, nocturia, dysuria, urinary urge incontinence, overactive bladder) Safety outcomes [breast cancer, breast cancer recurrence or progression, breast tenderness, cardiovascular risk]	International Prostate Symptom Score, OABSS, study-specific or author written checklist or questionnaire, symptom diary
Seyyedi, 2016 ⁸² 28070251 Iran (1) Shahrekord University of Medical Sciences (project no. 1440)	Married postmenopausal women 50-65 years old	Conjugated estrogen cream N=30 0.625 mg, 3 months Vaginal cream	Royal jelly N=30 15%, 3 months Vaginal cream	Placebo N=30 NR, 3 months Vaginal cream	Quality of life	Gynecological/pelvic/vaginal examination, MENQoL

Author, Year PMID Country (Sites) Funding	Population	Intervention Sample Size Dose, Timing, Duration Route	Comparison 1 Sample Size Dose, Timing, Duration Route	Comparison 2 Sample Size Dose, Timing, Duration Route	Outcomes Reported	Measures Used
Seyyedi, 2016 ⁸³ 27437306 Iran (1) NR	Married postmenopausal women aged 50- 65 referred to a Women's Clinic	Conjugated estrogen cream N=30 0.625 mg, 3 months Vaginal cream	Royal jelly N=30 15%, 3 months Vaginal cream	Placebo N=30 NR, 3 months Vaginal cream	Urinary symptoms, genital or vulvovaginal signs, sexual symptoms, quality of life	MENQoL, study-specific or author written checklist or questionnaire, VMI
Jokar, 2016 ⁴³ 26793732 Iran (1) Deputy of Research and Technology, Shiraz University of Medical Sciences (grant no. 6681)	Postmenopausal women with moderate-to- severe vulvovaginal dryness	Estrogen N=28 0.058 mg/day, 0.625 mg total, 8 weeks Vaginal cream	Hyaluronic acid N=28 5 mg/day, 8 weeks Vaginal cream	N/A	Urinary symptoms, genital or vulvovaginal signs	VAS
Simon, 2008 ⁸⁶ 18978105 US, Canada (49) Novo Nordisk	Non- hysterectomized, postmenopausal women with ≥3 urogenital symptoms	Estradiol N=205 10 mcg, 12 weeks Vaginal tablet	Placebo N=104 NR, 12 weeks Vaginal tablet	N/A	Dysuria, genital or vulvovaginal signs, vulvovaginal symptoms, vulvovaginal dryness/lubrication, dyspareunia, safety outcomes, adverse events	Endometrial biopsy, gynecological/pelvic/vaginal examination, MBS, study- specific or author written checklist or questionnaire, VMI
Bachmann, 2008 ¹¹ 18165394 US (8) Novo Nordisk	Postmenopausal women with moderate-to- severe vaginal dryness and soreness	Estradiol N=92 10 mcg, 12-week study with 52-week extension Vaginal tablet	Placebo N=47 NR, 12-week study with 52- week extension Vaginal tablet	N/A	Safety outcomes, adverse events	Endometrial biopsy, study- specific or author written checklist or questionnaire

Author, Year PMID Country (Sites) Funding	Population	Intervention Sample Size Dose, Timing, Duration Route	Comparison 1 Sample Size Dose, Timing, Duration Route	Comparison 2 Sample Size Dose, Timing, Duration Route	Outcomes Reported	Measures Used
Chompootawee, 1998 ¹⁶ 9728901 Thailand (NR) Rhatchada-Pisakesompoj Fund, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand	Postmenopausal women with urogenital symptoms	Estrogen N=20 250 mcg levonorgestrel + 30 mg estradiol, 8 weeks Vaginal tablet	Estrogen N=20 0.625 mg, 8 weeks Vaginal cream	N/A	Urinary symptoms, dysuria, vulvovaginal symptoms, vulvovaginal dryness/lubrication, dyspareunia, adverse events	Symptom diary
Antoniou, 1997 ³ 9089559 Greece (1) NR	Postmenopausal women with atrophic vaginitis	17 β -estradiol + progesterone N=28 2 mg (ring) & 100 mg (suppository), 52 weeks Vaginal ring (estrogen), vaginal suppository (progesterone)	Estrogen + levonogestrel N=28 50 mcg/day changed 2x/week (patch) & 20 mcg/day (IUD), 52 weeks Transdermal patch (estrogen), IUD (levonogestrel)	N/A	Safety outcomes, adverse events, treatment satisfaction	Endometrial biopsy, gynecological/pelvic/vaginal examination, symptom diary
Kalogirou, 1996 ⁴⁵ 9010746 Greece (1) NR	Postmenopausal women with symptoms and signs of atrophic vaginitis	17 β -estradiol + medroxyprogesterone acetate N=28 2 mg, 12 months Vaginal ring	Estradiol N=28 50 mcg/day (52 mg total), 12 months Transdermal & vaginal	N/A	Genital or vulvovaginal signs, safety outcomes, treatment satisfaction, gynecological/pelvic/vaginal examination	Study-specific or author written checklist or questionnaire, transvaginal ultrasound, VMI

Author, Year PMID Country (Sites) Funding	Population	Intervention Sample Size Dose, Timing, Duration Route	Comparison 1 Sample Size Dose, Timing, Duration Route	Comparison 2 Sample Size Dose, Timing, Duration Route	Outcomes Reported	Measures Used
Bachmann, 1997 ¹² 99103166611010464 6 NR (10) Pharmacia Inc.	Postmenopausal women with vaginal dryness and ≥1 symptom of atrophic vaginitis	Vaginal Estradiol Ring N=129 NR, 15 weeks Vaginal ring	Vaginal Conjugated Estrogen Cream N=67 2 g administered 3x/week, 15 weeks Vaginal cream	N/A	Genital or vulvovaginal signs, safety outcomes, adverse events, treatment satisfaction	Endometrial biopsy, gynecological/pelvic/vaginal examination

Abbreviations: g=grams; IUD=Intrauterine Device; MBS=most bothersome symptom; mcg=micrograms; MENQoL=Menopause-Specific Quality of Life; mg=milligrams; N/A=not applicable; NR=not reported; OABSS=Overactive Bladder Symptom Score; PMID=PubMed Identification; VAS=Visual Analogue Scale; VHI=Vaginal Health Index; VMI=Vaginal Maturation Index; VVA=vulvovaginal atrophy

Table C.9. Characteristics of included trials of non-estrogen hormonal interventions rated high ROB

Author, Year PMID Country (Sites) Funding	Population	Intervention Sample Size Dose, Timing, Duration Route	Comparison Sample Size Dose, Timing, Duration Route	Outcomes Reported	Measures Used
Dow, 1983 ²⁵ 6682336 UK (NR) NR	Women presenting with vasomotor symptoms and a range of other somatic and psychological symptoms	Estradiol n=20 6 months Implant (route unclear)	Estradiol + Testosterone n=20 6 months Implant (route unclear)	Sexual symptoms (including dyspareunia), psychological symptoms, treatment satisfaction	Study-specific or author written checklist or questionnaire

Abbreviations: NR=not reported; PMID=PubMed Identification; UK=United Kingdom

Table C.10. Characteristics of included trials of non-hormonal interventions rated high ROB

Author, Year PMID Country (Sites) Funding	Population	Intervention Sample Size Dose, Timing, Duration Route	Comparison Sample Size Dose, Timing, Duration Route	Outcomes Reported	Measures Used
De Seta, 2021 ²² 33832645 India (1) Industry	Postmenopausal women with VVA. Additional sample selection criteria not reported.	5 mL vaginal gel (with sea buckthorn, aloe vera, hyaluronic acid 1, glycogen) n=30 90 days (12 weeks total): daily for 14 days, then 2-week wash-out, then 2x/week at bedtime for 8 more weeks Vaginal	5 mL placebo gel n=30 90 days (12 weeks total): daily for 14 days, then 2-week wash-out, then 2x/week at bedtime for 8 more weeks Vaginal	Vulvovaginal symptoms, vulvovaginal dryness/lubrication, sexual symptoms, dyspareunia, adverse events, treatment satisfaction	FSFI, VAS, VHI, symptom diary, study-specific or author written checklist or questionnaire
Kim, 2017 ⁴⁷ 28383379 Republic of Korea (1) University grant	Women aged ≥20 who had primary breast cancer before menopause, had received adjuvant chemotherapy, and were sexually active with symptoms of dyspareunia.	3 mL pH-balanced vaginal gel (with lactate) n=69 3x/week at bedtime for 8 weeks Vaginal	3 mL placebo gel (without lactate) n=67 3x/week at bedtime for 8 weeks Vaginal	Sexual symptoms, dyspareunia, adverse events,	FSFI

Abbreviations: FSFI=Female Sexual Function Index; mL=milliliters; VAS=Visual Analogue Scale; VHI=Vaginal Health Index; VVA=vulvovaginal atrophy

Table C.11. Characteristics of included trials of energy-based interventions rated high or critical ROB

Author, Year Study Design Country (Sites) Funding	Population	Intervention Sample Size Dose, Timing, Duration Route	Comparison Sample Size Dose, Timing, Duration Route	Outcomes Reported	Measures Used
Aguiar, 2020 ² RCT Brazil (1) None	Postmenopausal women aged 50 years or older with complaints of dryness or urinary symptoms	CO ₂ laser n=24 3 sessions at 30-day intervals, 14 weeks Vaginal	Vaginal promestriene cream n=24 10 mg, 3 times weekly, 12 weeks Vaginal Lubricant 24 NR, with sexual activity, 12 weeks Vaginal	Urinary symptoms, adverse events	ICIQ-SF, ICIQ-OAB, count (percentage) reporting an adverse event

Author, Year Study Design Country (Sites) Funding	Population	Intervention Sample Size Dose, Timing, Duration Route	Comparison Sample Size Dose, Timing, Duration Route	Outcomes Reported	Measures Used
Behnia-Willison, 2017 ⁹² Observational Australia (NR) None	Women with GSM symptoms not responding to or not able to take conventional treatments such as estrogen therapy	CO ₂ laser n=102 3 sessions at 6 or more week intervals, 12 to 24 months after initial treatment Vagina, vestibule, fourchette	N/A	Serious adverse events	Count (percentage) reporting an adverse event
Eder, 2019 ⁹³ Observational USA (1) Lumenis Ltd.	Postmenopausal women with VVA-related symptoms	CO ₂ laser n=32 3 sessions at 4 week intervals, 18 months following last treatment; 2 received additional laser tx at 12 months and 13 at 15 months Vaginal	N/A	Serious adverse events	Count
Fernandes, 2023 ³¹ RCT Brazil (1) None	Breast cancer survivors with moderate-to-severe GSM symptoms; currently receiving adjuvant endocrine therapy	CO ₂ laser n=32 3 sessions at 1-month intervals 4 months Vaginal and vulvar	Radiofrequency n=32 3 sessions at 1-month intervals Vaginal and vulvar Promestriene n=30 10 mg/day for 21 days then twice per week until 4 months of treatment Vaginal	GSM symptoms, impression of improvement, complications	VAS, Likert scale, clinical evaluation
Gambacciani, 2017 ⁹⁴ Observational Italy (1) None	Breast cancer survivors with GSM	Er:YAG lasers n=43 3 sessions at 30 day intervals, 18 months Vagina, vestibule, introitus	N/A	Serious adverse events	Count (percentage) reporting an adverse event
Gambacciani, 2018 ⁹⁵ Observational Italy (1) None	Postmenopausal women with GSM	Er:YAG lasers n=230 3 sessions at 30 day intervals, 24 months Vagina, vestibule, introitus	N/A	Serious adverse events	Count (percentage) reporting an adverse event

Author, Year Study Design Country (Sites) Funding	Population	Intervention Sample Size Dose, Timing, Duration Route	Comparison Sample Size Dose, Timing, Duration Route	Outcomes Reported	Measures Used
Gaspar, 2017 ⁹⁶ Observational Argentina (1) None	Postmenopausal patients with one or more symptoms of GSM	Er:YAG lasers n=25 3 sessions at 3 week intervals, 18 months Vagina, vestibule, introitus	NA	Serious adverse events	Count (percentage) reporting an adverse event
Hickey, 2023 ⁴⁰ RCT Australia (5) Madorra, Inc.,	Age 22 to 70 years, self-reported mild–moderate–severe vaginal dryness and clinician assessed VVA	Ultrasound n=21 Applied at home 8 min/day for 12 weeks Open label study from 12 weeks to 1 year Introitus	Sham ultrasound n=21 Applied at home 8 min/day for 12 weeks Open label study from 12 weeks to 1 year Introitus	GSM symptoms, vaginal health, quality of life, urinary distress, adverse events	VAS, VHI, DIVA, EQ-5D-5L, clinician interview
Li, 2021 ⁹⁷ Observational China (8) Chinese Association of Plastics and Aesthetic	Postmenopausal with GSM-related symptoms; were not satisfied with previous local estrogen treatment, or had breast cancer treatment accompanied by GSM	CO ₂ laser n=108 3 sessions at 3 to 5 week intervals, 12 months Vaginal	NA	Serious adverse events	Count (percentage) reporting an adverse event
Lin, 2022 ⁹⁸ Observational Taiwan (1) Department of Medical Research, Kaohsiung Medical University Hospital	Postmenopausal patients with GSM	Er:YAG lasers n=64 3 sessions at 4 week intervals, 12 months Vulvovaginal	NA	Serious adverse events	Count (percentage) reporting an adverse event
Mension, 2023 ⁶⁰ RCT Spain Instituto de Salud Carlos III the European Union (equipment and materials provided by manufacturers)	Breast cancer survivors aged 30 years and older; receiving aromatase inhibitors, menopausal, signs or symptoms of GSM with dyspareunia	CO ₂ laser n=42 5 sessions 1 month apart Both groups received first-line therapy (nonhormonal moisturizers and a vaginal vibrator stimulation)	Sham laser n=42 5 sessions 1 month apart	Sexual function, dyspareunia, vaginal health, quality of life, adverse events	FSFI, VAS, VHI, Short-form 12, Common Terminology Criteria for Adverse Event scale.

Author, Year Study Design Country (Sites) Funding	Population	Intervention Sample Size Dose, Timing, Duration Route	Comparison Sample Size Dose, Timing, Duration Route	Outcomes Reported	Measures Used
Okui, 2023⁹⁹ Case-control Japan (1) Not reported	Breast cancer survivors with GSM	Er:YAG+Nd:YAG n=137 3 sessions at 30 day intervals Vagina and posterior labial commissure Follow-up at 1, 3, 6, 12, and 24 months	Er:YAG n=119 3 sessions at 30 day intervals Vagina	Sexual function, vaginal health, adverse events	FSFI, VHI score, self-report
Panyawongudom, 2023⁷⁰ RCT Thailand (1) Ratchadapisek Sompoch Endowment Fund and Chulalongkorn University Fund.	Postmenopausal women with vaginal atrophy symptoms	Er:YAG laser n=22 2 sessions every 4 weeks	Sham laser n=22 2 sessions every 4 weeks	Vaginal atrophy symptoms, vaginal atrophy, adverse events	VAS, vaginal atrophy score (not specified), self-report
Politano, 2019⁷⁵ RCT Brazil (1) None	Postmenopausal women age 50 to 70 years with vaginal symptoms	CO ₂ laser n=24 3 sessions at 30-day intervals, 14 weeks Vaginal	Vaginal promestriene cream n=24 10 mg, 3 times weekly, 12 weeks Vaginal Lubricant 24 NR, with sexual activity, 12 weeks Vaginal	Genital signs, vulvovaginal dryness/lubrication, sexual symptoms, dyspareunia, adverse events	FSFI, VHI
Quick, 2022¹⁰¹ Observational US (1) OSU FAME PRO (AQ) and by the OSU Spielman Development Funds (ML)	Non-metastatic breast cancer patients with GSM symptoms (had completed surgery, chemotherapy, and/or radiation for their breast cancer)	CO ₂ laser n=67 3 sessions at 30-45 day intervals, 2 years Vaginal (apex to introitus); vestibule and posterior fourchette	NA	Serious adverse events	Count (percentage) reporting an adverse event

Author, Year Study Design Country (Sites) Funding	Population	Intervention Sample Size Dose, Timing, Duration Route	Comparison Sample Size Dose, Timing, Duration Route	Outcomes Reported	Measures Used
Quick, 2021 ¹⁰⁰ Observational US (1) OSU FAME PRO (A.Q.) and by the OSU Spielman Development Funds (M.B.L.)	Breast cancer survivors with dyspareunia and/or vaginal dryness	CO ₂ laser n=67 3 sessions at 30-45 days intervals, 12 month Vaginal (full length) and vulvar	NA	Serious adverse events	Count (percentage) reporting an adverse event
Samuels, 2019 ¹¹³ Observational US (2) Syneron Medical Ltd.	Postmenopausal women with VVA symptoms	CO ₂ laser n=43 3 sessions at 1 month intervals, 12 months Extravaginally and internally	NA	Serious adverse events	Count (percentage) reporting an adverse event
Sarmiento, 2023 ⁸¹ RCT Brazil (1) None	Postmenopausal, 55 to 65 years old, sexually active, vulvovaginal atrophy (VHI<15)	Micro-ablative Fractional Radiofrequency n=45 3 sessions at 30-day intervals Vagina/vaginal introitus	Estradiol vaginal cream n=44 1 gm of Estradiol 3-propyl 17β-methyl diether-based cream, 2 times per week for 3 months Vaginal Physician visits n=43 Number of visits NR; Received clarification about GSM and managing symptoms	Sexual function, vaginal health, adverse events	FSFI, VHI, questionnaire developed for this study protocol
Silquini, 2021 ¹⁰⁴ Observational Italy (1) None	Postmenopausal women with GSM (including breast cancer survivors and no history of breast cancer)	CO ₂ laser n=135 3 sessions at 30 day intervals, 12 months after last laser application Vaginal walls, vaginal introitus, and vulvar zone	NA	Serious adverse events	Count
Silquini, 2017 ¹⁰³ Observational Italy (1) None	Menopausal women, symptoms of VVA	CO ₂ laser n=91 3 sessions at 4 week intervals, 15 months Vaginal, introitus, and vulvar	NA	Serious adverse events	Count (percentage) reporting an adverse event

Author, Year Study Design Country (Sites) Funding	Population	Intervention Sample Size Dose, Timing, Duration Route	Comparison Sample Size Dose, Timing, Duration Route	Outcomes Reported	Measures Used
Sokol, 2017 ^{105, 114} Observational US (2) DEKA M.E.L.A. Srl	Postmenopausal women with bothersome symptoms of VVA	CO ₂ laser n=30 3 sessions at 6 week intervals (+/-1 week), 2 months post-tx ¹¹⁴ and 12 months ¹⁰⁵ vaginal	NA	Serious adverse events	Count
Veron, 2021 ¹⁰⁶ Observational France (1) None	Women with history of breast cancer and VVA	CO ₂ laser n=46 3 sessions at 1 month intervals, 18 months after last laser session Vaginal	NA	Serious adverse events	Count
Vicariotto, 2017 ¹⁰⁷ Observational Italy (NR) None	Post-menopausal vaginal dryness and other VVA/GSM-related symptoms	Radiofrequency N=32 4-6 sessions at 12-16 day intervals, 12 months Vaginal	NA	Serious adverse events	Count (percentage) reporting an adverse event

Abbreviations: CO₂=carbon dioxide; DIVA=Day-to-Day Impact of Vaginal Aging; EQ-5D-5L=EuroQol scale; Er-YAG=Erbium-doped yttrium aluminum garnet laser; GSM=Genitourinary Syndrome of Menopause; ICIQ-OAB=International Consultation on Incontinence Questionnaire-Overactive Bladder; ICIQ-SF=International Consultation on Incontinence Questionnaire-Short Form; mg=milligrams; N/A=not applicable; NR=not reported; RCT=randomized control trial; US=United States; VAS=Visual Analog Scale; VHI=Vaginal Health Index; VVA=vulvovaginal atrophy

Detailed Results

Table C.12. Detailed effectiveness results for studies of estrogen hormonal interventions rated low or some concerns ROB

Outcome	Author, Year Trial ID	Follow-Up Measurement Tool/Definition Scoring Range Reported Result	Arm 1 Results	Arm 2 Results	Arm 3 Results	Comparator Arm Results
Vulvovaginal dryness/lubrication	Archer, 2018 ⁵ NR	12 weeks MBS 0 (none) to 3 (severe) Mean (SD), p-value	Estradiol N=248 Mean difference: -1.4 (0.9) p=0.13	N/A	N/A	Placebo cream N=240 Mean difference: -1.2 (0.9) p-value NR

Outcome	Author, Year Trial ID	Follow-Up Measurement Tool/Definition Scoring Range Reported Result	Arm 1 Results	Arm 2 Results	Arm 3 Results	Comparator Arm Results
	Constantine, 2017 ¹⁸ NCT02253173	12 weeks MBS 0 (none) to 3 (severe) LSM, p-value	Estradiol 4 µg N=186 Mean difference: -1.3 p <0.01	Estradiol 10 µg N=188 Mean difference: -1.5 p <0.0001	N/A	Placebo vaginal capsule N=187 Mean difference: -1.0 p-value NR
	Kingsberg, 2016 ⁴⁸ NCT02253173	12 weeks FSFI lubrication domain 0 (worst) to 6 (best) Mean score (SD) at baseline and follow-up, significance	Estradiol 4 µg N=186 Baseline: 2.1 (1.2) Week 12: 3.9 (1.8) Non-significant difference vs placebo	Estradiol 10 µg N=188 Baseline: 2.2 (1.2) Week 12: 4.4 (1.6) Significant difference vs placebo	N/A	Placebo vaginal capsule N=187 Baseline: 2.0 (1.3) Week 12: 3.6 (1.8)
	Fernandes, 2014 ²⁹ U1111-11255434	12 weeks FSFI Lubrication domain 0 (worst) to 6 (best) Mean (SD), p- value	Conjugated estrogen cream N=18 Baseline: 1.5 (2) Follow-up: 2.8 (2.9) Intergroup differences p=0.513; intragroup differences p=0.04	N/A	N/A	Placebo N=20 Baseline: 1.9 (1.6) Follow-up: 2.88 (2.2) Intragroup differences p=0.011
	Mitchell, 2018 ⁶² NCT02516202	12 weeks FSFI Lubrication domain (0 (worst) to 6 (best)); dryness severity scale (0 (best) to 3 (worst)) Mean (95% CI), p-value	Vaginal estradiol + placebo gel N=72 Week 12 – baseline: 1.4 (1.1, 1.8) Estradiol vs. placebo difference: 0.2 (-0.3, 0.8), p=0.54	Vaginal moisturizer + placebo tablet N=86 Week 12 – baseline: 0.9 (0.6, 1.3) Moisturizer vs. placebo difference: - 0.2 (-0.8, 0.3), p=0.32	N/A	Placebo tablet & gel N=77 Week 12 – baseline: 1.2 (0.8, 1.6)

Outcome	Author, Year Trial ID	Follow-Up Measurement Tool/Definition Scoring Range Reported Result	Arm 1 Results	Arm 2 Results	Arm 3 Results	Comparator Arm Results
	Bachmann, 2009 ¹⁰ NR	12 weeks Daily diary (ie, 4- point scale) 0 (none) to 3 (severe) Mean change in score, p-value	Conjugated Estrogen Cream 21/7 N=143 Mean change: -1.1 P<0.05 vs placebo 21/7	Placebo 21/7 N=72 Mean change: -0.7	Conjugated Estrogen Cream 2x/wk N=140 Mean change: - 1.1 P>0.05 vs placebo 2x/wk	Placebo 2x/wk N=68 Mean change: -0.8
	Freedman, 2009 ³⁴ NCT00361569	12 weeks 4-point severity scale 0 (none) to 3 (severe) Proportion of participants reporting improvement of sx and resolution of mod-severe sx , p-value	Synthetic Conjugated Estrogens Cream N=150 <i>Improvement</i> 78.9%, P=0.0004 vs placebo <i>Resolution</i> 33.3%, P=0.001 vs placebo	N/A	N/A	Placebo N=155 <i>Improvement</i> 58.4% <i>Resolution</i> 16.0%
	Lima, 2013 ¹⁰⁹ 093/10	12 weeks 4-point scale 0 (none) to 3 (severe) Proportion (%) reporting none, mild, moderate, or severe symptoms at 12 weeks	Conjugated Estrogen Cream N=30 None: 65% Mild: 35% Moderate: 0% Severe: 0%	N/A	N/A	Placebo N=30 None: 20% Mild: 44% Moderate: 36% Severe: 0%

Outcome	Author, Year Trial ID	Follow-Up Measurement Tool/Definition Scoring Range Reported Result	Arm 1 Results	Arm 2 Results	Arm 3 Results	Comparator Arm Results
	Eriksen, 1999 ²⁸ NR	36 weeks Self reported severity, 0-3 (none, mild, moderate, or severe) Percentage of symptom-free changes for vaginal dryness between baseline and termination.	Vaginal Estradiol Ring N=53 81%, P=0.001 vs control	N/A	N/A	No-Treatment Control N=55 17%
	Ayton, 1996 ⁷ NR	12 weeks MBS 0 (none) to 3 (severe) Percentage	Vaginal Estradiol Ring N=131 Unable to extract from figure	N/A	N/A	Vaginal Conjugated Estrogen Cream N=63 Unable to extract from figure
	Nachtigall, 1995 ⁶³ NR	12 weeks Author-created questionnaire Narrative	Estradiol ring N=129 “In the summary for patient symptomatology improvement rates the equivalence criteria were satisfied for three symptoms, vaginal dryness, vaginal burning, and dyspareunia.”	N/A	N/A	Conjugated estrogens cream N=67 “In the summary for patient symptomatology improvement rates the equivalence criteria were satisfied for three symptoms, vaginal dryness, vaginal burning, and dyspareunia.”
Vulvovaginal discomfort/irritation	Constantine, 2017 ^{18, 84} NCT02253173	12 weeks MBS 0 (none) to 3 (severe) Mean difference	Estradiol 4 µg N=186 Mean difference: -0.8	Estradiol 10 µg N=188 Mean difference: -0.8	N/A	Placebo vaginal capsule N=187 Mean difference: -0.6

Outcome	Author, Year Trial ID	Follow-Up Measurement Tool/Definition Scoring Range Reported Result	Arm 1 Results	Arm 2 Results	Arm 3 Results	Comparator Arm Results
	Simon, 2019 ⁸⁴ NCT02253173	12 weeks VVA Symptom Self-Assessment Questionnaire 0 (none) to 3 (severe) Percentage of participants that improved by ≥ 2 levels, p-value	Estradiol 4 μg N=186 41.3%, p < 0.05	Estradiol 10 μg N=186 51.1%, p < 0.001	N/A	Placebo vaginal capsule N=186 30.9%
	Bachmann, 2009 ¹⁰ NR	12 weeks Daily diary (ie, 4- point scale) 0 (none) to 3 (severe) Mean change in score, p-value	Estrogen 21/7 N=143 Vaginal itching mean change: -0.2, P \leq 0.01 vs placebo 21/7 Vaginal burning mean change: -0.5, P>0.05 vs. placebo 21/7	Placebo 21/7 N=72 Vaginal itching mean change: -0.5, P \leq 0.01 vs CEC 21/7 Vaginal burning mean change: -0.4	Estrogen 2x/wk N=140 Vaginal itching mean change: - 0.3, P>0.05 vs. placebo 21/7 Vaginal burning mean change: - 0.4, P>0.05 vs. placebo 21/7	Placebo 2x/wk N=68 Vaginal itching mean change: -0.2 Vaginal burning mean change: -0.2
	Freedman, 2009 ³⁴ NCT00361569	12 weeks 4-point severity scale 0 (none) to 3 (severe) Proportion of participants reporting improvement of sx %, p-value	Estrogen N=150 <i>Improvement</i> 88.3%, P=0.026 vs placebo	N/A	N/A	Placebo N=155 <i>Improvement</i> 71.7%

Outcome	Author, Year Trial ID	Follow-Up Measurement Tool/Definition Scoring Range Reported Result	Arm 1 Results	Arm 2 Results	Arm 3 Results	Comparator Arm Results
	Eriksen, 1999 ²⁸ NR	36 weeks Self reported severity, 0-3 (none, mild, moderate, or severe) Percentage of symptom-free changes for pruritus vulvae between baseline and termination.	Vaginal Estradiol Ring N=53 80%, p-value NS vs control	N/A	N/A	No-Treatment Control N=55 53%
	Nachtigall, 1995 ⁶³ NR	12 weeks Author-created questionnaire Narrative	Estradiol ring N=129 “In the summary for patient symptomatology improvement rates the equivalence criteria were satisfied for three symptoms, vaginal dryness, vaginal burning, and dyspareunia.”	N/A	N/A	Conjugated estrogens cream N=67 “In the summary for patient symptomatology improvement rates the equivalence criteria were satisfied for three symptoms, vaginal dryness, vaginal burning, and dyspareunia.”
	Goetsch, 2023 ³⁶ NCT03240081	12 weeks VPAQ 0 (none) to 4 (severe) Median (IQR)	Estradiol 50 µg + 100 µg N=25 Baseline: 3.2 (1.0) Follow up: 1.8 (1.2) p < 0.001	N/A	N/A	N/A
Dysuria	Archer, 2018 ⁵ NR	12 weeks 4-point severity, 0-3 (none, mild, moderate, or severe) Mean (SD)	Estradiol N=248 Unable to extract from figure	N/A	N/A	Placebo cream N=240 Unable to extract from figure

Outcome	Author, Year Trial ID	Follow-Up Measurement Tool/Definition Scoring Range Reported Result	Arm 1 Results	Arm 2 Results	Arm 3 Results	Comparator Arm Results
	Eriksen, 1999 ²⁸ NR	36 weeks 4-point severity, 0-3 (none, mild, moderate, or severe) Percentage of symptom-free changes for dysuria between baseline and termination	Vaginal Estradiol Ring N=53 50%, p-value NS vs placebo	N/A	N/A	No-Treatment Control N=55 44%
	Ayton, 1996 ⁷ NR	12 weeks MBS 4-point severity, 0-3 (none, mild, moderate, or severe) Percentages	Vaginal Estradiol Ring N=131 Unable to extract from figure	N/A	N/A	Vaginal Conjugated Estrogen Cream N=63 Unable to extract from figure
Other urinary symptoms	Eriksen, 1999 ²⁸ NR	36 weeks 4-point severity, 0-3 (none, mild, moderate, or severe) Percentage of symptom-free changes for urge incontinence between baseline and termination, p-value	Vaginal Estradiol Ring N=53 50%, P=0.03 vs control	N/A	N/A	No-Treatment Control N=55 16%

Outcome	Author, Year Trial ID	Follow-Up Measurement Tool/Definition Scoring Range Reported Result	Arm 1 Results	Arm 2 Results	Arm 3 Results	Comparator Arm Results
		36 weeks 4-point severity, 0-3 (none, mild, moderate, or severe) N (%) of subjects who had a recurrent UTI Cumulative UTI- free proportion of subjects	Vaginal Estradiol Ring N=53 27 (51%) 45%, P=0.008 vs. control	N/A	N/A	No-Treatment Control N=55 44 (80%) 20%
	Tseng, 2008 ⁸⁸ NR	12 weeks IIQ-7 Add score range Mean (SD), p- value	Tolterodine N=40 Baseline: 10.2 (4.5), not significant Follow-up: 6.5 (2.7), p < 0.001	Tolterodine + conjugated estrogens N=40 Baseline: 9.4 (3.6), not significant Follow-up: 6.1 (2.5), p < 0.001	N/A	N/A
		12 weeks UDI-6 Add score range Mean (SD), p- value	Tolterodine N=40 Baseline: 9.5 (3.9), p=0.042 Follow-up: 7.2 (2.9), p < 0.001	Tolterodine + conjugated estrogens N=40 Baseline: 8.6 (3.8), p=0.042 Follow-up: 6.9 (2.7), p < 0.001	N/A	N/A
		12 weeks Urgency/24 hours Patient-reported from bladder diary Mean (SD), p- value	Tolterodine N=40 Baseline: 4.5 (0.8) Follow-up: 3.5 (0.5) p-value NS	Tolterodine + conjugated estrogens N=40 Baseline: 4.3 (0.7) Follow-up: 3.3 (0.6) p-value NS	N/A	N/A

Outcome	Author, Year Trial ID	Follow-Up Measurement Tool/Definition Scoring Range Reported Result	Arm 1 Results	Arm 2 Results	Arm 3 Results	Comparator Arm Results
		12 weeks Urge incontinence/24 hours Patient-reported from bladder diary Mean (SD), p- value	Tolterodine N=40 Baseline: 1.8 (0.7) Follow-up: 1.5 (0.5) p-value NS	Tolterodine + conjugated estrogens N=40 Baseline: 2.1 (1.1) Follow-up: 1.5 (0.5) p-value NS	N/A	N/A
	Goetsch, 2023 ³⁶ NCT03240081	12 weeks UDI-6 Add score range Median (IQR), p- value	Estradiol 50 µg + 100 µg N=46 Baseline: 19.6 (12.4) Follow up: 14.8 (13.0) p=0.12	N/A	N/A	N/A
Dyspareunia	Constantine, 2019 ²⁰ NCT02253173	12 weeks 0 (none) to 3 (severe) Mean (SD), p- value	Estradiol 4 µg N=172 Baseline: 2.6 (0.5) Follow-up: 1.1 (1.0) p-value NR	Estradiol 10 µg N=171 Baseline: 2.6 (0.5) Follow-up: 0.9 (0.9) p-value NR	N/A	Placebo vaginal capsule N=176 Baseline: 2.7 (0.5) Follow-up: 1.4 (1.1) p-value NR
	Mitchell, 2018 ¹¹⁵ NCT02516202	12 weeks FSFI pain domain Mean (95% CI), p-value	Vaginal estradiol + placebo gel – FSFI pain N=73 Week 12 - baseline: 1.4 (0.9, 1.8) Estradiol vs. placebo difference: 0.4 (-0.2, 1.0), p=0.47	Vaginal moisturizer + placebo tablet N=86 Week 12 - baseline: 1.0 (0.7, 1.4) Moisturizer vs. placebo difference: 0.1 (-0.4, 0.7), p=0.76	N/A	Placebo tablet & gel N=79 Week 12 - baseline: 0.9 (0.5, 1.4)
		12 weeks 4-point severity, 0-3 (none, mild, moderate, or severe) Mean (95% CI), p-value	Vaginal estradiol + placebo gel N=73 Week 12 - baseline: - 1.5 (-1.7, -1.2) Estradiol vs. placebo difference: 0.1 (-0.3, 0.4), p=0.21	Vaginal moisturizer + placebo tablet N=83 Week 12 - baseline: - 1.1 (-1.4, -0.9) Moisturizer vs. placebo difference: 0.4 (0.1, 0.7), p < 0.08	N/A	Placebo tablet & gel N=83 Week 12 - baseline: -1.5 (-1.8, -1.3)

Outcome	Author, Year Trial ID	Follow-Up Measurement Tool/Definition Scoring Range Reported Result	Arm 1 Results	Arm 2 Results	Arm 3 Results	Comparator Arm Results
	Simon, 2019 ⁸⁴ NCT02253173	12 weeks VVA Symptom Self-Assessment Questionnaire 0 (none) to 3 (severe) Percentage of participants that improved by ≥ 2 levels, p-value	Estradiol 4 μg N=186 41.4%, p < 0.05	Estradiol 10 μg N=188 47.3%, p < 0.001	N/A	Placebo vaginal capsule N=187 35.8%
	Archer, 2018 ⁵ NR	12 weeks 4-point severity, 0-3 (none, mild, moderate, or severe) Mean (estimated from figure), p- value	Estradiol N=134 2-week change from baseline: -0.7 12-week change from baseline: -1.1 p-value NR	N/A	N/A	Placebo cream N=130 2-week change from baseline: -0.7 12-week change from baseline: -1.1 p-value NR
	Constantine, 2017 ¹⁷ NCT02253173	12 weeks MBS 4-point severity, 0-3 (none, mild, moderate, or severe) Means stratified across baseline characteristics	Estradiol 4 μg Means stratified by baseline characteristics	Estradiol 10 μg Means stratified by baseline characteristics	N/A	Placebo vaginal capsule Means stratified by baseline characteristics
	Constantine, 2017 ¹⁸ NCT02253173	12 weeks MBS 0 (none) to 3 (severe) LSM (SE), p- value	Estradiol 4 μg N=151 Mean difference: -1.52 (-0.07) p < 0.01	Estradiol 10 μg N=154 Mean difference: -1.69 (0.07) p < 0.0001	N/A	Placebo vaginal capsule N=163 Mean difference: -1.28 (- 0.07) p-value NR

Outcome	Author, Year Trial ID	Follow-Up Measurement Tool/Definition Scoring Range Reported Result	Arm 1 Results	Arm 2 Results	Arm 3 Results	Comparator Arm Results
	Kingsberg, 2016 ⁴⁸ NCT02253173	12 weeks FSFI pain domain 0 (worst) to 6 (best) Mean score (SD) at baseline and follow-up, significance	Estradiol 4 µg N=186 Baseline: 1.6 (1.1) Week 12: 3.8 (2.0) Non-significant difference vs placebo	Estradiol 10 µg N=188 Baseline: 1.8 (1.2) Week 12: 4.3 (1.9) Significant difference vs placebo	N/A	Placebo vaginal capsule N=187 Baseline: 1.7 (1.2) Week 12: 3.6 (1.9)
	Fernandes, 2014 ²⁹ U1111-11255434	12 weeks FSFI Sexual Functioning Total domain 0 (worst) to 6 (best) Mean (SD), p- value	Conjugated estrogen cream N=18 Baseline: 1.3 (2) Follow-up: 3 (2.9) Intergroup differences p=0.583; intragroup differences p=0.022	N/A	N/A	Placebo N=20 Baseline: 2.1 (2.1) Follow-up: 3.1 (2.4) Intragroup differences p=0.127
	Bachmann, 2009 ¹⁰ NR	12 weeks Daily diary (ie, 4- point scale) 0 (none) to 3 (severe) Mean change in score, p-value	Estrogen 21/7 N=143 Mean change: -1.4, P<0.001 vs placebo 21/7	Placebo 21/7 N=72 Mean change: -0.4	Estrogen 2x/wk N=140 Mean change: - 1.4, P≤0.01 vs placebo 2x/wk	Placebo 2x/wk N=68 Mean change: -0.7
	Freedman, 2009 ³⁴ NCT00361569	12 weeks 4-point severity scale 0 (none) to 3 (severe) Proportion of participants reporting improvement of sx and resolution of mod-severe sx , p-value	Estrogen N=150 <i>Improvement</i> 70.0%, P=0.0004 vs placebo <i>Resolution</i> 33.8%, P=0.0005 vs placebo	N/A	N/A	Placebo N=155 <i>Improvement</i> 40.0% <i>Resolution</i> 8.8%

Outcome	Author, Year Trial ID	Follow-Up Measurement Tool/Definition Scoring Range Reported Result	Arm 1 Results	Arm 2 Results	Arm 3 Results	Comparator Arm Results
	Lima, 2013 ¹⁰⁹ 093/10	12 weeks 4-point scale 0 (none) to 3 (severe) Proportion (%) reporting none, mild, moderate, or severe symptoms at 12 weeks	Conjugated Estrogen Cream N=30 None: 40% Mild: 55% Moderate: 5% Severe: 0%	N/A	N/A	Placebo N=30 None: 4% Mild: 56% Moderate: 40% Severe: 0%
	Eriksen, 1999 ²⁸ NR	36 weeks 4-point severity, 0-3 (none, mild, moderate, or severe) Percentage of symptom-free changes for dyspareunia between baseline and termination, p-value	Vaginal Estradiol Ring N=53 71%, P=0.003 vs control	N/A	N/A	No-Treatment Control N=55 10%
	Nachtigall, 1995 ⁶³ NR	12 weeks Author-created questionnaire Narrative	Estradiol ring N=129 “In the summary for patient symptomatology improvement rates the equivalence criteria were satisfied for three symptoms, vaginal dryness, vaginal burning, and dyspareunia.”	N/A	N/A	Conjugated estrogens cream N=67 “In the summary for patient symptomatology improvement rates the equivalence criteria were satisfied for three symptoms, vaginal dryness, vaginal burning, and dyspareunia.”

Outcome	Author, Year Trial ID	Follow-Up Measurement Tool/Definition Scoring Range Reported Result	Arm 1 Results	Arm 2 Results	Arm 3 Results	Comparator Arm Results
	Ayton, 1996 ⁷ NR	12 weeks MBS 4-point severity, 0-3 (none, mild, moderate, or severe) Percentage	Vaginal Estradiol Ring N=131 Unable to extract from figure	N/A	N/A	Vaginal Conjugated Estrogen Cream N=63 Unable to extract from figure
Quality of Life	Gibson, 2020 ³⁵	12 weeks DIVA scale w/ 4 domains: activities of daily living, emotional well-being, sexual functioning Add score range Mean (95% CI), p-value	Vaginal estradiol + placebo gel N=98 Activities of daily living: -0.4 (-0.5, -0.3), p=0.45 Emotional well being: - 0.8 (-1.0, -0.6), p=0.1 Sexual functioning: - 1.2 (-1.5, -1.0), p=0.59 Self concept and body image: -1.1 (-1.3, -0.8), p=0.16 Difference between estradiol group & dual placebo group - Activities of daily living: -0.1 (-0.3, 0.0) Emotional well being: - 0.2 (-0.5, 0.0) Sexual functioning: - 0.1 (-0.5, 0.2) Self concept and body image: -0.2 (-0.5, 0.1)	Vaginal moisturizer + placebo tablet N=98 Activities of daily living: -0.3 (-0.4, -0.2), p=0.1 Emotional well being: - 0.7 (-0.8, -0.5), p=0.19 Sexual functioning: - 1.1 (-1.3, -0.8), p=0.37 Self concept and body image: -0.9 (-1.1, - 0.6), p=0.98 Difference between moisturizer group & dual placebo group - Activities of daily living: -0.1 (-0.2, 0.1) Emotional well being: - 0.1 (-0.3, 0.1) Sexual functioning: 0.0 (-0.3, 0.4) Self concept and body image: 0.0 (-0.3, 0.3)	N/A	Placebo tablet & gel N=94 Activities of daily living: - 0.3 (-0.4, -0.1) Emotional well being: -0.6 (-0.8, -0.4) Sexual functioning: -1.1 (- 1.3, -0.8) Self concept and body image: -0.8 (-1.1, -0.6)

Outcome	Author, Year Trial ID	Follow-Up Measurement Tool/Definition Scoring Range Reported Result	Arm 1 Results	Arm 2 Results	Arm 3 Results	Comparator Arm Results
	Diem, 2018 ²⁴ NCT02516202	12 weeks MENQOL Total Score 1 (best) to 8 (worst) Mean (95% CI)	Vaginal estradiol + placebo gel N=89 Follow up: -1.0 (-1.2, - 0.8) p=0.01 Estradiol vs. dual placebo: -0.3, 95% CI (-0.5, 0.0)	Vaginal moisturizer + placebo tablet N=94 Follow up: -0.5 (-0.7, - 0.4) p=0.38 Moisturizer vs. dual placebo -0.2 (-0.1, 0.4)	N/A	Placebo tablet & gel N=86 Mean difference: -0.7 (- 0.9, -0.6)
Sexual Functioning	Tanmahasamut, 2020 ⁸⁷ Thai Clinical Trials Registry 20170322001	8 weeks FSFI Total Score 2 (worst) to 36 (best) Mean, p-value	Estradiol N=38 Baseline: 33 Follow up: 47.2 Mean difference: 14.2 p <0.001	N/A	N/A	Placebo N=37 Baseline: 31.6 Follow up: 30.8 Mean difference: -0.8
	Mitchell, 2018 ⁶² NCT02516202	12 weeks FSFI Total Score 2 (worst) to 36 (best) Mean (95% CI)	Vaginal estradiol + placebo gel N=64 Mean difference: 5.4 (4.0, 6.9)	Vaginal moisturizer + placebo tablet N=80 Mean difference: 3.1 (1.7, 4.5)	N/A	Placebo tablet & gel N=70 Mean difference 4.5 (2.8, 6.1)
	Kingsberg, 2016 ⁴⁸ NCT02253173	12 weeks FSFI Total Score 2 (worst) to 36 (best) Mean (SD)	Estradiol 4 µg N=173 Mean difference: 7.91 (8.4)	Estradiol 10 µg N=172 Follow up: 24.8 Mean difference: 9.43 (7.6)	N/A	Placebo vaginal capsule N=175 Follow up: 22 Mean difference: 7.46 (8.5)
	Fernandes, 2014 ²⁹ U1111-11255434	12 weeks FSFI Total Score 2 (worst) to 36 (best) Mean (SD), p- value	Conjugated estrogen cream N=18 Baseline: 12.7 (10.1) Follow-up: 18.2 (13) Intergroup differences p=0.225; intragroup differences p=0.138	N/A	N/A	Placebo N=20 Baseline: 13.1 (9) Follow-up: 15.8 (10) Intragroup differences p=0.011

Outcome	Author, Year Trial ID	Follow-Up Measurement Tool/Definition Scoring Range Reported Result	Arm 1 Results	Arm 2 Results	Arm 3 Results	Comparator Arm Results
Mood (anxiety)	Diem, 2018 ²⁴ NCT02516202	Week 12 from baseline GAD-7: 0 (best) to 21 (worst) PHQ-8: 0 (best) to 12 (worst) Mean difference (95% CI), p-value	Vaginal estradiol + placebo gel N=98 Anxiety: -1.2 (-1.8, - 0.5) Depression: -0.5 (-1.2, 0.1)	N/A	N/A	Vaginal moisturizer + placebo tablet N=99 Anxiety: 0 (-0.6, 0.7) Depression: -0.2 (-0.8, 0.4) Anxiety: vaginal estradiol vs. dual placebo: 0.6 (- 0.4, 1.6), p=0.99 Depression: vaginal estradiol vs. dual placebo: 0.3, p=0.83
Change in MBS	Tanmahasamut, 2020 ⁸⁷ Thai Clinical Trials Registry 20170322001	8 weeks 4-point severity, 0-3 (none, mild, moderate, or severe) of vaginal dryness, vaginal soreness, vaginal irritation, vaginal discharge, and dyspareunia Mean (SD), p- value	Estradiol N=38 Mean difference: -2.0 (0.43) p <0.001	N/A	N/A	Placebo N=37 Mean difference: -1.6 (0.41) p <0.001
	Mitchell, 2018 ⁶² NCT02516202	12 weeks 4-point severity, 0-3 (none, mild, moderate, or severe) of vulvovaginal itching, pain, irritation, dryness, or pain with penetration Mean (SD)	Vaginal estradiol + placebo gel N=96 Mean difference: -1.4 (0.99)	Vaginal moisturizer + placebo tablet N=99 Mean difference: -1.2 (1.05)	N/A	Placebo tablet & gel N=95 -1.3

Outcome	Author, Year Trial ID	Follow-Up Measurement Tool/Definition Scoring Range Reported Result	Arm 1 Results	Arm 2 Results	Arm 3 Results	Comparator Arm Results
	Bachmann, 2009 ¹⁰ NR	12 weeks 4-point severity, 0-3 (none, mild, moderate, or severe) of vaginal dryness, itching, burning, & dyspareunia Mean, p-value	CE cream 21/7 N=143 Mean difference: -1.3 p ≤0.001	Placebo cream 21/7 N=72 Mean difference: -0.08	CE cream 2x/wk N=140 Mean difference: -1.4 p ≤0.001	Placebo cream 2x/wk N=68 Mean difference -0.7
	Freedman, 2009 ³⁴ NCT00361569	12 weeks 4-point severity, 0-3 (none, mild, moderate, or severe) of dryness, soreness, irritation, pain with intercourse, or bleeding after intercourse Mean, p-value	SCE-A N=135 Mean difference: -1.71 p <0.0001	N/A	N/A	Placebo cream N=140 Mean difference -1.11
Treatment satisfaction	Mitchell, 2018 ⁶² NCT02516202	12 weeks % reporting "meaningful benefit;" Author- developed Likert scale: 0=not satisfied to 10=completely satisfied Mean (SD)	Vaginal estradiol + placebo gel N=97 Follow up: 8.6 (2.6)	Vaginal moisturizer + placebo tablet N=99 Mean difference: 7.7 (3.2)	N/A	Placebo tablet & gel N=99 Mean difference: 8.1 (3.0)
	Ayton, 1996 ⁷ NR	12 weeks Grading of the delivery system as either excellent or good (%), p- value	Vaginal Estradiol Ring N=131 84%, p < 0.0001	N/A	N/A	Vaginal Conjugated Estrogen Cream N=63 43%, p < 0.0001

Outcome	Author, Year Trial ID	Follow-Up Measurement Tool/Definition Scoring Range Reported Result	Arm 1 Results	Arm 2 Results	Arm 3 Results	Comparator Arm Results
	Nachtigall, 1995 ⁶³ NR	12 weeks Author-created questionnaire Percentage, p- value	Estradiol ring N=113 At week 12, 85% of patients using the ring rated it 'very easy' to use, compared with 35% using cream (p=0.001). Furthermore, 67% rated product comfort of the ring as excellent, compared with 18% of cream users (p=0.001)	N/A	N/A	Conjugated estrogens cream N=60 At week 12, 85% of patients using the ring rated it 'very easy' to use, compared with 35% using cream (p=0.001). Furthermore, 67% rated product comfort of the ring as excellent, compared with 18% of cream users (p=0.001)
Genital signs and vaginal health	Archer, 2018 ⁵ NR	12 weeks Vaginal cytology (% superficial and parabasal cells, pH) Mean (SD) change, p-value vs. placebo	Estrogen (n=248) <i>Superficial</i> : 8.6 (14.5), P<0.001 (sig) <i>Parabasal</i> : -37.4 (42.6), P<0.001 (sig) <i>pH</i> : -1.26 (0.99), P<0.001 (sig)	N/A	N/A	Placebo (n=240) <i>Superficial</i> : 0.8 (5.7) <i>Parabasal</i> : -4.4 (42.9) <i>pH</i> : -0.31 (0.80)

Outcome	Author, Year Trial ID	Follow-Up Measurement Tool/Definition Scoring Range Reported Result	Arm 1 Results	Arm 2 Results	Arm 3 Results	Comparator Arm Results
	Bachmann, 2009 ¹⁰ NR	12 and 52 weeks Vaginal cytology (% superficial and parabasal cells, pH) Week 12: Mean (SE) change, p- value vs. placebo Week 52: Mean (SD) change	CE cream 21/7 N=143 Week 12 <i>Superficial</i> : 27.9 (1.7), P<0.001 <i>Parabasal</i> : -60.6 (2.2), P<0.001 <i>pH</i> : -1.6 (0.1), P<0.001 Week 52 <i>Superficial</i> : 25.7 (26.0), P-value NS <i>Parabasal</i> : -63.4 (44.8), P-value NS <i>pH</i> : -1.8 (1.0), P-value NS	Placebo 21/7 N=72 Week 12 <i>Superficial</i> : 3.0 (2.4) <i>Parabasal</i> : -21.5 (3.0) <i>pH</i> : -0.4 (0.1) Week 52 <i>Superficial</i> : 24.1 (24.6) <i>Parabasal</i> : -61.7 (42.2) <i>pH</i> : -1.7 (0.8)	Estrogen 2x/wk N=140 Week 12 <i>Superficial</i> : 25.8 (1.7), P<0.001 <i>Parabasal</i> : -58.2 (2.2), P<0.001 <i>pH</i> : -1.6 (0.1), P<0.001 Week 52 <i>Superficial</i> : 17.1 (19.4), P-value NS <i>Parabasal</i> : -55.8 (49.3), P-value NS <i>pH</i> : -1.5 (1.0), P-value NS	Placebo 2x/wk N=68 Week 12 <i>Superficial</i> : 1.0 (2.4) <i>Parabasal</i> : -6.6 (3.1) <i>pH</i> : -0.3 (0.1) Week 52 <i>Superficial</i> : 20.9 (22.8) <i>Parabasal</i> : -57.3 (45.2) <i>pH</i> : -1.7 (1.1)
	Constantine, 2017 ¹⁸ NCT02253173	12 weeks Vaginal cytology (% superficial and parabasal cells, pH) LSM (SE) change from baseline, p- value vs. placebo	4 mcg (n=170) <i>Superficial</i> : 17.5 (1.54) P<0.0001 <i>Parabasal</i> : -40.6 (1.76) P<0.0001 <i>pH</i> : -1.32 (0.07) P<0.0001	10 mcg (n=171) <i>Superficial</i> : 16.7 (1.54) P<0.0001 <i>Parabasal</i> : -44.1 (1.75) P<0.0001 <i>pH</i> : -1.42 (0.07) P<0.0001	N/A	Placebo (n=172) <i>Superficial</i> : 5.6 (1.54) <i>Parabasal</i> : -6.7 (1.75) <i>pH</i> : -0.28 (0.07)

Outcome	Author, Year Trial ID	Follow-Up Measurement Tool/Definition Scoring Range Reported Result	Arm 1 Results	Arm 2 Results	Arm 3 Results	Comparator Arm Results
	Constantine, 2017 ¹⁷ NCT02253173	12 weeks Vaginal cytology (% superficial, pH) LSM change from baseline to 12 weeks, p-value vs. placebo	4 mcg (n=170) ≤56: Superficial: 17.23, P<0.05 pH: -1.36, P<0.0001 57-61: Superficial: 18.74, P≤0.001 (sig) pH: -1.37, P<0.0001 ≥62: Superficial: 16.75, P≤0.001 pH: -1.23, P<0.0001	10 mcg (n=171) ≤56: Superficial: 14.93, P<0.05 pH: -1.30, P<0.0001 57-61: Superficial: 19.62, P≤0.001 pH: -1.58, P<0.0001 ≥62: Superficial: 16.18, P≤0.001 pH: -1.40, P<0.0001	N/A	Placebo (n=172) ≤56: Superficial: 7.31 pH: -0.48 57-61: Superficial: 5.22 pH: -0.34 ≥62: Superficial: 4.05 pH: -0.05
	Freedman, 2009 ³⁴ NCT00361569	12 weeks Vaginal cytology (VMI, % superficial and parabasal cells, pH) Mean change, p- value vs. placebo	Estrogen (n=150) <i>VMI</i> Baseline: 31.31 Week 12: 62.77 Change: 31.46 P<0.00001 <i>Superficial</i> Change: 25.16 P<0.00001 <i>Parabasal</i> Change: -37.75 P<0.00001 <i>pH</i> Baseline: 6.30 Week 12: 4.84 Change: 1.48 (23.4%) P<0.0001	N/A	N/A	Placebo (n=155) <i>VMI</i> Baseline: 31.84 Week 12: 37.00 Change: 5.16 <i>Superficial</i> Change: 3.11 <i>Parabasal</i> Change: -7.20 <i>pH</i> Baseline: 6.30 Week 12: 5.96 Change: 0.31 (4.9%)

Outcome	Author, Year Trial ID	Follow-Up Measurement Tool/Definition Scoring Range Reported Result	Arm 1 Results	Arm 2 Results	Arm 3 Results	Comparator Arm Results
	Mitchell, 2018 ⁶² NCT02516202	12 weeks Vaginal cytology (pH ≤/ >5, superficial cells ≤/ >5%) N (%)	Estrogen (n=97) <i>pH</i> Baseline: ≤5: 18 (18) >5: 81 (79) Week 12: Change from >5 to ≤5: 36 (46) P<0.001 <i>Superficial</i> Baseline: ≤5%: 86 (84) >5%: 6 (6) Missing: 10 (10) Week 12: Change from ≤5% to >5%: 45 (57) P<0.001	N/A	N/A	Placebo (n=98) <i>pH</i> Baseline: ≤5: 9 (9) >5: 90 (90) Week 12: Change from >5 to ≤5: 10 (12) <i>Superficial</i> Baseline: ≤5%: 81 (81) >5%: 7 (7) Missing: 12 (12) Week 12: Change from ≤5% to >5%: 8 (11)
	Raghunandan, 2010 ⁷⁸ NR	12 weeks VHI Add score range Mean (SD), p- value	Estrogen N=25 Baseline: 13.12 (2.52), p-value NS Follow-up: 18.96 (2.32), p < 0.01 Mean change: 44.5	Estrogen + testosterone N=25 Baseline: 13.24 (1.61), p-value NS Follow-up: 20.12 (1.72), p < 0.01 Mean change: 51.9	N/A	Placebo N=25 Baseline: 13.32 (3.32), p- value NS Follow-up: 15.84 (2.59), p < 0.01 Mean change: 18.9
	Raghunandan, 2010 ⁷⁸ NR	12 weeks VMI Add score range Mean (SD), p- value	Estrogen N=25 Baseline: 46.10 (5.26), p-value NS Follow-up: 52.98 (5.84), p < 0.01 Mean change: 15.0	Estrogen + testosterone N=25 Baseline: 45.74 (6.16), p-value NS Follow-up: 53.2 (5.68), p < 0.01 Mean change: 16.3	N/A	Placebo N=25 Baseline: 46.78 (5.69), p- value NS Follow-up: 47.98 (5.77), p < 0.01 Mean change: 2.5

Outcome	Author, Year Trial ID	Follow-Up Measurement Tool/Definition Scoring Range Reported Result	Arm 1 Results	Arm 2 Results	Arm 3 Results	Comparator Arm Results
	Tanmahasamut, 2020 ⁸⁷ Thai Clinical Trials Registry 20170322001	8 weeks Vaginal cytology (% superficial and parabasal cells, pH) Mean at baseline and follow-up, p- value vs. placebo	Estrogen (n=38) <i>Superficial</i> Baseline: 3.2 Week 8: 28.2 P<0.001 <i>Parabasal</i> Baseline: 58.2 Week 8: 0.6 P<0.001 <i>pH</i> Baseline: 7.4 Week 8: 5.2 P<0.001	N/A	N/A	Placebo (n=37) <i>Superficial</i> Baseline: 4.8 Week 8: 5.7 <i>Parabasal</i> Baseline: 49.8 Week 8: 41.2 <i>pH</i> Baseline: 7.5 Week 8: 7.4
	Tanmahasamut, 2020 ⁸⁷ Thai Clinical Trials Registry 20170322001	8 weeks VHI; VMI 1 (worst) to 5 (excellent) Mean	Estradiol N=38 Follow up: VHI: 20.1 VMI: 63.5	N/A	N/A	Placebo N=37 Follow up: VHI: 12.5 VMI: 31.5

Abbreviations: CE=conjugated estrogen; CI=confidence interval; DIVA=Day-to-Day Impact of Vaginal Aging; FSFI=Female Sexual Function Index; IQR=interquartile range; MBS=most bothersome symptom; mcg=micrograms; MENQoL=Menopause-Specific Quality of Life; N/A=not applicable; NR=not reported; PHQ-8=Patient Health Questionnaire; RR=risk ratio; SD=standard deviation; UDI-6=Urinary Distress Index; VHI=Vaginal Health Index; VPAQ=Vulvar Pain Assessment Questionnaire; VSI=Vaginal Symptom Index; VVA=vulvovaginal atrophy

Table C.13. Detailed harms results for studies of estrogen hormonal interventions rated low or some concerns

Author, Year Total N Follow-Up Intervention Vs. Comparator	Outcome	Intervention n (%)	Comparator n (%)
Archer, 2018⁵ N=573 12 weeks 0.003% estradiol cream vs. placebo	Any AE/TEAE	134 (46.9)	130 (45.3)
	SAEs	2 (0.7)	2 (0.7)
	Discontinuation due to AE	8 (2.8)	5 (1.7)
	Specific AEs	UTI: 15 (5.2) Vulvovaginal mycotic infection: 15 (5.2)	UTI: 17 (5.9) Vulvovaginal mycotic infection: 3 (1.0)
	Endometrial safety	--	--
Ayton, 1996⁷ N=195 12 weeks	Any AE/TEAE	--	--
	SAEs	--	--
	Discontinuation due to AE	9	5
	Specific AEs	--	--

Author, Year Total N Follow-Up Intervention Vs. Comparator	Outcome	Intervention n (%)	Comparator n (%)
2 mg estradiol ring vs. 0.625 mg CEC	Endometrial safety	Intercurrent vaginal bleeding: 8 (6) Bleeding in response to progesterone challenge after 12 weeks: 5 Proliferative endometrium: 1	Intercurrent vaginal bleeding: 5 (8) Bleeding in response to progesterone challenge after 12 weeks: 5 Proliferative endometrium: 2
Bachmann, 2009¹⁰ N=423 12 weeks 0.3 mg CEC vs. placebo 21/7 or 2x/wk	Any AE/TEAE	21/7: 95 (66.4) 2x/wk: 100 (71.4)	21/7: 46 (63.9) 2x/wk: 47 (69.1)
	SAEs	"A total of 5 (1.2%) participants in the double-blind phase"	"A total of 5 (1.2%) participants in the double-blind phase"
	Discontinuation due to AE	21/7: 6 (4.2) 2x/wk: 4 (2.9)	21/7: 1 (1.4) 2x/wk: 2 (2.9)
	Specific AEs	Headache: 21/7: 14 (9.8) 2x/wk: 26 (18.6) Infection: 21/7: 7 (4.9) 2x/wk: 16 (11.4)	Headache: 21/7: 8 (11.1) 2x/wk: 12 (17.6) Infection: 21/7: 5 (6.9) 2x/wk: 5 (7.4)
	Endometrial safety	--	--
Constantine, 2017¹⁸ N=574 12 weeks 4 mcg or 10 mcg estradiol capsule vs. placebo	Any AE/TEAE	4 mcg: 97 (50.8) 10 mcg: 94 (49.2)	111 (57.8)
	SAEs	4 mcg: 0 10 mcg: 4	1
	Discontinuation due to AE	4 mcg: 1 10 mcg: 3	3
	Specific AEs	Headache: 4 mcg: 12 (6.3) 10 mcg: 14 (7.3) Vaginal discharge: 4 mcg: 5 (2.6) 10 mcg: 6 (3.1) Vulvovaginal pruritus: 4 mcg: 4 (2.1) 10 mcg: 3 (1.6) UTI: 4 mcg: 5 (2.6) 10 mcg: 5 (2.6)	Headache: 15 (7.8) Vaginal discharge: 13 (6.8) Vulvovaginal pruritus: 10 (5.2) UTI: 4 (2.1)
	Endometrial safety <i>Endometrial biopsy</i>	No diagnoses of endometrial hyperplasia or malignancy from endometrial biopsies were observed at week 12.	--
Eriksen, 1999²⁸ N=108	Any AE/TEAE	--	--
	SAEs	3	1

Author, Year Total N Follow-Up Intervention Vs. Comparator	Outcome	Intervention n (%)	Comparator n (%)
36 weeks 2 mg estradiol ring vs. no treatment	Discontinuation due to AE	5 (3 local discomfort, 1 hot flushes, 1 UTI)	0
	Specific AEs	--	--
	Endometrial safety	Vaginal bleeding: 3	Vaginal bleeding: 0
Fernandes, 2018 ³⁰ N=38* 12 weeks 0.625 mg CEC vs. placebo	Any AE/TEAE	--	--
	SAEs	--	--
	Discontinuation due to AE	1 (allergic vaginitis)	0
	Specific AEs	--	--
	Endometrial safety TVU (mean [SD] mm)	Baseline: 3.1 (1.6) Week 12: 3.6 (2.6) P=0.8 vs. placebo	Baseline: 2.5 (1.0) Week 12: 2.6 (2.1)
Freedman, 2009 ³⁴ N=305 12 weeks 0.625 mg CEC vs. placebo	Any AE/TEAE	AE: 83 (55.3) TEAE: 74 (49.3)	AE: 72 (46.5) TEAE: 68 (43.9)
	SAEs	1	1
	Discontinuation due to AE	3 (2.0)	2 (1.3)
	Specific AEs	--	--
	Endometrial safety	--	--
Goetsch, 2023 ³⁶ N=48 12 weeks 50 mcg vs. 100 mcg estradiol cream	Any AE/TEAE	--	--
	SAEs	--	--
	Discontinuation due to AE	--	--
	Specific AEs	Breast tenderness: 3 (12) Vaginal spotting or bleeding: 1 (4) Stinging with cream application: 2 (8)	Breast tenderness: 3 (14) Vaginal spotting or bleeding: 0 (0) Stinging with cream application: 2 (9)
	Endometrial safety TVU (mean [SD] mm)	Baseline: 2.6 (0.8) Week 12: 2.7 (0.8) NS vs. placebo	TVU (mean [SD] mm) Baseline: 3.0 (0.9) Week 12: 3.0 (1.1)
Lima, 2013 ¹⁰⁹ N=60† [all with intact uterus] 12 weeks 0.625 mg CEC vs. placebo	Any AE/TEAE	--	--
	SAEs	--	--
	Discontinuation due to AE	7 (5 mastalgia and 2 pelvic pain)	0
	Specific AEs	--	--
	Endometrial safety TVU (median [max-min] mm)	Baseline: 3 (1-4) Week 12: 2 (1-3)	Baseline: 2 (1-4) Week 12: 2 (1-3)
Mitchell, 2018 ⁶² N=202‡ 12 weeks	Any AE/TEAE	Any MedDRA-classified AE: 50 (49) Any study questionnaire AE: 26 (26)	Any MedDRA-classified AE: 46 (46) Any study questionnaire AE: 24 (24)
	SAEs	--	--
	Discontinuation due to AE	--	--

Author, Year Total N Follow-Up Intervention Vs. Comparator	Outcome	Intervention n (%)	Comparator n (%)
10 mcg estradiol tablet vs. placebo	Specific AEs	Vaginal candidiasis: 8 (8) Vaginal discharge: 2 (2) Vaginal odor: 1 (1) Vulvovaginal burning: 1 (1) Vulvovaginal itching: 2 (2) UTI: 2 (2) Breast tenderness: 3 (3) Breast disorders (non-cancer): 3 (3) GI signs/symptoms: 4 (4)	Vaginal candidiasis: 2 (2) Vaginal discharge: 2 (2) Vaginal odor: 5 (5) Vulvovaginal burning: 1 (1) Vulvovaginal itching: 2 (2) UTI: 4 (4) Breast tenderness: 2 (2) Breast disorders (non-cancer): 5 (5) GI signs/symptoms: 6 (6)
	Endometrial safety	--	--
Nachtigall, 1995⁶³ N=196 12 weeks 2 mg estradiol ring vs. 2g CEC	Any AE/TEAE	--	--
	SAEs	2	1
	Discontinuation due to AE	5	0
	Specific AEs	Vaginal infections higher in ring group (data NR by study authors)	Breast symptoms higher for cream than ring (data NR by study authors)
	Endometrial safety	Bleeding in response to progesterone challenge after 12 weeks: 3 (21) Endometrial thickness >5mm: 6% Mild proliferative endometrium: 0 (0) Moderate endometrial proliferation or hyperplasia in an endometrial polyp: 2 (5)	Bleeding in response to progesterone challenge after 12 weeks: 1 (3) Endometrial thickness >5mm: 12% Mild proliferative endometrium: 3 (10) Moderate endometrial proliferation or hyperplasia in an endometrial polyp: 0 (0)
Nelken, 2011⁶⁵ N=54 12 weeks 2 mg estradiol ring vs. 5 mg oxybutynin	Any AE/TEAE	--	--
	SAEs	--	--
	Discontinuation due to AE	0	4
	Specific AEs	Dry mouth: 6 (22) Headache: 7 (26) Constipation: 2 (7) Vaginal discharge: 11 (41) Blurry vision: 5 (19) Nausea/vomiting: 3 (11)	Dry mouth: 23 (85) Headache: 10 (37) Constipation: 14 (52) Vaginal discharge: 1 (4) Blurry vision: 12 (44) Nausea/vomiting: 2 (7)
	Endometrial safety	--	--
Raghunandan, 2010⁷⁸ N=50 [¶] 12 weeks 0.625 mg CEC vs. placebo	Any AE/TEAE	--	--
	SAEs	--	--
	Discontinuation due to AE	--	--
	Specific AEs	Vaginal discharge: 4 (16)	No adverse effects observed
	Endometrial safety TVU (mean mm)	Baseline: 2.72 Week 12: 2.80 P-value NS vs. placebo	Baseline: 2.75 Week 12: 2.76

Author, Year Total N Follow-Up Intervention Vs. Comparator	Outcome	Intervention n (%)	Comparator n (%)
Tanmahasamut, 2020 ⁸⁷ N=80 8 weeks 25 mcg estradiol gel vs. placebo	Any AE/TEAE	"No adverse events were reported in either group."	--
	SAEs	--	--
	Discontinuation due to AE	--	--
	Specific AEs	--	--
	Endometrial safety TVU (mean mm)	Baseline: 2.08 Week 8: 1.56 P-value NS vs. placebo	Baseline: 2.05 Week 8: 1.58

Abbreviations: 21/7=21 days on/7 days off; 2x/wk=twice weekly; AE=adverse event/effect; CEC=conjugated estrogens cream; mm=millimeter; NR=not reported; NS=non-significant; OAB=overactive bladder; SAE=serious adverse event; SD=standard deviation; TCTR=Thai Clinical Trials Registry; TEAE=treatment-emergent adverse event; TVU=transvaginal ultrasound; UTI=urinary tract infection

-- NR

*Total N includes only estrogen and placebo arms from Fernandes (2018),³⁰ which reports safety outcomes for Fernandes (2014).²⁹ See Table C.21 and Table C.23 for testosterone and polyacrylic acid cream arm results, respectively.

†Total N includes only conjugated estrogens cream and placebo arms from Lima (2013).¹⁰⁹

‡Total N includes only estradiol and placebo arms from Mitchell (2018).⁶² See Table C.23 for vaginal moisturizer arm results.

¶Total N includes only estrogen and placebo arms from Raghunandan (2010).⁷⁸ See Table C.21 for estrogen + testosterone arm results.

Table C.14. Detailed effectiveness results for studies of DHEA rated low or some concerns ROB

Outcome	Author, Year Trial ID	Follow-Up Measurement Tool/Definition Scoring Range Reported Result	Arm 1 Results	Arm 2 Results	Arm 3 Results	Comparator Arm Results
Vulvovaginal dryness	Archer, 2015 ⁶ NCT01256684	12 weeks 4-point scale 0 (none) to 3 (severe) Mean (SEM), p-value	DHEA 0.25% (3.25 mg) N=70 Baseline: 2.20 (0.05) Week 12: 0.91 (0.10) Change: -1.29 (0.11) P=0.008 vs placebo	DHEA 0.50% (6.5 mg) N=62 Baseline: 2.37 (0.06) Week 12: 0.92 (0.10) Change: -1.45 (0.12) P=0.01 vs placebo	N/A	Placebo N=60 Baseline: 2.33 (0.06) Week 12: 1.32 (0.12) Change: -1.02 (0.14)

Outcome	Author, Year Trial ID	Follow-Up Measurement Tool/Definition Scoring Range Reported Result	Arm 1 Results	Arm 2 Results	Arm 3 Results	Comparator Arm Results
	Barton, 2018 ¹³ NCT01376349	12 weeks FSFI lubrication domain 0 (worst) to 6 (best) Mean (SD), (95% CI), p-value	DHEA 3.25 mg N=123 Baseline: 1.5 (1.3), (1.3, 1.7) 12 weeks: 2.8 (2.0), (2.5, 3.2) Change: 1.3 (1.8), (1.0, 1.6) P>0.05 vs placebo	DHEA 6.50 mg N=112 Baseline: 1.4 (1.3), (1.1, 1.6) 12 weeks: 3.0 (2.0), (2.6, 3.4) Change: 1.6 (1.7), (1.3, 1.9) P<0.05 vs placebo	N/A	Placebo N=118 Baseline: 1.4 (1.2), (1.2, 1.6) 12 weeks: 2.5 (1.9), (2.1, 2.8) Change: 1.1 (1.7), (0.7, 1.4)
	Labrie, 2009 ⁵³ NCT01846442	MENQOL (dryness during intercourse) 1 (best) to 8 (worst) Avg % decrease in score, p-value	DHEA 0.25% N=53 58% P<0.0001 vs placebo	DHEA 0.50% N=56 53% P=0.004 vs placebo	DHEA 1.0% N=54 57% P=0.0001 vs placebo	Placebo N=53 0.28
	Labrie, 2014 ⁵⁵ NCT01846442	12 weeks MENQOL (dryness during intercourse) 1 (best) to 8 (worst) Avg % change, p-value	DHEA 0.25% N=53 45% P=0.003 vs placebo	DHEA 0.50% N=56 50% P=0.0003 vs placebo	DHEA 1.0% N=54 54% P≤0.0001 vs placebo	Placebo N=53 0.23
	Labrie, 2015 ⁵⁶ NCT02013544	12 weeks FSFI lubrication domain 0 (worst) to 6 (best) Mean (SEM), p-value	DHEA 0.50% N=325 Baseline: 2.00 (0.07) Week 12: 4.13 (0.10) Change: 2.13* P=0.0005 vs placebo	N/A	N/A	Placebo N=157 Baseline: 1.91 (0.10) Week 12: 3.53 (0.14) Change: 1.62*
	Labrie, 2018 ⁵¹ NCT02013544	12 weeks 4-point scale 0 (none) to 3 (severe) Mean (SEM), p-value	DHEA 0.50% N=273 Baseline: 2.30 (0.03) Week 12: 0.86 (0.05) Change: -1.44 (0.06) P=0.004 vs placebo	N/A	N/A	Placebo N=132 Baseline: 2.30 (0.04) Week 12: 1.13 (0.08) Change: -1.17 (0.09)

Outcome	Author, Year Trial ID	Follow-Up Measurement Tool/Definition Scoring Range Reported Result	Arm 1 Results	Arm 2 Results	Arm 3 Results	Comparator Arm Results
Dyspareunia	Archer, 2015 ⁶ NCT01256684	12 weeks 4-point scale 0 (none) to 3 (severe) Mean (SEM), p-value	DHEA 0.25% (3.25 mg) N=79 Baseline: 2.56 (0.06) Week 12: 1.54 (0.12) Change: -1.01 (0.11) P value NR	DHEA 0.50% (6.5 mg) N=81 Baseline: 2.63 (0.05) Week 12: 1.36 (0.12) Change: -1.27 (0.11) P=0.01 vs placebo	N/A	Placebo N=77 Baseline: 2.58 (0.06) Week 12: 1.71 (0.11) Change: -0.87 (0.11)
	Barton, 2018 ¹³ NCT01376349	12 weeks FSFI pain domain 0 (worst) to 6 (best) Mean (SD), (95% CI), p-value	DHEA 3.25 mg N=123 Baseline: 1.6 (1.5), (1.4, 1.9) 12 weeks: 3.0 (2.0), (2.7, 3.4) Change: 1.4 (1.7), (1.1, 1.7) P<0.05 vs placebo	DHEA 6.50 mg N=112 Baseline: 1.4 (1.3), (1.2, 1.6) 12 weeks: 3.5 (2.0), (3.1, 3.9) Change: 2.0 (1.6), (1.7, 2.3) P≤0.001 vs placebo	N/A	Placebo N=118 Baseline: 1.6 (1.4), (1.4, 1.9) 12 weeks: 2.5 (2.0), (2.1, 2.8) Change: 1.0 (1.8), (0.6, 1.3)
	Labrie, 2010 ⁵⁴ NCT01846442	12 weeks 4-point scale 0 (none) to 3 (severe) Mean (SEM), p-value	DHEA 0.25% N=53 Baseline: 2.5 (0.13) Week 12: 1.3 (0.20) Change: -1.2* P=0.001 vs placebo	DHEA 0.50% N=56 Baseline: 2.7 (0.09) Week 12: 1.1 (0.20) Change: -1.6* P<0.0001 vs placebo	DHEA 1.0% N=54 Baseline: 2.6 (0.10) Week 12: 1.2 (0.19) Change: -1.4* P<0.0001 vs placebo	Placebo N=53 Baseline: 2.5 (0.13) Week 12: 2.1 (0.18) Change: -0.4*
	Labrie, 2011 ⁵⁰ NCT01846442	12 weeks 4-point scale 0 (none) to 3 (severe) Mean (SEM), p-value	DHEA 0.25% N=29 Baseline: 2.8 (0.08) Week 12: 1.4 (0.22) Change: -1.3 (0.20) P=0.002 vs placebo	DHEA 0.50% N=30 Baseline: 2.7 (0.08) Week 12: 1.1 (0.22) Change: -1.6 (0.21) P<0.0001 vs placebo	DHEA 1.0% N=29 Baseline: 2.6 (0.09) Week 12: 1.2 (0.20) Change: -1.4 (0.18) P=0.0003 vs placebo	Placebo N=26 Baseline: 2.8 (0.08) Week 12: 2.3 (0.18) Change: -0.4 (0.16)
	Labrie, 2015 ⁵⁶ NCT02013544	12 weeks FSFI pain domain 0 (worst) to 6 (best) Mean (SEM), p-value	DHEA 0.50% N=325 Baseline: 1.61 (0.07) Week 12: 3.82 (0.11) Change: 2.21 P=0.001 vs placebo	N/A	N/A	Placebo N=157 Baseline: 1.68 (0.10) Week 12: 3.24 (0.16) Change: 1.56

Outcome	Author, Year Trial ID	Follow-Up Measurement Tool/Definition Scoring Range Reported Result	Arm 1 Results	Arm 2 Results	Arm 3 Results	Comparator Arm Results
	Labrie, 2018 ⁵¹ NCT02013544	12 weeks 4-point scale 0 (none) to 3 (severe) Mean (SEM), p-value	DHEA 0.50% N=325 Baseline: 2.54 (0.03) Week 12: 1.13 (0.05) Change: -1.42 (0.06) P=0.0002 vs placebo	N/A	N/A	Placebo N=157 Baseline: 2.56 (0.04) Week 12: 1.50 (0.08) Change: -1.06 (0.08)
Change in MBS (Dyspareunia or vulvovaginal dryness)	Barton, 2018 ¹³ NCT01376349	12 weeks 4-point scale 0 (none) to 3 (severe) Mean (95% CI), p-value	DHEA 3.25 mg N=123 Change: -1.6 (-1.79, -1.35) P=0.6 vs placebo	DHEA 6.50 mg N=112 Change: -1.8 (- 1.97, -1.54) P=0.03 vs placebo	N/A	Placebo N=118 Change: -1.5 (-1.74, -1.27)
Change in MBS (Vulvovaginal discomfort/irritation)	Labrie, 2009 ⁵² NCT01846442	12 weeks 4-point scale 0 (none) to 3 (severe) % patients in arm describing symptom score change	DHEA 0.25% N=53 % patients in arm describing symptom score change of : -3 : 0 -2 : 100 -1 : 0 0 : 0 +1 : 0	DHEA 0.50% N=56 % patients in arm describing symptom score change of : -3 : 25 -2 : 25 -1 : 50 0 : 0 +1 : 0	DHEA 1.0% N=54 % patients in arm describing symptom score change of : -3 : 0 -2 : 20 -1 : 40 0 : 20 +1 : 20	Placebo N=53 % patients in arm describing symptom score change of : -3 : 0 -2 : 50 -1 : 0 0 : 50 +1 : 0
Change in MBS (Not specified)	Labrie, 2009 ⁵² NCT01846442	12 weeks 4-point scale 0 (none) to 3 (severe) Mean (SEM), p-value	DHEA 0.25% N=53 Change: -1.2 (0.14) P=0.002 vs placebo	DHEA 0.50% N=56 Change: -1.5 (0.14) P<0.0001 vs placebo	DHEA 1.0% N=54 Change: -1.3 (0.14) P=0.0001 vs placebo	Placebo N=53 Change: -0.6 (0.13)
	Labrie, 2010 ⁵⁴ NCT01846442	12 weeks 4-point scale 0 (none) to 3 (severe) Mean (SEM), p-value	DHEA 0.25% N=53 Baseline: 2.4 (0.10) Week 12: 1.2 (0.15) Change: -1.2 (0.14) P=0.002 vs placebo	DHEA 0.50% N=56 Baseline: 2.4 (0.10) Week 12: 0.9 (0.14) Change: -1.5 (0.14) P<0.0001 vs placebo	DHEA 1.0% N=54 Baseline: 2.3 (0.10) Week 12: 1.0 (0.13) Change: -1.3 (0.14) P=0.0001 vs placebo	Placebo N=53 Baseline: 2.3 (0.12) Week 12: 1.7 (0.15) Change: -0.6 (0.13)

Outcome	Author, Year Trial ID	Follow-Up Measurement Tool/Definition Scoring Range Reported Result	Arm 1 Results	Arm 2 Results	Arm 3 Results	Comparator Arm Results
Sexual function	Barton, 2018 ¹³ NCT01376349	12 weeks FSFI total 2 (worst) to 36 (best) Mean (SD), (95% CI), p-value	DHEA 3.25 mg N=123 Baseline: 12.5 (7.9), (11.2, 13.8) 12 weeks: 17.9 (9.6), (16.2, 19.7) Change: 5.5 (7.5), (4.2, 6.8)	DHEA 6.50 mg N=112 Baseline: 11.6 (7.3), (10.4, 12.8) 12 weeks: 19.1 (8.7), (17.5, 20.7) Change: 7.1 (7.3), (5.8, 8.5) P≤0.001 vs placebo	N/A	Placebo N=118 Mean (SD), (95% CI) Baseline: 12.2 (7.5), (11.0, 13.5) 12 weeks: 16.2 (9.3), (14.5, 17.9) Change: 3.8 (7.4), (2.4, 5.1)
	Labrie, 2009 ⁵³ NCT01846442	ASFQ total Unclear Avg % improvement in score	DHEA 0.25% N=53 55% P=0.051 vs placebo	DHEA 0.50% N=56 42% P=0.09 vs placebo	DHEA 1.0% N=54 50% P=0.004 vs placebo	Placebo N=53 Improvement in summary score from baseline NR
	Labrie, 2014 ⁵⁵ NCT01846442	12 weeks ASFQ total Unclear Avg % increase, p- value	DHEA 0.25% N=53 54% P=0.04 vs placebo	DHEA 0.50% N=56 39% P=0.1 vs placebo	DHEA 1.0% N=54 48% P=0.005 vs placebo	Placebo N=53 0.16
	Labrie, 2015 ⁵⁶ NCT02013544	12 weeks FSFI total 2 (worst) to 36 (best) Mean (SEM), p-value	DHEA 0.50% N=300 Baseline: 14.29 (0.37) Week 12: 23.14 (0.47) Change: 8.85 (0.45) P=0.0006 vs placebo	N/A	N/A	Placebo N=149 Baseline: 14.25 (0.53) Week 12: 20.53 (0.69) Change: 6.28 (0.68)
	Panjari, 2009 ⁶⁹ NR	Sabbatsberg Sexual Self-Rating Scale (SSS) 0 (worst) to 84 (best) Mean (SD) Difference between arms (95% CI), p-value	DHEA N=41 Baseline: 25.8 (6.7) Week 26: 32.7 (10.9) Change: 6.9 (11.4)	N/A	N/A	Placebo N=40 Baseline: 25.7 (7.3) Week 26: 29.5 (16.5) Change: 3.9 (13.9) Difference (95% CI): -3.0 (-2.6, 8.7)

Outcome	Author, Year Trial ID	Follow-Up Measurement Tool/Definition Scoring Range Reported Result	Arm 1 Results	Arm 2 Results	Arm 3 Results	Comparator Arm Results
Vaginal atrophy	Archer, 2015 ⁶ NCT01256684	12 weeks Gynecological exam (vaginal smear) N/A Percentage (mean [SE]) of superficial and parabasal cells, p-value	DHEA 0.25% (3.25 mg) N=79 Superficial cells Baseline: 0.68% (0.13%) Week 12: 5.43% (0.57%) Change: 4.75% (0.58%) P<0.0001 vs placebo Parabasal cells Baseline: 65.72% (4.56%) Week 12: 28.43% (3.62%) Change: -37.29% (4.16%) P<0.0001 vs placebo	DHEA 0.50% (6.5 mg) N=81 Superficial cells Baseline: 0.68% (0.12%) Week 12: 6.30% (0.59%) Change: 5.62% (0.61%) P<0.0001 vs placebo Parabasal cells Baseline: 65.05% (4.63%) Week 12: 17.65% (2.87%) Change: -47.40% (4.72%) P<0.0001 vs placebo	N/A	Placebo N=77 Superficial cells Baseline: 0.73% (0.15%) Week 12: 1.64% (0.33%) Change: 0.91% (0.31%) Parabasal cells Baseline: 68.48% (4.41%) Week 12: 66.86% (4.37%) Change: -1.62% (3.22%)

Outcome	Author, Year Trial ID	Follow-Up Measurement Tool/Definition Scoring Range Reported Result	Arm 1 Results	Arm 2 Results	Arm 3 Results	Comparator Arm Results
	Labrie, 2009 ⁵² NCT01846442	12 weeks Gynecological exam (vaginal smear) N/A Percentage (mean [SE]) of superficial and parabasal cells, p-value	DHEA 0.25% N=29 Superficial cells Baseline: 0.4% (0.15%) Week 12: 5.7% (1.33%) Change: 5.3% (1.39%) P=0.009 vs placebo Parabasal cells Baseline: 65.5% (6.92%) Week 12: 16.9% (3.66%) Change: -48.6% (6.78%) P<0.0001 vs placebo	DHEA 0.50% N=30 Superficial cells Baseline: 0.4% (0.11%) Week 12: 5.2% (1.19%) Change: 4.8% (1.20%) P<0.0001 vs placebo Parabasal cells Baseline: 53.4% (7.49%) Week 12: 11.0% (3.43%) Change: -42.4% (7.36%) P<0.0001 vs placebo	DHEA 1.0% N=29 Superficial cells Baseline: 0.4% (0.16%) Week 12: 6.5% (1.53%) Change: 6.1% (1.54%) P=0.0002 vs placebo Parabasal cells Baseline: 61.8% (6.88%) Week 12: 6.90% (1.77%) Change: -54.9% (6.60%) P<0.0001 vs placebo	Placebo N=26 Superficial cells Baseline: 0.6% (0.2%) Week 12: 0.5% (0.19%) Change: -0.1% (0.23%) Parabasal cells Baseline: 46.7% (8.64%) Week 12: 47.8% (7.52%) Change: 1.1% (3.62%)
	Labrie, 2018 ⁵¹ NCT02013544	12 weeks Gynecological exam (vaginal smear) N/A Percentage (mean [SE]) of superficial and parabasal cells, p-value	DHEA 0.50% N=325 Superficial cells Baseline: 1.02% (0.08%) Week 12: 11.22% (0.56%) Change: 10.20% (0.57%) P<0.0001 vs placebo Parabasal cells Baseline: 54.25% (2.14%) Week 12: 12.74% (1.02%) Change: -41.51% (2.01%) P<0.0001 vs placebo	N/A	N/A	Placebo N=157 Superficial cells Baseline: 1.04% (0.11%) Week 12: 2.78% (0.27%) Change: 1.75% (0.27%) Parabasal cells Baseline: 51.66% (3.00%) Week 12: 39.68% (2.68%) Change: -11.98% (2.36%)

Outcome	Author, Year Trial ID	Follow-Up Measurement Tool/Definition Scoring Range Reported Result	Arm 1 Results	Arm 2 Results	Arm 3 Results	Comparator Arm Results
Distress, bother, or interference of GU symptoms	Labrie, 2009 ⁵³ NCT01846442	12 weeks MENQOL total 1 (best) to 8 (worst) Mean (SEM), % decrease, p-value	DHEA 0.25% N=53 Change: -0.83 (0.131), 27% P=0.001 vs placebo	DHEA 0.50% N=56 Change: -0.48 (0.096), 17.5% P=0.07 vs placebo	DHEA 1.0% N=54 Change: -0.64 (0.103), 21% P=0.03 vs placebo	Placebo N=53 Change: -0.28 (0.13), 9.5%
	Labrie, 2014 ⁵⁵ NCT01846442	12 weeks MENQOL total 1 (best) to 8 (worst) Avg % change, p-value	DHEA 0.25% N=53 24% P=0.0006 vs placebo	DHEA 0.50% N=56 18% P=0.1 vs placebo	DHEA 1.0% N=54 20% P=0.01 vs placebo	Placebo N=53 0.088
	Panjari, 2009 ⁶⁹ NR	26 weeks MENQOL total 1 (best) to 8 (worst) Mean (SD) Difference between arms (95% CI), p-value, p-value	DHEA N=43 Baseline: 2.7 (1.1) Week 26: 2.4 (1.2) Change: -0.3 (1.3)	N/A	N/A	Placebo N=42 Baseline: 3.1 (1.1) Week 26: 3.0 (1.2) Change: -0.1 (1.2) Difference (95% CI), p-value: -0.4 (-0.9, 0.1), P=0.1
Psychological symptoms	Labrie, 2009 ⁵³ NCT01846442	12 weeks PGWB total 0 (worst) to 110 (best) Mean (SD), % increase, p-value	DHEA 0.25% N=53 Change: 7.40 (1.69), 9.3%	DHEA 0.50% N=56 Change: 2.92 (1.54), 3.5%	DHEA 1.0% N=54 Change: 3.06 (1.909), 3.9%	Placebo N=53 Change: 0.67 (1.936), 1%
	Panjari, 2009 ⁶⁹ NR	26 weeks PGWB total 0 (worst) to 110 (best) Mean (SD) Difference between arms (95% CI), p-value	DHEA N=43 Baseline: 83.8 (11.8) Week 26: 84.0 (14.7) Change: 0.21 (12.52)	N/A	N/A	Placebo N=42 Baseline: 80.3 (13.9) Week 26: 82.7 (14.1) Change: 2.38 (13.19) Difference (95% CI): -0.9 (-6.1, 4.4)

Abbreviations: ASFQ=Abbreviated Sexual Function Questionnaire; CTCAE=Common Terminology Criteria of Adverse Events; DHEA=dehydroepiandrosterone; FSFI=Female Sexual Function Index; MENQOL=Menopause-Specific Quality of Life; mg=milligrams; N/A=not applicable; PGWB=Psychological General Well-Being Index; SEM=standard error of mean; SSS=Sabbatsberg Sexual Self-Rating Scale

Table C.15. Detailed harms results for studies of DHEA rated low or some concerns ROB

Author, Year Total N* Follow-Up Intervention Vs. Comparator	Outcome	Intervention n (%)	Comparator n (%)
Archer, 2015⁶ N=255 12 weeks 3.25 mg or 6.5 mg DHEA vaginal ovule vs. placebo	Any AE/TEAE	3.25 mg: 48 (55.8) 6.5 mg: 46 (52.9)	35 (43.8)
	SAEs	3.25 mg: 3.5% 6.5 mg: 1.1%	0%
	Discontinuation due to AE	3.25 mg: 4 (4.6) 6.5 mg: 2 (2.3)	1 (1.2)
	Specific AEs	Application site discharge: 3.25 mg: 6 (7.0) 6.5 mg: 5 (5.7) UTI: 3.25 mg: 6 (7.0) 6.5 mg: 5 (5.7) Headache: 3.25 mg: 4 (4.7) 6.5 mg: 5 (5.7)	Application site discharge: 5 (6.3) UTI: 4 (5.0) Headache: 1 (1.3)
	Endometrial safety <i>Endometrial biopsy</i>	Insufficient tissue: 3.25 mg: 2 (8) 6.5 mg: 5 (18)	Insufficient tissue: 2 (7)
Barton, 2018¹³ N=443 12 weeks 3.25 mg or 6.5 mg DHEA vaginal gel vs. placebo	Any AE/TEAE	There were no statistically significant differences between groups in any grade toxicity. Data NR by authors.	--
	SAEs	--	--
	Discontinuation due to AE	3.25 mg: 13 (8.8) 6.5 mg: 17 (11.4)	14 (9.5)
	Specific AEs	Self-reported side effects of voice changes and headaches were statistically significantly worse in the DHEA group(s) compared with placebo	--
	Endometrial safety	--	--
Labrie, 2009⁵² N=216 12 weeks 3.25 mg or 6.5 mg DHEA vaginal ovule vs. placebo	Any AE/TEAE	No AEs on labs (including liver and blood counts), but authors did not provide any data or statistical tests	--
	SAEs	No drug-related SAEs	--
	Discontinuation due to AE	--	--
	Specific AEs	--	--
	Endometrial safety <i>Endometrial biopsy</i>	Data NR by study authors.	--
Labrie, 2018⁵¹ N=558	Any AE/TEAE	179 (47.9)	77 (42.8)
	SAEs	--	--

Author, Year Total N* Follow-Up Intervention Vs. Comparator	Outcome	Intervention n (%)	Comparator n (%)
12 weeks 6.5 mg DHEA vaginal ovule vs. placebo	Discontinuation due to AE	5 (1.5)	3 (1.9)
	Specific AEs	Application site discharge: 23 (6.1) UTI: 17 (4.5) Hot flush: 6 (1.6)	Application site discharge: 10 (5.6) UTI: 5 (2.8) Hot flush: 7 (3.9)
	Endometrial safety <i>Endometrial biopsy</i>	No effect on endometrial histology (data NR by study authors)	--
Panjari, 2009⁶⁸ N=93 52 weeks 50 mg DHEA oral capsule vs. placebo	Any AE/TEAE	31 (5 androgenic AEs, 26 other AEs)	24 (0 androgenic AEs, 24 other AEs)
	SAEs	None	None
	Discontinuation due to AE	6 (2 androgenic AEs, 4 nonandrogenic)	3 (0 androgenic AEs, 3 nonandrogenic)
	Specific AEs	Acne: 3 Increased facial hair: 2	Acne: 0 Increased facial hair: 0
	Endometrial safety <i>TVU (mean mm) in women with a uterus</i>	Baseline: ≤4mm 26, >4 mm 0 52 weeks or exit: ≤4mm 25, >4 mm 1 Breakthrough vaginal bleeding: 3	Baseline: ≤4mm 26, >4 mm 0 52 weeks or exit: ≤4mm 26, >4 mm 0 Breakthrough vaginal bleeding: 2

Abbreviations: AE=adverse event; DHEA=dehydroepiandrosterone; mm=millimeter; NR=not reported; SD=standard deviation; SAE=serious adverse event; TEAE=treatment-emergent adverse event; TVU=transvaginal ultrasound; UTI=urinary tract infection

-- NR

*Includes hysterectomized participants unless otherwise noted

Table C.16. Detailed effectiveness results for studies of oxytocin rated low or some concerns ROB

Outcome	Author, Year Trial ID	Follow-Up Measurement Tool/Definition Scoring Range Reported Result	Arm 1 Results	Arm 2 Results	Arm 3 Results	Comparator Arm Results
Vulvovaginal dryness	Abedi, 2020 ¹ IRCT20160602028220N2	8 weeks FSFI lubrication domain 0 (worst) to 6 (best) Mean (SD), 95% CI	Oxytocin N=44 Baseline: 2.8 (0.85) 8 weeks: 4.53 (0.64) 95% CI 1.07, 1.31	N/A	N/A	Placebo N=42 Baseline: 3.02 (0.58) 8 weeks: 3.48 (0.60)
	Fianu Jonasson, 2020 ³² NR	12 weeks 4-point scale (VVA symptoms self-assessment questionnaire) 0 (none) to 3 (severe) Mean, p-value	Oxytocin gel N=79 Baseline: 2.46 Week 12: 1.30 Change: -1.15 P=0.8 vs comparator	N/A	N/A	Aqueous Hypromellose-based gel N=78 Baseline: 2.18 Week 12: 0.97 Change: -1.21

Outcome	Author, Year Trial ID	Follow-Up Measurement Tool/Definition Scoring Range Reported Result	Arm 1 Results	Arm 2 Results	Arm 3 Results	Comparator Arm Results
Dyspareunia	Abedi, 2020 ¹ IRCT20160602028220N2	8 weeks FSFI pain domain 0 (worst) to 6 (best) Mean (SD), 95% CI	Oxytocin N=44 Baseline: 3.3 (1.15) 8 weeks: 5.53 (0.75) 95% CI 1.59, 2.23	N/A	N/A	Placebo N=42 Baseline: 3.07 (0.77) 8 weeks: 3.62 (0.72)
	Fianu Jonasson, 2020 ³² NR	12 weeks 4-point scale (VVA symptoms self- assessment questionnaire) 0 (none) to 3 (severe) Mean, p-value	Oxytocin gel N=79 Baseline: 2.54 Week 12: 1.62 Change: -0.88 P=0.4 vs comparator	N/A	N/A	Aqueous Hypromellose- based gel N=78 Baseline: 2.41 Week 12: 1.41 Change: -1.05
	Zohrabi, 2020 ⁹⁰ IRCT20160602028220N2	8 weeks Study checklist Unclear Subjective symptom severity, n (%), p-value	Oxytocin N=44 Baseline: Negative: 2 (4.5) Mild: 13 (29.5) Moderate: 14 (31.8) Severe: 15 (34.1) P=0.5 vs placebo 8 weeks: Negative: 39 (88.6) Mild: 5 (11.4) Moderate: 0 Severe: 0 P<0.001 vs placebo	N/A	N/A	Placebo N=42 Baseline: Negative: 2 (4.8) Mild: 12 (28.6) Moderate: 9 (21.4) Severe: 19 (45.2) 8 weeks: Negative: 3 (7.1) Mild: 19 (45.2) Moderate: 13 (31.0) Severe: 7 (16.7)
Vulvovaginal discomfort or irritation	Zohrabi, 2020 ⁹⁰ IRCT20160602028220N2	8 weeks Study checklist Unclear Mean (SD), p-value	Oxytocin N=44 Baseline: 6.2 (2.67) 8 weeks: 0.38 (0.96) P=0.0001 vs placebo	N/A	N/A	Placebo N=42 Baseline: 6.54 (2.82) 8 weeks: 4.9 (2.9)
Change in MBS (Unspecified)	Fianu Jonasson, 2020 ³² NR	12 weeks 4-point scale (VVA symptoms self- assessment questionnaire) 0 (none) to 3 (severe) Mean, p-value	Oxytocin gel N=79 Baseline: 2.61 Week 12: 1.44 Change: -1.16 P=0.4 vs comparator	N/A	N/A	Aqueous Hypromellose- based gel N=78 Baseline: 2.45 Week 12: 1.17 Change: -1.28

Outcome	Author, Year Trial ID	Follow-Up Measurement Tool/Definition Scoring Range Reported Result	Arm 1 Results	Arm 2 Results	Arm 3 Results	Comparator Arm Results
Sexual function	Abedi, 2020 ¹ IRCT20160602028220N2	8 weeks FSFI total 2 (worst) to 36 (best) Mean (SD), 95% CI	Oxytocin N=44 Baseline: 17.35 (3.4) 8 weeks: 24.19 (2.56) 95% CI 4.03, 6.35	N/A	N/A	Placebo N=42 Baseline: 17.66 (2.78) 8 weeks: 19.00 (2.84)
Vaginal atrophy	Fianu Jonasson, 2020 ³² NR	12 weeks Vaginal cytology N/A Average % of superficial cells, p- value	Oxytocin gel N=79 Baseline: 0.25 Week 12: 4.03 Change: 3.77 P=0.5 vs comparator	N/A	N/A	Aqueous Hypromellose- based gel N=78 Baseline: 0.45 Week 12: 2.38 Change: 1.94
	Zohrabi, 2020 ⁹⁰ IRCT20160602028220N2	8 weeks VMI N/A Mean (SD), p-value	Oxytocin N=44 Superficial cells Baseline: 0.59 (1.38) P=0.3 vs placebo Week 8: 38.7 (7.18) P=0.0001 vs placebo Intermediate cells Baseline: 14.54 (8.53) P=0.26 vs placebo Week 8: 27.56 (5.77) P=0.0001 vs placebo Parabasal cells Baseline: 84.8 (9.18) P=0.35 vs place	N/A	N/A	Placebo N=42 Superficial cells Baseline: 0.35 (0.79) Week 8: 3.69 (2.76) Intermediate cells Baseline: 16.6 (8.59) Week 8: 19.07 (8.56) Parabasal cells Baseline: 83.02 (8.57) Week 8: 77.23 (8.97) VMI Baseline: 8.58 (4.35) Week 8: 13.25 (5.06)

Abbreviations: FSFI=Female Sexual Function Index; N/A=not applicable; SD=standard deviation; VMI=Vaginal Maturation Index; VVA=vulvovaginal atrophy

Table C.17. Detailed harms results for studies of oxytocin rated low or some concerns ROB

Author, Year Total N* Follow-Up Intervention Vs. Comparator	Outcome	Intervention n (%)	Comparator n (%)
Fianu Jonasson, 2020 N=161 12 weeks 400 IU oxytocin gel vs. placebo gel	Any AE/TEAE	32 (39.5)	27 (33.8)
	SAEs	1	0
	Discontinuation due to AE	3	0
	Specific AEs	Most frequent AEs reported: vaginal discharge, UTI, vaginal odor (data NR by study authors)	--
	Endometrial safety <i>TVU measuring thickness</i>	"no safety or tolerability concerns were identified"	--
Zohrabi, 2020 N=96 8 weeks 400 IU oxytocin gel vs. placebo gel	Any AE/TEAE	--	--
	SAEs	--	--
	Discontinuation due to AE	1	1
	Specific AEs	--	--
	Endometrial safety	--	--

Abbreviations: AE=adverse event; IU=international unit; NR=not reported; SD=standard deviation; SAE=serious adverse event; TEAE=treatment-emergent adverse event; TVU=transvaginal ultrasound; UTI=urinary tract infection

-- NR

*Includes hysterectomized participants unless otherwise noted

Table C.18. Detailed effectiveness results for studies of SERMs rated low or some concerns ROB

Outcome	Author, Year Trial ID	Follow-Up Measurement Tool/Definition Scoring Range Reported Result	Arm 1 Results	Arm 2 Results	Arm 3 Results	Comparator Arm Results
Vulvovaginal dryness	Archer, 2019 ⁴ NCT02638337	12 weeks FSFI lubrication domain 0 (worst) to 6 (best) LSM (SE)	Ospemifene N=313 1.29 (0.12)	N/A	N/A	Placebo N=314 Change: 0.89 (0.12) Difference of LSM (95% CI) 0.40 (0.07, 0.73) P=0.02
	Archer, 2019 ⁴ NCT02638337	12 weeks 4-point scale 0 (none) to 3 (severe) Mean (SD), OR (95% CI), p-value	Ospemifene N=313 Change: -1.29 (1.01) OR (95% CI) 2.23 (1.62, 3.06) P<0.0001 vs placebo	N/A	N/A	Placebo N=314 Change: -0.91 (0.96)

Outcome	Author, Year Trial ID	Follow-Up Measurement Tool/Definition Scoring Range Reported Result	Arm 1 Results	Arm 2 Results	Arm 3 Results	Comparator Arm Results
	Bachmann, 2010 ⁸ NCT00276094	12 weeks 4-point scale 0 (none) to 3 (severe) Mean	Ospemifene 30 mg N=282 Change: -1.22 P=0.04 vs placebo	Ospemifene 60 mg N=276 Change: -1.26 P=0.02 vs 60 mg	N/A	Placebo N=268 Change: -0.84
	Kessel, 2003 ⁴⁶ NR	6 months SAQ: How frequently did you notice dryness? 0 (very much) to 3 (not at all) Mean (SD), p-value	Raloxifene N=39 Change: 0.77 (1.13) P=0.4 vs placebo	N/A	N/A	Placebo N=43 Change: 0.98 (1.28)
	Parsons, 2003 ⁷² NR	3 months 4-point scale 0 (none) to 3 (severe)	Raloxifene + NHM N=46 See figure 1 - mean change is presented graphically, values not provided	Raloxifene + CEC N=44 See figure 1 - mean change is presented graphically, values not provided	Placebo + NHM N=43 See figure 1 - mean change is presented graphically, values not provided	Placebo + CEC N=45 See figure 1 - mean change is presented graphically, values not provided
	Pinkerton, 2003 ⁷⁴ NR	6 months 4-point scale 0 (none) to 3 (severe)	Raloxifene N=43 See figure 1B - mean change is presented graphically, values not provided	N/A	N/A	Placebo N=44 See figure 1B - mean change is presented graphically, values not provided
	Portman, 2014 ⁷⁷ NCT00729469	12 weeks 4-point scale 0 (none) to 3 (severe) Mean (SD) change, p-value	Ospemifene N=160 Change: -1.3 (1.08) P=0.08 vs placebo	N/A	N/A	Placebo N=154 Change: -1.1 (1.02)
Vulvovaginal discomfort or irritation	Archer, 2019 ⁴ NCT02638337	12 weeks 4-point scale 0 (none) to 3 (severe) Mean (SD), p-value	Ospemifene N=313 Change: -1.4 (1.0)	N/A	N/A	Placebo N=314 Change: -1.4 (1.0) OR (95% CI) 1.03 (0.65, 1.64) P=0.9

Outcome	Author, Year Trial ID	Follow-Up Measurement Tool/Definition Scoring Range Reported Result	Arm 1 Results	Arm 2 Results	Arm 3 Results	Comparator Arm Results
	Parsons, 2003 ⁷² NR	3 months 4-point scale 0 (none) to 3 (severe)	Raloxifene + NHM N=46 See figure 1 - mean change is presented graphically, values not provided	Raloxifene + CEC N=44 See figure 1 - mean change is presented graphically, values not provided	Placebo + NHM N=43 See figure 1 - mean change is presented graphically, values not provided	Placebo + CEC N=45 See figure 1 - mean change is presented graphically, values not provided
	Pinkerton, 2003 ⁷⁴ NR	6 months 4-point scale 0 (none) to 3 (severe)	Raloxifene N=43 See figure 1B - mean change is presented graphically, values not provided	N/A	N/A	Placebo N=44 See figure 1B - mean change is presented graphically, values not provided
Dysuria	Parsons, 2003 ⁷² NR	3 months 4-point scale 0 (none) to 3 (severe)	Raloxifene + NHM N=46 See figure 1 - mean change is presented graphically, values not provided	Raloxifene + CEC N=44 See figure 1 - mean change is presented graphically, values not provided	Placebo + NHM N=43 See figure 1 - mean change is presented graphically, values not provided	Placebo + CEC N=45 See figure 1 - mean change is presented graphically, values not provided
	Pinkerton, 2003 ⁷⁴ NR	6 months 4-point scale 0 (none) to 3 (severe)	Raloxifene N=43 See figure 1B - mean change is presented graphically, values not provided	N/A	N/A	Placebo N=44 See figure 1B - mean change is presented graphically, values not provided
Dyspareunia	Archer, 2019 ⁴ NCT02638337	12 weeks FSFI pain domain 0 (worst) to 6 (best) LSM (SE), 95% CI, p-value	Ospemifene N=313 1.47 (0.12)	N/A	N/A	Placebo N=314 Change: 1.01 (0.12) Difference of LSM (95% CI) 0.45 (0.11, .080) P=0.01
	Archer, 2019 ⁴ NCT02638337	12 weeks 4-point scale 0 (none) to 3 (severe) Mean (SD), OR (95% CI), p-value	Ospemifene N=313 -1.6 (1.0)	N/A	N/A	Placebo N=314 Change: -1.2 (1.1) OR (95% CI) 1.97 (1.35, 2.88) P=0.0004

Outcome	Author, Year Trial ID	Follow-Up Measurement Tool/Definition Scoring Range Reported Result	Arm 1 Results	Arm 2 Results	Arm 3 Results	Comparator Arm Results
	Bachmann, 2010 ⁸ NCT00276094	12 weeks 4-point scale 0 (none) to 3 (severe) Mean, p-value	Ospemifene 30 mg N=282 Change: -1.02 P-value NS vs placebo	Ospemifene 60 mg N=276 Change: -1.19 P=0.023 vs placebo	N/A	Placebo N=268 Change from baseline unclear
	Kessel, 2003 ⁴⁶ NR	6 months SAQ: Did you feel pain on penetration? 0 (very much) to 3 (not at all) Mean (SD), p-value	Raloxifene N=39 Change: 0.77 (0.93) P=0.8 vs placebo	N/A	N/A	Placebo N=43 Change: 0.86 (1.00)
	Parsons, 2003 ⁷² NR	3 months 4-point scale 0 (none) to 3 (severe)	Raloxifene + NHM N=46 See figure 1 - mean change is presented graphically, values not provided	Raloxifene + CEC N=44 See figure 1 - mean change is presented graphically, values not provided	Placebo + NHM N=43 See figure 1 - mean change is presented graphically, values not provided	Placebo + CEC N=45 See figure 1 - mean change is presented graphically, values not provided
	Pinkerton, 2003 ⁷⁴ NR	6 months 4-point scale 0 (none) to 3 (severe)	Raloxifene N=43 See figure 1B - mean change is presented graphically, values not provided	N/A	N/A	Placebo N=44 See figure 1B - mean change is presented graphically, values not provided
	Portman, 2013 ⁷⁶ NCT00729469	12 weeks 4-point scale 0 (none) to 3 (severe) Mean (SD) change, p-value	Ospemifene N=303 Change: -1.5 (1.1) P=0.0001 vs placebo	N/A	N/A	Placebo N=302 Change: -1.2 (1.1)
Sexual function	Archer, 2019 ⁴ NCT02638337	12 weeks FSFI total 2 (worst) to 36 (best) LSM (SE), difference (95% CI), p-value	Ospemifene N=313 Change: 5.7 (0.6)	N/A	N/A	Placebo N=314 Change: 4.1 (0.5) Difference of LSM (95% CI) 1.6 (0.08, 3.09) P=0.04

Outcome	Author, Year Trial ID	Follow-Up Measurement Tool/Definition Scoring Range Reported Result	Arm 1 Results	Arm 2 Results	Arm 3 Results	Comparator Arm Results
	Constantine, 2015 ¹⁹ NCT00729469	12 weeks FSFI total 2 (worst) to 36 (best) LSM	Ospemifene N=463 Change: 6.69 P<0.001 vs placebo	N/A	N/A	Placebo N=456 Change: 4.14
	Kessel, 2003 ⁴⁶ NR	3 months SAQ 3 domain scores Increase indicates improvement Domain scores: mean baseline and change at 6 months	Raloxifene N=39 Pleasure Baseline: 11.80 Change: 1.00 Discomfort Baseline: 3.20 Change: 1.54 Habit Baseline: -0.02 Change: 0.10	N/A	N/A	Placebo N=43 Pleasure Baseline: 10.46 Change: 0.00 Discomfort Baseline: 2.85 Change: 1.74 Habit Baseline: -0.02 Change: -0.07
Vaginal atrophy	Bachmann, 2010 ⁸ NCT00276094	12 weeks Vaginal smear N/A Mean (SD) % of superficial and parabasal cells, % change, p-value	Ospemifene 30 mg N=282 Superficial cells Baseline: 1.3% (2.9%) Change: 7.8% P<0.001 vs placebo Parabasal cells Baseline: 40.1% (38.3%) Change: 21.9% P<0.001 vs placebo	Ospemifene 60 mg N=276 Superficial cells Baseline: 1.0 (3.4) Change: 10.8% P<0.001 vs placebo Parabasal cells Baseline: 39.3 (39.0) Change: 30.1% P<0.001 vs placebo	N/A	Placebo N=268 Superficial cells Baseline: 0.9 (2.6) Change: 2.2% Parabasal cells Baseline: 38.5 (37.6) Change: 3.98%
	Goldstein, 2019 ³⁸ NCT02638337	12 weeks VHI 5 (worst) to 25 (best) LSM (SD), difference (95% CI), p-value	Ospemifene N=277 Change: 5.16 (0.21)	N/A	N/A	Placebo N=278 Change: 2.33 (0.21) Difference in LSM change (95% CI) 2.83 (2.25, 3.41) P<0.0001

Outcome	Author, Year Trial ID	Follow-Up Measurement Tool/Definition Scoring Range Reported Result	Arm 1 Results	Arm 2 Results	Arm 3 Results	Comparator Arm Results
	Parsons, 2003 ⁷² NR	3 months 4-point scale; 5 domains of vaginal atrophy + global score, objective evaluation at 3 months 0 (none) to 3 (severe) Mean (SD) percent change from baseline, p-value	Raloxifene + NHM N=46 Rugal atrophy: -25.8, P<0.05 vs R + CEC Pallor: -31.7 (49.0), P<0.05 vs R + CEC Petechiae: -44.9 (639), P<0.05 vs R + CEC Mucosal thinning: -26.0 (64.4), P<0.05 vs R + CEC Dryness: -31.7 (52.0) Global score: -32.9 (38.8), P<0.05 vs R + CEC	Raloxifene + CEC N=44 Rugal atrophy: -45.9 (41.1), P<0.05 vs R + NHM Pallor: -48.3 (45.7), P<0.05 vs R + NHM Petechiae: -75.0 (43.0), P<0.05 vs R + NHM Mucosal thinning: - 46.0 (53.1), P<0.05 vs R + NHM Dryness: -45.3 (49.4) Global score: -49.2 (36.7), P<0.05 vs R + NHM	Placebo + NHM N=43 Rugal atrophy: -20.2 (52.4), P<0.05 vs P + CEC Pallor: -35.9 (58.3), P<0.05 vs P + CEC Petechiae: -39.1 (62.1), P<0.05 vs P + CEC Mucosal thinning: - 29.5 (51.5), P<0.05 vs P + CEC Dryness: -39.3 (54.6), P<0.05 vs P + CEC Global score: -30.3 (41.3), P<0.05	Placebo + CEC N=45 Rugal atrophy: -48.3 (34.4), P<0.05 vs P + NHM Pallor: -44.2 (47.2), P<0.05 vs P + NHM Petechiae: -75.0 (64.8), P<0.05 vs P + NHM Mucosal thinning: -61.7 (39.4), P<0.05 vs P + NHM Dryness: -55.3 (54.5) Global score: -55.3 (32.8), P<0.05 vs P + NHM
	Parsons, 2003 ⁷² NR	VMV, 3 month change 0 (worst) to 100 (best), p-value	Raloxifene + NHM N=46 Change: 9.2 (22.3)	Raloxifene + CEC N=44 Change: 23.9 (32.5) P<0.05 vs Raloxifene + NHM	Placebo + NHM N=43 Change: 2.3 (26.5)	Placebo + CEC N=45 Change: 23.2 (30.9) P<0.05 vs Placebo + NHM
	Simon, 2013 ⁸⁵ NCT01585558	52 weeks Visual evaluation of the vagina (4-point scale) 0 (none) to 3 (severe) Mean (SD) change	Ospemifene 30 mg N=49 Petechiae: -0.8 (0.85) Pallor: -1.3 (0.74) Friability: -0.9 (0.91) Vaginal dryness in mucosa: -1.7 (0.96) Vaginal redness in mucosa: -0.8 (0.96)	Ospemifene 60 mg N=58 Petechiae: -0.7 (0.91) Pallor: -1.2 (1.15) Friability: -0.7 (0.95) Vaginal dryness in mucosa: -1.4 (1.06) Vaginal redness in mucosa: -0.6 (1.03)	N/A	Placebo N=35 Petechiae: -0.4 (0.73) Pallor: -0.6 (1.03) Friability: -0.5 (0.92) Vaginal dryness in mucosa: -1.1 (1.02) Vaginal redness in mucosa: -0.5 (1.07)
Distress, bother, or interference of GU symptoms	Bachmann, 2010 ⁹ NR	12 weeks MENQOL total 1 (best) to 8 (worst) Adjusted mean change, p-value	BZA 20 mg N=110 Change: -0.37 P<0.05 vs placebo	BZA 20 mg/CE 0.45 mg N=219 Change: -1.09 P≤0.001 vs placebo, P<0.001 vs BZA 20 mg	BZA 20 mg/CE 0.625 mg N=218 Change: -1.18, P≤0.001 vs placebo, P<0.001 vs BZA 20 mg	Placebo N=105 Change: -0.67

Outcome	Author, Year Trial ID	Follow-Up Measurement Tool/Definition Scoring Range Reported Result	Arm 1 Results	Arm 2 Results	Arm 3 Results	Comparator Arm Results
Treatment satisfaction	Bachmann, 2010 ⁹ NR	12 weeks MS-TSQ 0 (worst) to 4 (best) % of subjects reporting overall satisfaction at week 12, p-value	BZA 20 mg N=110 40.4% P<0.05 vs placebo	BZA 20 mg/CE 0.45mg N=219 62.6% P<0.05 vs placebo, P<0.001 vs BZA 20 mg	BZA 20 mg/CE 0.625 mg N=218 69.4% P<0.001 vs placebo, P<0.001 vs BZA 20 mg	Placebo N=105 0.474
	Archer, 2019 ⁴ NCT02638337	12 weeks 5-point scale (very satisfied to very dissatisfied); 0-100 at Week 12 0 (worst) to 4 (best) % per category, p- value	Ospemifene N=221 Very/Moderately Satisfied: 69.7, P=0.0007 vs placebo Equally Satisfied & Dissatisfied: 19.5 Moderately/Very Dissatisfied: 10.9	N/A	N/A	placebo N=198 Very/Moderately Satisfied: 53.5 Equally Satisfied & Dissatisfied: 24.7 Moderately/Very Dissatisfied: 21.7
	Parsons, 2003 ⁷² NR	3 months Treatment satisfaction 1 (worst) to 7 (best)	Raloxifene + NHM N=46 “At baseline, there was no significant difference between any of the treatment groups in the overall satisfaction score. The median across treatment groups was 4.00, indicating neutral to mild satisfaction. After 3 months, median overall satisfaction values increased by 1.00 from baseline across treatment groups, indicating improvement (P<.03). There were no significant differences between raloxifene and placebo treatment”	Raloxifene + CEC N=44	Placebo + NHM N=43	Placebo + CEC N=45

Abbreviations: BZA=bazedoxifene; CEC=conjugated estrogen cream; FSFI=Female Sexual Function Index; ITT=intention to treat; LSM=least squares means; MENQoL=Menopause-Specific Quality of Life; mg=milligrams; MS-TSQ=Menopause Symptoms Treatment Satisfaction Questionnaire; N/A=not applicable; NHM=non-

hormonal moisturizer; SAQ=Sexual Activity Questionnaire; SD=standard deviation; SE=standard error; TEAE=Treatment emergent adverse effect; VHI=Vaginal Health Index; VMV=Vaginal Maturation Value

Table C.19. Detailed harms results for studies of SERMs rated low or some concerns ROB

Author, Year Total N* Follow-Up Intervention Vs. Comparator	Outcome	Intervention n (%)	Comparator n (%)
Archer, 2019⁴ N=627 12 weeks 60 mg ospemifene tablet vs. placebo	Any AE/TEAE	112 (35.3)	103 (33.2)
	SAEs	5 (1.6)	3 (1.0)
	Discontinuation due to AE	5 (1.6)	3 (1.0)
	Specific AEs	Hot flushes: 20 (6.3) UTI: 7 (2.2) Headache: 5 (1.6)	Hot flushes: 8 (2.6) UTI: 10 (3.2) Headache: 7 (2.3)
	Endometrial safety <i>Biopsy in participants with a uterus and TVU (mean mm [SD] change from baseline to 12 weeks)</i>	Active proliferation: 5 (5.6) Atrophy: 24 (26.7) Inactive: 24 (26.7) Weakly proliferative: 11 (12.2) Unsatisfactory biopsy: 25 (27.8) Change in thickness: 0.63 (1.59) Vaginal bleeding: 4 (1.3)	Active proliferation: 0 (0) Atrophy: 59 (66.3) Inactive: 5 (5.6) Weakly proliferative: 1 (1.1) Unsatisfactory biopsy: 24 (27.0) Mean change in mm: -0.23 (0.85) Vaginal bleeding: 1 (0.3)
Bachmann, 2010^{8, 85} N=826, 180 12 and 52 weeks 30 mg or 60 mg ospemifene tablet vs. placebo	Any AE/TEAE	12 weeks: 30 mg: 182 (64.5) 60 mg: 164 (59.4) 52 weeks: 30 mg: 38 (61.3) 60 mg: 44 (63.8)	12 weeks: 140 (52.2) 52 weeks: 22 (44.9)
	SAEs	12 weeks: 30 mg: 5 (1.8) 60 mg: 0 (0) 52 weeks: 30 mg: 2 (3.2) 60 mg: 5 (7.2)	12 weeks: 4 (1.5) 52 weeks: 1 (2.0)
	Discontinuation due to AE	12 weeks: 30 mg: 15 (5.3) 60 mg: 13 (4.7) 52 weeks: 30 mg: 3 (4.8) 60 mg: 4 (5.8)	12 weeks: 13 (4.9) 52 weeks: 1 (2.0)

Author, Year Total N* Follow-Up Intervention Vs. Comparator	Outcome	Intervention n (%)	Comparator n (%)
	Specific AEs	<p>12 weeks:</p> <p>Hot flashes:</p> <p>30 mg: 27 (9.6)</p> <p>60 mg: 23 (8.3)</p> <p>UTI:</p> <p>30 mg: 13 (4.6)</p> <p>60 mg: 20 (7.2)</p> <p>Headache:</p> <p>30 mg: 17 (6.0)</p> <p>60 mg: 7 (2.5)</p> <p>52 weeks:</p> <p>Hot flashes:</p> <p>30 mg: 2 (3.2)</p> <p>60 mg: 5 (7.2)</p> <p>UTI:</p> <p>30 mg: 4 (6.5)</p> <p>60 mg: 6 (8.7)</p>	<p>12 weeks:</p> <p>Hot flashes: 9 (3.4)</p> <p>UTI: 6 (2.2)</p> <p>Headache: 14 (5.2)</p> <p>52 weeks:</p> <p>Hot flashes: 2 (4.1)</p> <p>UTI: 4 (8.2)</p>
	Endometrial safety <i>Biopsy at 52 weeks (n=133) and TVU (mean mm [SD] change from baseline to 12 [n=826] and 52 weeks [129])</i>	<p>Atrophic/inactive/insufficient:</p> <p>30 mg: 44 (95)</p> <p>60 mg: 53 (96.4)</p> <p>Weakly proliferative:</p> <p>30 mg: 1 (2.2)</p> <p>60 mg: 1 (1.8)</p> <p>Atypical epithelial proliferation:</p> <p>30 mg: 1 (2.2)</p> <p>60 mg: 0</p> <p>Proliferative pattern, disordered type:</p> <p>30 mg: 0</p> <p>60 mg: 1 (1.8)</p> <p>Hyperplasia or carcinoma:</p> <p>30 mg: 0</p> <p>60 mg: 0</p> <p><i>Change in thickness after 12 weeks:</i></p> <p>30 mg: 0.42 (1.35)</p> <p>60 mg: 0.72 (1.59)</p> <p><i>After 52 weeks (30 mg n=46, 60 mg n=53):</i></p> <p>30 mg: 0.68 (2.57)</p> <p>60 mg: 1.14 (1.56)</p>	<p>Atrophic/inactive/insufficient: 32 (100)</p> <p>Weakly proliferative: 0</p> <p>Atypical epithelial proliferation: 0</p> <p>Proliferative pattern, disordered type: 0</p> <p>Hyperplasia or carcinoma: 0</p> <p><i>After 12 weeks: -0.02 (1.03)</i></p> <p><i>After 52 weeks (n=30): -0.04 (1.15)</i></p>
	Any AE/TEAE	308 (84.6)	47 (75.8)

Author, Year Total N* Follow-Up Intervention Vs. Comparator	Outcome	Intervention n (%)	Comparator n (%)
Goldstein, 2014³⁹ N=426 (all with intact uterus) 52 weeks	SAEs	18 (4.9)	4 (6.5)
	Discontinuation due to AE	49 (13.5)	6 (9.7)
	Specific AEs	UTI: 61 (16.8) Hot flush: 46 (12.6)	UTI: 15 (24.2) Hot flush: 4 (6.5)
	Endometrial safety <i>Biopsy and TVU (mean mm [SD] change from baseline to 52 weeks)</i>	Atrophic: 267 (86.1) Inactive: 1 (0.3) Weakly proliferative: 7 (2.3) Active proliferative: 3 (1.0) Hyperplasia: 1 (0.3) Change in thickness: 0.75 (1.5)	Atrophic: 45 (80.4) Inactive: 0 (0) Weakly proliferative: 0 (0) Active proliferative: 0 (0) Hyperplasia: 0 (0) Change in thickness: 0.17 (1.3)
Portman, 2013⁷⁶ N=314 12 weeks	Any AE/TEAE	186 (61.4)	154 (51.0)
	SAEs	4 (1.3)	4 (1.3)
	Discontinuation due to AE	14 (4.6)	10 (3.3)
	Specific AEs	Hot flushes: 20 (6.6) UTI: 17 (5.6) Vaginal candidiasis: 14 (4.6) Vaginal discharge: 14 (4.6) Vulvar and vaginal mycotic infection: 13 (4.3) Headache: 10 (3.3)	Hot flushes: 13 (4.3) UTI: 11 (3.6) Vaginal candidiasis: 1 (0.3) Vaginal discharge: 2 (0.7) Vulvar and vaginal mycotic infection: 1 (0.3) Headache: 12 (4.0)
	Endometrial safety <i>Biopsy and TVU (mean mm [SD] change from baseline to 12 weeks)</i>	"No cases of endometrial hyperplasia, polyps, or cancer were observed" (data NR by authors) Change in thickness: 0.40 (1.25)	"No cases of endometrial hyperplasia, polyps, or cancer were observed" Change in thickness: 1.10 (1.29)
Portman, 2014⁷⁷ N=605 12 weeks	Any AE/TEAE	104 (65)	78 (50.6)
	SAEs	2 (1.3)	3 (1.9)
	Discontinuation due to AE	12 (7.5)	5 (3.2)
	Specific AEs	--	--
	Endometrial safety <i>Biopsy and TVU (mean mm [SD] change from baseline to 12 weeks)</i>	"No cases of endometrial hyperplasia, endometrial polyps, or carcinoma were observed" (data NR by authors) Change in thickness: 0.82 (1.68)	"No cases of endometrial hyperplasia, endometrial polyps, or carcinoma were observed" Change in thickness: -0.11 (1.20)
Kagan, 2010⁴⁴ N=215† (all with intact uterus) 12 weeks	Any AE/TEAE	90 (81.8)	75 (71.4)
	SAEs	2 (0.9)	4 (3)
	Discontinuation due to AE	8 (7.3)	7 (6.7)
	Specific AEs	Accidental injury: 12 (10.9) Migraine: 2 (1.8) Vasodilation: 17 (15.5)	Accidental injury: 2 (1.9) Migraine: 7 (6.7) Vasodilation: 4 (3.8)

Author, Year Total N* Follow-Up Intervention Vs. Comparator	Outcome	Intervention n (%)	Comparator n (%)
		Vaginitis: 7 (6.4)	Vaginitis: 1 (1.0)
	Endometrial safety <i>Biopsy and TVU</i>	Data NR by study authors	Data NR by study authors
Pinkerton, 2003⁷⁴ N=91 (all with intact uterus) 6 months	Any AE/TEAE	--	--
	SAEs	--	--
	Discontinuation due to AE	2	2
	Specific AEs	--	--
	Endometrial safety <i>Biopsy and TVU</i>	“No hyperplasia, carcinoma, or clinically significant endometrial proliferation” in both groups (data NR by study authors) No statistically significant difference in endometrial thickness between groups (data NR by authors)	--

Abbreviations: AEs=adverse event; NR=not reported; SAE=serious adverse event; SD=standard deviation; TEAE=treatment-emergent adverse event; TVU=transvaginal ultrasound; UTI=urinary tract infection

-- NR

*Includes hysterectomized participants unless otherwise noted

†Total N only includes bazedoxifene and placebo arms from Bachmann (2010),⁹ which reported results for Kagan (2010).⁴⁴

Table C.20. Detailed effectiveness results for studies of testosterone rated low or some concerns ROB

Outcome	Author, Year Trial ID	Follow-Up Measurement Tool/Definition Scoring Range Reported Result	Arm 1 Results	Arm 2 Results	Arm 3 Results	Comparator Arm Results
Vulvovaginal dryness	Davis, 2018 ²¹ ACTRN12615000083 594	26 weeks FSFI lubrication domain 0 (worst) to 6 (best) Median (IQR), p-value	Testosterone N=21 Change: 0.6 (0, 2.4) P=0.046 vs placebo	N/A	N/A	Placebo N=16 Change: 0 (-0.15, 1.35) Linear regression of difference (Week 26 – Week 0) (95% CI), p-value: 0.7 (-0.21, 1.72), P=0.1

Outcome	Author, Year Trial ID	Follow-Up Measurement Tool/Definition Scoring Range Reported Result	Arm 1 Results	Arm 2 Results	Arm 3 Results	Comparator Arm Results
	Fernandes, 2014 ²⁹ U1111–11255434	12 weeks FSFI lubrication domain 0 (worst) to 6 (best) Mean (SD), p-value	Testosterone N=19 Baseline: 1.6 (1.6) Week 12: 3.9 (2.7) intergroup differences P=0.03	Estrogen N=18 Baseline: 1.5 (2.0) Week 12: 2.8 (2.9) intergroup differences P=0.5	Polyacrylic Acid N=19 Baseline: 2.9 (2.2) Week 12: 4.4 (2.4) intergroup differences P=0.002	Placebo N=20 Baseline: 1.9 (1.6) Week 12: 2.88 (2.2)
	Tungmunsakulchai, 2015 ⁸⁹ NCT01724658	8 weeks FSFI lubrication domain 0 (worst) to 6 (best) Mean, p-value	Testosterone N=35 Baseline: 3.27 Week 8: 5.08 P=0.3 vs placebo at 8 weeks	N/A	N/A	Placebo N=35 Baseline: 2.80 Week 8: 4.64
Dyspareunia	Davis, 2018 ²¹ ACTRN12615000083 594	26 weeks FSFI pain domain 0 (worst) to 6 (best) Median (IQR) change, linear regression of difference (95%) p- value	Testosterone N=21 Change: 1.2 (0, 3.2) P=0.4 vs placebo	N/A	N/A	Placebo N=16 Change: 0.4 (0, 1.4) Linear regression of difference (Week 26 – Week 0) (95% CI), p-value: 0.76 (-0.48, 2.00), P=0.2
	Fernandes, 2014 ²⁹ U1111–11255434	12 weeks FSFI pain domain 0 (worst) to 6 (best) Mean (SD), p-value	Testosterone N=19 Baseline: 1.5 (1.6) Week 12: 4.3 (2.6) intergroup differences P=0.01	Estrogen N=18 Baseline: 1.3 (2.0) Week 12: 3.0 (2.9) intergroup differences P=0.6	Polyacrylic Acid N=19 Baseline: 2.6 (2.1) Week 12: 4.3 (2.6) intergroup differences P=0.03	Placebo N=20 Baseline: 2.1 (2.1) Week 12: 3.1 (2.4)
	Tungmunsakulchai, 2015 ⁸⁹ NCT01724658	8 weeks FSFI pain domain 0 (worst) to 6 (best) Mean, p-value	Testosterone N=35 Baseline: 3.03 Week 8: 5.36 P=0.2 vs placebo at 8 weeks	N/A	N/A	Placebo N=35 Baseline: 2.85 Week 8: 4.88

Outcome	Author, Year Trial ID	Follow-Up Measurement Tool/Definition Scoring Range Reported Result	Arm 1 Results	Arm 2 Results	Arm 3 Results	Comparator Arm Results
Sexual function	Chaikittisilpa, 2019 ¹⁴ TCRT20180423001	8 weeks FSFI total 2 (worst) to 36 (best) Mean (SD), p-value	Testosterone N=32 Baseline: 19.5 (5.2), P=1.0 vs placebo 8 weeks: 26.9 (5.0), P=0.04 vs placebo Change: 7.2 (5.5), P=0.02 vs placebo	N/A	N/A	Placebo N=33 Baseline: 19.6 (4.1) 8 weeks: 24.1 (5.5) Change: 4.6 (3.9)
	Davis, 2018 ²¹ ACTRN12615000083 594	26 weeks FSFI satisfaction domain 0.8 (worst) to 6 (best) Median (IQR) change, linear regression of difference (95%) p- value	Testosterone N=21 Change: 1.2 (0.4, 2.0) P=0.046 vs placebo	N/A	N/A	Placebo N=16 Change: 0.6 (0, 1.4) Linear regression of difference (Week 26 – Week 0) (95% CI), p-value: 0.73 (0.02, 1.43), P=0.04
	Davis, 2018 ²¹ ACTRN12615000083 594	26 weeks FSDS-R total 0 (best) to 52 (worst) Median (IQR) change, linear regression of difference (95%) p- value	Testosterone N=21 Change: -9 (-13, -1) P=0.2 vs placebo	N/A	N/A	Placebo N=16 Placebo Change: -4 (-8, 0) Linear regression of difference (Week 26 – Week 0) (95% CI), p-value: -10.28 (- 18.89, -1.67), P=0.02
	Fernandes, 2014 ²⁹ U1111–11255434	12 weeks FSFI total 2 (worst) to 36 (best) Mean (SD), p-value	Testosterone N=19 Baseline: 9.9 (6.8) Week 12: 24.9 (12.0) intergroup differences P=0.003	Estrogen N=18 Baseline: 12.7 (10.1) Week 12: 18.2 (13.0) intergroup differences P=0.2	Polyacrylic Acid N=19 Baseline: 18.5 (10.5) Week 12: 23.4 (10.3) intergroup differences P=0.007	Placebo N=20 Baseline: 13.1 (9.0) Week 12: 15.8 (10.0)

Outcome	Author, Year Trial ID	Follow-Up Measurement Tool/Definition Scoring Range Reported Result	Arm 1 Results	Arm 2 Results	Arm 3 Results	Comparator Arm Results
	Melisko, 2017 ⁵⁹ NCT00698035	12 weeks Cancer Rehab Evaluation System (CARES) 0 (best) to 4 (worst) Mean (SD)	Testosterone N=30 Sexual interest subscale: Baseline: 1.4 (0.8) Week 12: 1.0 (0.6) Sexual dysfunction subscale: Baseline: 2.9 (0.8) Week 12: 1.9 (1.1) Single-item sexual satisfaction score: Baseline: 3.2 (1.6) Week 12: 4.0 (1.5)	N/A	N/A	Estradiol N=32 Sexual interest subscale: Baseline: 1.2 (0.9) Week 12: 0.9 (0.7) Sexual dysfunction subscale: Baseline: 2.9 (1.1) Week 12: 2.0 (1.1) Single-item sexual satisfaction score: Baseline: 2.5 (1.6) Week 12: 4.0 (1.5)
	Penteado, 2008 ⁷³ Trial ID NR	12 months Study interviews Lower=worse Mean (SD), p-value	EP + A N=27 Orgasm Baseline: 3.70 (4.28) 12 months: 20.33 (19.72) Sexual desire Baseline: 3.70 (3.72) 12 months: 9.04 (2.70) Sexual excitation Baseline: 3.63 (3.76) 12 months: 9.00 (2.77) Vaginal dryness (%) Baseline: 81 12 months: 19, P<0.01, $\chi^2=21.41$ compared to	N/A	N/A	EP N=24 Orgasm Baseline: 7.71 (11.80) 12 months: 23.71 (46.11) Sexual desire Baseline: 4.60 (4.36) 12 months: 7.24 (3.64) Sexual excitation Baseline: 4.84 (4.22) 12 months: 7.32 (3.63) Vaginal dryness (%) Baseline: 67 12 months: 21

Outcome	Author, Year Trial ID	Follow-Up Measurement Tool/Definition Scoring Range Reported Result	Arm 1 Results	Arm 2 Results	Arm 3 Results	Comparator Arm Results
	Penteado, 2008 ⁷³ Trial ID NR	12 months Patient monthly calendars 0 (worse) to >1 (best) n (%) by orgasmic capacity (OC) category; OC=ratio between avg monthly frequency of orgasms and the avg monthly frequency of sexual relations	EP + A N=27 Baseline to 12 months 0: 10 (37.0%) to 5 (18.0%) 0 < OC < 1: 14 (51.9%) to 4 (14.8%) 1: 1 (3.7%) to 12 (44.4%) >1: 2 (7.4%) to 6 (22.2%)	N/A	N/A	EP N=24 Baseline to 12 months 0: 7 (29.2%) to 3 (12.0%) 0 < OC < 1: 14 (58.3%) to 12 (50.0%) 1: 2 (8.3%) to 6 (25.0%) >1: 1 (4.2%) to 3 (12.5%)
	Penteado, 2008 ⁷³ Trial ID NR	12 months Sexual Energy Scale, perception of effect of treatment N/A n (%) by category	EP + A N=29 worse: 0 no change: 6 (20.7) slight improvement: 2 (6.9) moderate improvement: 1 (3.4) much improvement: 10 (34.5) complete relief of all problems: 10 (34.5)	N/A	N/A	EP N=27 worse: 0 no change: 9 (33.3) slight improvement: 6 (22.2) moderate improvement: 5 (18.5) much improvement: 4 (14.8) complete relief of all problems: 3 (11.1)
	Tungmunsakulchai, 2015 ⁸⁹ NCT01724658	8 weeks FSFI total 2 (worst) to 36 (best) Mean (SD)	Testosterone N=35 Baseline: 18.5 (5.8) Week 8: 28.6 (3.6) P=0.2 vs placebo at baseline P=0.04 vs placebo at 8 weeks	N/A	N/A	Placebo N=35 Baseline: 16.3 (7.0) Week 8: 25.3 (6.7)

Outcome	Author, Year Trial ID	Follow-Up Measurement Tool/Definition Scoring Range Reported Result	Arm 1 Results	Arm 2 Results	Arm 3 Results	Comparator Arm Results
Vaginal atrophy	Melisko, 2017 ⁵⁹ NCT00698035	12 weeks Gynecological exam (4-point scale) 0 (none) to 3 (severe) Baseline to Week 12, Mean (SD) change, p- value	Testosterone N=34 Rugae: 1.5 to 0.9, - 0.71 (0.84), P<0.001 Pallor: 1.5 to 0.7, - 0.91 (0.75), P<0.001 Petechiae: 1.1 to 0.5, -0.74 (1.38), P=0.01 Elasticity: 1.2 to 0.4, -0.88 (0.64), P<0.001 Dryness: 1.5 to 0.8, -0.71 (0.91), P<0.001	N/A	N/A	Estradiol N=35 Rugae: 1.6 to 0.6, - 1.03 (0.80), P<0.001 Pallor: 1.4 to 0.6, - 0.88 (0.84), P<0.001 Petechiae: 1.1 to 0.1, -1.0 (1.07), P<0.001 Elasticity: 0.9 to 0.3, -0.62 (0.49), P<0.001 Dryness: 1.5 to 0.5, -1.03 (0.80), P<0.001

Abbreviations: CI=confidence interval; FSDS-R=Female Sexual Distress Scale-Revised; FSFI=Female Sexual Function Index; IQR=interquartile range; N/A=not applicable; SD=standard deviation

Table C.21. Detailed harms results for studies of testosterone rated low or some concerns ROB

Author, Year Total N Follow-Up Intervention Vs. Comparator	Outcome	Intervention n (%)	Comparator n (%)
Chaikittisilpa, 2019¹⁴ N=70 8 weeks 1 mg estradiol oral tablet + 50 mg testosterone transdermal gel OR placebo gel	Any AE/TEAE	--	--
	SAEs	Authors state there were no SAEs	--
	Discontinuation due to AE	2 (5.7)	2 (5.7)
	Specific AEs	Acne: 42.4%	Acne: 29.0%
	Endometrial safety TVU	Vaginal bleeding: 2 Endometrial thickness increased in both groups (NS difference). Authors did not detect any serious endometrial pathology	Vaginal bleeding: 2
Fernandes, 2018³⁰ N=40 [†] (all with intact uterus) 12 weeks 300 mcg testosterone cream (1 g) vs. lubricant	Any AE/TEAE	Women who used topical testosterone did not show androgenic side effects such as acne, increased hair growth, and clitoral hypertrophy	No AEs reported
	SAEs	--	--
	Discontinuation due to AE	--	--
	Specific AEs	--	--

Author, Year Total N Follow-Up Intervention Vs. Comparator	Outcome	Intervention n (%)	Comparator n (%)
	Endometrial safety TVU (<i>mean [SD] mm</i>)	Baseline: 2.8 (1.2) Week 12: 2.5 (0.6) P=0.6 vs. placebo Vaginal bleeding: 0	Baseline: 2.5 (1.0) Week 12: 2.6 (2.1) Vaginal bleeding: 0
Melisko, 2017⁵⁹ N=76 12 weeks 1% testosterone vaginal cream (0.5 g) vs. 7.5 mcg estradiol vaginal ring	Any AE/TEAE	--	--
	SAEs	--	--
	Discontinuation due to AE	1	1
	Specific AEs	Vaginal discharge: 2 Facial hair growth: 5 Vaginal or vulvar itching and/or irritation: 0 Vaginal odor: 3 Urinary tract or yeast infection: 3	Vaginal discharge: 4 Facial hair growth: 1 Vaginal or vulvar itching: 4 Vaginal odor: 0 Urinary tract or yeast infection: 1
	Endometrial safety	--	--
Raghunandan, 2010⁷⁸ N=50† 12 weeks 2% testosterone vaginal gel (0.5 g) + 0.625 mg estrogen vaginal cream (1 g) vs. placebo	Any AE/TEAE	--	--
	SAEs	--	--
	Discontinuation due to AE	--	--
	Specific AEs	"Local testosterone therapy was not associated with side effects like acne, hirsutism, weight gain, and voice change."	"No adverse effects"
	Endometrial safety TVU (<i>mean [SD] mm</i>)	Baseline: 2.74 (0.17) Week 12: 2.72 (0.16) Mean change: 0.72 p-value vs. placebo NS	Baseline: 2.75 (0.13) Week 12: 2.76 (0.17) Mean change: 0.36
Tungmunsakulchai, 2015⁸⁹ N=70 8 weeks 1 mg oral estrogen + 40 mg oral testosterone OR placebo	Any AE/TEAE	--	--
	SAEs	Authors state there were no SAEs	--
	Discontinuation due to AE	--	--
	Specific AEs	Acne: 6 (17.6) Hirsutism: 3 (8.8) Vaginal bleeding: 0 (0)	Acne: 5 (14.2) Hirsutism: 3 (8.5) Vaginal bleeding: 0 (0)
	Endometrial safety	--	--

Abbreviations: AE=adverse effect; g=gram; mcg=microgram; mm=millimeter; NR=not reported; NS=not significant; SAE=serious adverse event; SD=standard deviation; TEAE=treatment-emergent adverse event; TVU=transvaginal ultrasound

-- NR

*Route of delivery for testosterone + estrogen vs. estrogen alone comparison is either transdermal testosterone gel + oral estrogen tablet¹⁴ or oral testosterone + oral estrogen.⁸⁹

†Total N includes only testosterone + estrogen and placebo arms from Raghunandan (2010).⁷⁸ See Table C.13 for estrogen alone arm results.

‡Total N includes only testosterone and placebo arms from Fernandes (2018),³⁰ which reports safety outcomes for Fernandes (2014).²⁹ See Table C.13 and Table C.23 for conjugated estrogens cream and polyacrylic acid cream arm results, respectively.

Table C.22. Detailed effectiveness results for studies of non-hormonal moisturizers rated low or some concerns ROB

Outcome	Author, Year Follow-Up	Measurement Tool/Definition	Intervention N Randomized	Comparator N Randomized	Reported Results
Vulvovaginal dryness	Fernandes, 2014 ²⁹ 12 weeks	FSFI lubrication domain Mean (SD) change from baseline	Polyacrylic acid cream n=20 Baseline: 2.9 (2.2) Week 12: 4.4 (2.4)	Placebo n=20 Baseline: 1.9 (1.6) Week 12: 2.88 (2.2)	Between-group mean change from baseline: NR. Between group change p=0.002
	Lee, 2011 ⁵⁷ 12 weeks	VAS (dryness with pain) Mean (SD) change from baseline	Lactic acid gel n=49 VAS dryness/pain: Baseline: 8.2 (0.8) 12 weeks: 4.2 (1.4)	Placebo gel n=49 VAS dryness/pain: Baseline: 7.9 (0.9) 12 weeks: 6.5 (1.5)	Dryness: Between-group mean change from baseline: NR. EPC calculated: I: -3.97 C: -1.41 Between group change p=0.001
	Mitchell, 2018 ⁶² 12 weeks	FSFI lubrication domain Mean (95% CI) change from baseline	Vaginal moisturizing gel n=100 Baseline: 2.2 (1.9 to 2.4) Week 12 minus baseline: 0.9 (0.6 to 1.3)	Placebo n=100 Baseline: 2.2 (2.0 to 2.5) Week 12 minus baseline: 1.2 (0.8 to 1.6)	Week 12 minus baseline difference: 0.2 (-0.8 to 0.3) p=0.54
	Nappi, 2022 ⁶⁴ 12 weeks	VRS Dryness Score 1. Proportion of subjects having a reduction ≥ 1 point from baseline to 3 months (adjusted mixed model) 2. Absolute change from baseline between groups	Hyaluronic acid gel n=46 89.8% (95% CI: 76.8-95.9%)	Water-based lubricant N=34 79.7% (95% CI: 61.62-90.57%)	VRS Dryness: 1. Compare proportions improved: p=0.229 (NS) 2. Absolute change from baseline between groups (range -3 to +1 points): p=.0023 <i>"in favor of the hyaluronic acid treatment"</i>
Dyspareunia	Fernandes, 2014 ²⁹	FSFI pain domain Mean (SD) change from baseline	Polyacrylic acid cream n=20 Baseline: 2.6 (2.1) Week 12: 4.3 (2.6)	Placebo n=20 Baseline: 2.1 (2.1) Week 12: 3.1 (2.4)	Between-group mean change from baseline: NR. Between group change p=0.033

Outcome	Author, Year Follow-Up	Measurement Tool/Definition	Intervention N Randomized	Comparator N Randomized	Reported Results
	Lee, 2011 ⁵⁷ 12 weeks	VAS (dyspareunia) Mean (SD) change from baseline	Lactic acid gel n=49 Baseline: 8.2 (1.0) 12 weeks: 5.5 (1.1)	Placebo gel n=49 Baseline: 8.1 (1.0) 12 weeks: 6.1 (1.4)	Between-group mean change from baseline: NR. EPC calculated: I: -2.75 C: -2.0 Between group change p=0.040
	Mitchell, 2018 ⁶² 12 weeks	FSFI pain domain Mean (95% CI) change from baseline	Vaginal moisturizing gel n=100 Baseline: 1.4 (1.2 to 1.7) Week 12 minus baseline: 1.0 (0.7 to 1.4)	Placebo n=100 Baseline: 1.8 (1.5 to 2.1) Week 12 minus baseline: 0.9 (0.5 to 1.4)	Week 12 minus baseline difference: 0.1 (-0.4 to 0.7) p=0.76
	Nappi, 2022 ⁶⁴ 12 weeks	FSFI Pain Domain Change from baseline at 1- and 3-months	Hyaluronic acid gel n=46 NR	Water-based lubricant n=34 NR	Results reported in supplementary material only, which we were unable to obtain.
Sexual function	Fernandes, 2014 ²⁹	FSFI total score Mean (SD) change from baseline	Polyacrylic acid cream n=20 Baseline: 18.5 (10.5) Week 12: 23.4 (10.3)	Placebo n=20 Baseline: 13.1 (9.0) Week 12: 15.8 (10.0)	Between-group mean change from baseline: NR. Between group change p=0.007
	Mitchell, 2018 ⁶² 12 weeks	FSFI total score Mean (95% CI) change from baseline	Vaginal moisturizing gel n=100 Baseline: 15.1 (13.7 to 16.5) Week 12 minus baseline: 3.1 (1.7 to 4.5)	Placebo n=100 Baseline: 16.1 (14.6 to 17.5) Week 12 minus baseline: 3.1 (1.7 to 4.5)	Week 12 minus baseline difference: -1.3 (-3.5 to 0.8) p=0.17
	Nappi, 2022 ⁶⁴ 12 weeks	FSDS-R Change from baseline at 1- and 3-months	Hyaluronic acid gel n=46 NR	Water-based lubricant n=34 NR	<i>"At 3-months FSDS-R improved compared to baseline only in group A (within group p=0.026) [Hyaluronic acid]; no significant differences observed between groups."</i>

Outcome	Author, Year Follow-Up	Measurement Tool/Definition	Intervention N Randomized	Comparator N Randomized	Reported Results
Satisfaction with treatment	Mitchell, 2018 ⁶² 12 weeks	Satisfaction with treatment received (Likert scale: 0=not satisfied to 10=completely satisfied) Mean (SD)	Vaginal moisturizing gel n=100 7.7 (3.2)	Placebo n=100 8.1 (3.0)	"Mean (SD) treatment satisfaction was similar between groups"
	Nappi, 2022 ⁶⁴ 12 weeks	Patients global assessment of overall satisfaction, 4-pt scale	Hyaluronic acid gel n=46 NR	Water-based lubricant n=34 NR	"Overall, patients highly satisfied with treatment" (Results reported in supplementary material only, which was not able to be obtained by review authors.)
Change in most bothersome symptom	Mitchell, 2018 ⁶² 12 weeks	Change in severity of most bothersome symptom between enrollment and 12 weeks Mean (95% CI)	Vaginal moisturizing gel n=100 Baseline: 2.5 (2.3 to 2.6) Week 12 minus baseline: -1.2 (-1.4 to -1.0)	Placebo n=100 Baseline: 2.5 (2.4 to 2.6) Week 12 minus baseline: -1.3 (-1.5 to -1.10)	Week 12 minus baseline difference: 0.2 (-0.1 to 0.4) p=0.31
Vaginal atrophy	Lee, 2011 ⁵⁷ 12 weeks	pH indicator strip VHI VMI Mean (SD)	Lactic acid gel n=49 <i>pH</i> Baseline: 6.49 (1.08) Week 12: 5.00 (0.82) <i>VHI</i> Baseline: 15.78 (3.71) Week 12: 21.05 (3.91) <i>VMI</i> : Baseline: 45.48 (3.49) Week 12: 51.18 (3.75)	Placebo gel n=49 <i>pH</i> Baseline: 6.22 (1.09) Week 12: 5.69 (0.95) <i>VHI</i> Baseline: 14.27 (3.74) Week 12: 16.98 (3.88) <i>VMI</i> : Baseline: 46.42 (3.71) Week 12: 47.87 (2.73)	pH: P<0.001 VHI: P<0.001 VMI: P<0.001 All comparisons of week 12 measurements

Outcome	Author, Year Follow-Up	Measurement Tool/Definition	Intervention N Randomized	Comparator N Randomized	Reported Results
	Mitchell, 2018 ⁶² 12 weeks	Vaginal cytology (pH ≤/≥5, superficial cells ≤/≥5%) N (%)	Vaginal moisturizing gel n=100 <i>pH</i> Baseline: ≤5: 12 (12) >5: 87 (87) Week 12: Change from >5 to ≤5: 8 (9) <i>Superficial</i> Baseline: ≤5%: 78 (78) >5%: 11 (11) Missing: 11 (11) Week 12: Change from ≤5% to >5%: 8 (11)	Placebo n=100 <i>pH</i> Baseline: ≤5: 9 (9) >5: 90 (90) Week 12: Change from >5 to ≤5: 10 (12) <i>Superficial</i> Baseline: ≤5%: 81 (81) >5%: 7 (7) Missing: 12 (12) Week 12: Change from ≤5% to >5%: 8 (11)	pH: P=0.1 Superficial: P=0.95
	Nappi, 2022 ⁶⁴ 12 weeks	pH test strip (Mild=5-5.49, Moderate=5.5-6.49, Severe>6.5) VHI score change from baseline to 3 months (5=worst to 25=best) Mean (SD) Median (range)	Hyaluronic acid gel n=46 <i>Change of pH categories</i> -3: 1 (2.2) -2: 4 (8.7) -1: 19 (41.3) 0: 16 (34.8) 1: 6 (13.0) 2: 0 <i>VHI Score change</i> 4.4 (2.62) 4.5 (-1.0, 9.0)	Water-based lubricant n=34 <i>Change of pH categories:</i> -3: 0 -2: 1 (2.9) -1: 2 (5.9) 0: 27 (79.4) 1: 3 (8.8) 2: 1 (2.9) <i>VHI Score change</i> 1.5 (1.60) 1.0 (-2.0, 5.0)	P<0.0001

Abbreviations: C=comparator; CI=confidence interval; EPC=Evidence-Based Practice Center; FSFI=Female Sexual Function Index; I=intervention; NR=not reported; SD=standard deviation; VAS=Visual Analog Scale; VRS=Verbal Rating Scale

Table C.23. Detailed harms results for studies of non-hormonal moisturizers rated low or some concerns ROB

Author, Year Total N Follow-Up Intervention Vs. Comparator	Outcome	Intervention n (%)	Comparator n (%)
Fernandes, 2014²⁹ N=40* 12 weeks	Any AE/TEAE	"No adverse events reported in either arm."	--
	SAEs	--	--
	Discontinuation due to AE	0	0

Author, Year Total N Follow-Up Intervention Vs. Comparator	Outcome	Intervention n (%)	Comparator n (%)
Polyacrylic acid cream vs. lubricant	Specific AEs	--	--
Lee, 2011 ⁵⁷ N=98 12 weeks Lactic acid gel vs. placebo gel	Any AE/TEAE	19 (38.8)	16 (32.7)
	SAEs	0 "major complications"	0 "major complications"
	Discontinuation due to AE	2	2
	Specific AEs	Irritation/burning: n=18, P=0.3 vs. placebo Itching: n=8, P=0.1 vs. placebo Vaginal discharge: n=5, P=0.5 vs. placebo	Irritation/burning: n=13 Itching: n=3 Vaginal discharge: n=3
Mitchell, 2018 ⁶² N=200 [†] 12 weeks Vaginal moisturizer vs. placebo	Any AE/TEAE	Any MedDRA-classified AE: 53 (53) Any study questionnaire AE: 22 (22)	Any MedDRA-classified AE: 46 (46) Any study questionnaire AE: 24 (24)
	SAEs	--	--
	Discontinuation due to AE	--	--
	Specific AEs	Vaginal candidiasis: 3 (3) Vaginal discharge: 5 (5) Vaginal odor: 1 (1) Vulvovaginal burning: 6 (6) Vulvovaginal itching: 6 (6) UTI: 7 (7) GI signs/symptoms: 7 (7)	Vaginal candidiasis: 2 (2) Vaginal discharge: 2 (2) Vaginal odor: 5 (5) Vulvovaginal burning: 1 (1) Vulvovaginal itching: 2 (2) UTI: 4 (4) GI signs/symptoms: 6 (6)
Nappi, 2022 ⁶⁴ N=80 12 weeks Hyaluronic acid-based vaginal gel vs. water-based lubricant	Any AE/TEAE	"5 AEs were reported in 4 patients, one of moderate intensity and the others considered mild."	--
	SAEs	"No severe AE was reported, and no AE was considered as related to the study device by the investigators."	--
	Discontinuation due to AE	--	--
	Specific AEs	--	--

Abbreviations: AE=adverse effect; MedDRA=Medical Dictionary for Regulatory Activities; NR=not reported; SAE=serious adverse effect; TEAE=treatment-emergent adverse effect; UTI=urinary tract infection

-- NR

*Total N includes only polyacrylic acid cream and placebo arms from Fernandes (2014).²⁹ See Table C.13 for conjugated estrogens cream arm results and Table C.21 for testosterone arm results.

[†]Total N includes only vaginal moisturizer and placebo arms from Mitchell (2018).⁶² See Table C.13 for estradiol arm results.

Table C.24. Detailed effectiveness results for studies of CO₂ lasers rated low or some concerns ROB

Outcome	Author, Year Trial ID	Follow-Up Measurement Tool/Definition Scoring Range Reported Result	Arm 1 Results	Comparator Arm Results
Vulvovaginal dryness	Page, 2022 ⁶⁶ NCT04021966	3 months VAS (10 point; 0=no symptoms) Mean change (SD)	CO₂ Laser N=29 -0.69 (4.07)	Sham Laser N=29 -0.00 (4.27) P>0.05 for change between groups
	Li, 2021 ⁵⁸ ACTRN1261600 1403426	12 months VAS (100 point; 0=no symptoms) Mean change (95% CI) and mean difference between groups at 12 months	CO₂ Laser N=38 -18.0 (-38.6, 2.5)	Sham Laser N=40 -12.0 (-38.3, 14.4) Difference Between Groups -6.1 (-38.5, 26.3); P=0.54
	Salvatore, 2021 ⁸⁰ NCT03754205	4 months VAS (10 point; 0=no symptoms) Mean change (SD)	CO₂ Laser N=28 -5.6 (2.6)	Sham Laser N=30 -1.9 (2) P<0.001 for change between groups
	Salvatore, 2021 ⁸⁰ NCT03754205	4 months FSFI Lubrication Domain Mean change (SD)	CO₂ Laser N=28 2.5 (2.0)	Sham Laser N=30 0.7 (1.2) P=0.005 for change between groups
	Ruanphoo, 2020 ⁷⁹ TCTR201606270 02	3 months ICIQ-VS (One question about dryness) Median (IQR) at 3 months	CO₂ Laser N=44 3.24 (0.00-4.00)	Sham Laser N=44 2.00 (0.26-4.00) P=0.56 between groups
	Eftekhari, 2020 ²⁶ IRCT201609160 29835N3	6 months FSFI Lubrication Domain Mean (SD) at 6 months	CO₂ Laser N=25 3.09 (0.61)	Vaginal Conjugated Estrogen Cream N=25 3.0 (0.83) P=0.73 between groups
	Paraiso, 2020 ⁷¹ NCT02691936	6 months VAS (10 cm; 0=no symptoms) Mean (SD) difference from baseline	CO₂ Laser N=30 -5.48 (2.68)	Vaginal Conjugated Estrogen Cream N=32 -5.76 (2.48) P=0.67 for difference between groups

Outcome	Author, Year Trial ID	Follow-Up Measurement Tool/Definition Scoring Range Reported Result	Arm 1 Results	Comparator Arm Results
		6 months FSFI Lubrication Domain Mean (SD) difference from baseline	CO₂ Laser N=33 0.11 (1.2)	Vaginal Conjugated Estrogen Cream N=29 0.35 (1.4) P=0.50 for difference between groups
	Alvisi, 2022 ⁹¹ NR	3 months VAS (10 point; 0=no symptoms) Mean change (95% CI)	CO₂ Laser N=25 -3.3 (-4.4, -2.3)	CO₂ Laser + Hyaluronic Acid Gel N=25 -2.6 (-3.7, -1.6) P>0.05 between groups
	Alvisi, 2022 ⁹¹ NR	3 months FSFI Lubrication Domain Mean (95% CI) at 3 months	CO₂ Laser N=12 0.5 (-0.2, 1.2)	CO₂ Laser + Hyaluronic Acid Gel N=13 1.0 (0.3, 1.7)
Vaginal/vulvar irritation	Page, 2022 ⁶⁶ NCT04021966	3 months VAS (10 point; 0=no symptoms) Mean change (SD)	CO₂ Laser N=29 Burning domain -1.03 (2.85) Itching domain -0.24 (2.76)	Sham Laser N=29 Burning domain -1.38 (3.77) Itching domain -1.55 (1.84) P>0.05 between groups for burning and itching
	Li, 2021 ⁵⁸ ACTRN1261600 1403426	12 months VAS (100 point; 0=no symptoms) Mean (95% CI) at 3, 6, and 12 months post-baseline and mean difference in change from baseline to 12 months	CO₂ Laser Burning: N=42 3 months 15 (9, 21) N=42 6 months 19 (10, 27) N=38 12 months 9 (4, 13) Mean difference (95%CI) at 12 months -21.9 (- 45.7, 1.9) Itching: N=42 3 months 12 (7, 18) N=42 6 months 13 (6, 19) N=38 12 months 6 (2, 10) Mean difference (95%CI) at 12 months -15.4 (- 34.6, 3.7)	Sham Laser Burning: N=41 3 months 14 (8, 19) N=40 6 months 21 (12, 30) N=40 12 months 17 (9, 24) Mean difference (95%CI) at 12 months -16.0 (- 45.6, 13.6) Mean difference between groups -5.9 (-42.7, 30.9); P=0.46 Itching: N=41 3 months 18 (12, 24) N=40 6 months 16 (9, 23) N=40 12 months 14 (8, 19) Mean difference (95%CI) at 12 months -8.3 (- 24.8, 8.3) Mean difference between groups -7.2 (-31.7, 17.4); P=0.16

Outcome	Author, Year Trial ID	Follow-Up Measurement Tool/Definition Scoring Range Reported Result	Arm 1 Results	Comparator Arm Results
	Salvatore, 2021 ⁸⁰ NCT03754205	4 months VAS (10 points; 0=no symptoms) Mean (SD) change	CO₂ Laser N=28 Burning -2.3 (2.8) Itching -2.9 (2.8)	Sham Laser N=30 Burning -1 (1.9); P=0.014 between groups Itching -1.4 (1.9); P=0.015 between groups
	Paraiso, 2020 ⁷¹ NCT02691936	6 months VAS (10 point; 0=no symptoms) Mean (SD) change	CO₂ Laser N=30 Itching: -1.84 (3.01) Irritation: -3.29 (3.73)	Vaginal Conjugated Estrogen Cream N=32 Itching: -1.24 (2.96) P=0.45 between groups Irritation: -3.49 (3.19) P=0.87 between groups
	Alvisi, 2022 ⁹¹ NR	3 months VAS (10 point; 0=no symptoms) Mean (95% CI)) change	CO₂ Laser N=25 Burning: -2.3 (-3.4, -1.3) Itching: -1.4 (-2.4, -0.5)	CO₂ Laser + Hyaluronic Acid Gel N=25 Burning: -2.1 (-3.2, -1.1) Itching: -1.4 (-2.4, -0.5); P>0.05 between groups
Dysuria	Page, 2022 ⁶⁶ NCT04021966	3 months VAS (10 points; 0=no symptoms) Mean (SD) change	CO₂ Laser N=29 -0.62 (2.54)	Sham Laser N=29 -0.43 (2.73) P>0.05 for change between groups
	Li, 2021 ⁵⁸ ACTRN1261600 1403426	12 months VAS (100 points; 0=no symptoms) Mean (95% CI) at 3, 6, and 12 months post-baseline and mean difference in change from baseline to 12 months	CO₂ Laser N=42 3 months 7 (2, 12) N=42 6 months 9 (3, 14) N=38 12 months 4 (0, 7) Mean difference (95%CI) at 12 months -11.4 (- 26.6, 3.8)	Sham Laser N=41 3 months 7 (3, 11) N=40 6 months 4 (2, 5) N=40 12 months 8 (3, 12) Mean difference (95% CI) at 12 months 2.2 (- 9.3, 13.7) Difference in change between groups (95% CI) -13.6 (-32.2, 5.1); P=0.34
	Salvatore, 2021 ⁸⁰ NCT03754205	4 months VAS (10 point; 0=no symptoms) Mean (SD) change	CO₂ Laser N=28 -0.9 (2.1)	Sham Laser N=30 -0.3 (1.5) P=0.181 for change between groups
	Alvisi, 2022 ⁹¹ NR	3 months VAS (10 point; 0=no symptoms) Mean (95% CI)) change	CO₂ Laser N=25 -0.1 (-0.8, 0.5)	CO₂ Laser + Hyaluronic Acid Gel N=25 -0.4 (-1.0, 0.2)

Outcome	Author, Year Trial ID	Follow-Up Measurement Tool/Definition Scoring Range Reported Result	Arm 1 Results	Comparator Arm Results
Dyspareunia	Page, 2022 ⁶⁶ NCT04021966	3 months VAS (10 points; 0=no symptoms) Mean (SD) change	CO₂ Laser N=29 -2.31 (4.51)	Sham Laser N=29 -2.17 (3.45) P>0.05 for change between groups
	Li, 2021 ⁵⁸ ACTRN1261600 1403426	12 months VAS (100 point; 0=no symptoms) Mean change (95% CI) and mean difference between groups at 12 months	CO₂ Laser N=38 -28.8 (-67.6, 10.0)	Sham Laser N=40 -4.0 (-35.3, 27.4) Difference in change between groups -24.9 (-73.3, 23.6); P=0.75
	Salvatore, 2021 ⁸⁰ NCT03754205	4 months VAS (10 point; 0=no symptoms) Mean change (SD)	CO₂ Laser N=28 -6.0 (2.6)	Sham Laser N=30 -1.1 (1.8) P<0.001 for change between groups
	Salvatore, 2021 ⁸⁰ NCT03754205	4 months FSFI Pain Domain Mean change (SD)	CO₂ Laser N=28 3.1 (2.0)	Sham Laser N=30 0.4 (1.1) P<0.001 for change between groups
	Eftekhari, 2020 ²⁶ IRCT201609160 29835N3	6 months FSFI Pain Domain Mean (SD) at 6 months	CO₂ Laser N=25 4.4 (0.88)	Vaginal Conjugated Estrogen Cream N=25 3.69 (0.86) P=0.007 between groups
	Paraiso, 2020 ⁷¹ NCT02691936	6 months FSFI Pain Domain Mean (SD) change	CO₂ Laser N=33 -0.59 (2.8)	Vaginal Conjugated Estrogen Cream N=29 -0.04 (3.3) P=0.81 for differences between groups
	Alvisi, 2022 ⁹¹ NR	3 months FSFI Pain Domain Mean (95% CI)) change	CO₂ Laser N=12 0.7 (0.0, 1.5)	CO₂ Laser + Hyaluronic Acid Gel N=13 1.3 (0.6, 2.0) ADD P>0.05??>
Sexual function	Page, 2022 ⁶⁶ NCT04021966	3 months FSFI Total (score<26.55=dysfun ction) Mean (SD) change	CO₂ Laser N=29 3.51 (6.22)	Sham Laser N=29 3.14 (7.71) P>0.05 for change St groups

Outcome	Author, Year Trial ID	Follow-Up Measurement Tool/Definition Scoring Range Reported Result	Arm 1 Results	Comparator Arm Results
	Salvatore, 2021 ⁸⁰ NCT03754205	4 months FSFI Total (score <26.55=dysfunction) Mean (SD) change	CO₂ Laser N=28 12.3 (8.9)	Sham Laser N=30 2.4 (4.9) P=0.001 for change between groups
	Eftekhari, 2020 ²⁶ IRCT201609160 29835N3	6 months FSFI Total (score <27=dysfunction) Mean (SD) at 6 months	CO₂ Laser N=25 23.16 (4.87)	Vaginal Conjugated Estrogen Cream N=25 18.97 (4.54) P=0.003 between groups
	Paraiso, 2020 ⁷¹ NCT02691936	6 months FSFI Total Mean (SD) change	CO₂ Laser N=30 1.7 (6.7)	Vaginal Conjugated Estrogen Cream N=32 4.9 (8.3) P=0.1 for change between groups
	Alvisi, 2022 ⁹¹ NR	3 months FSFI Total (score < 26.5=dysfunction) Mean (95% CI) change	CO₂ Laser N=12 3.7 (0.5, 6.8)	CO₂ Laser + Hyaluronic Acid Gel N=13 3.5 (0.4, 6.5) P>0.05 between groups
	Eftekhari, 2021 ²⁷ IRCT201907080 44143N1	3 months PISQ-12 (Physical Behavior) 5-point Likert scale (never to always) Mean (SD) at 3 months	CO₂ Laser N=78 10.5 (4.2) Change Between Groups Radiofrequency vs Laser P<.0001 Radiofrequency vs Placebo P=0.04 Laser vs Placebo P<0.001	Radiofrequency N=80 16.3 (2.9) Placebo* N=79 14.5 (2.7)
Distress, bother, or interference of GU symptoms	Page, 2022 ⁶⁶ NCT04021966	3 months ICIQ-OAB (range 0 to 16) Mean (SD) change	CO₂ Laser N=29 -0.55 (1.76)	Sham Laser N=29 -0.31 (1.91) P>0.05 for change between groups

Outcome	Author, Year Trial ID	Follow-Up Measurement Tool/Definition Scoring Range Reported Result	Arm 1 Results	Comparator Arm Results
	Li, 2021 ⁵⁸ ACTRN1261600 1403426	12 months FSSQ (range 5 to 54; 5=lowest sexual satisfaction) Mean (95% CI) at 6 and 12 months post-baseline and mean difference in change from baseline to 12 months	CO₂ Laser N=23 6 months: 23 [18, 28] N=19 12 months: 24 [18, 30] Mean difference at 12 months (95% CI) 4.7 (-10.6, 20.0)	Sham Laser N=20 6 months: 24 [19, 30] N=23 12 months: 21 [17, 25] Mean difference at 12 months (95% CI): 1.9 (-11.5, 15.4) Mean difference (95% CI) between groups: 2.8 (-1.0, 22.5); P=0.67
	Li, 2021 ⁵⁸ ACTRN1261600 1403426	12 months AQoL-6D (range 0 to 100; 0=worst QoL) Mean (95% CI) at 6 and 12 months post-baseline and mean difference in change from baseline to 12 months	N=42 6 months: 78 (74, 82) N=38 12 months: 81 (78, 84) Mean difference after 12 months: 6.3 (95% CI -1.3, 13.8)	N=40 6 months: 81 (79, 84) N=40 12 months: 78 (74, 83) Mean difference after 12 months: 1.4 (95% CI -3.4, 6.2) Mean difference (95% CI) between groups: 4.8 (-3.9, 13.8); P=0.58
	Salvatore, 2021 ⁸⁰ NCT03754205	4 months UDI-6 (range 0 to 100; higher score=more intense symptoms) Mean (SD) change	CO₂ Laser N=28 -8.0 (15.3)	Sham Laser N=30 -2.6 (9.6) P=0.36 for change between groups
	Paraiso, 2020 ⁷¹ NCT02691936	6 months UDI-6 NR Mean (SD) change	CO₂ Laser N=30 -9.4 (15.7)	Vaginal Conjugated Estrogen Cream N=32 -6.2 (12.0) P=0.37 for change between groups
	Paraiso, 2020 ⁷¹ NCT02691936	6 months DIVA NR Mean (SD) change	CO₂ Laser N=30 -3.3 (3.2)	Vaginal Conjugated Estrogen Cream N=32 -4.4 (3.1) P=0.18 for change between groups
	Alvisi, 2022 ⁹¹ NR	3 months FSDS (score <15 is 'normal') Mean (95% CI) change	CO₂ Laser N=12 -7.5 (-11.5, -3.5)	CO₂ Laser + Hyaluronic Acid Gel N=13 -2.6 (-6.4, 1.2) P>0.05 for change between groups

Outcome	Author, Year Trial ID	Follow-Up Measurement Tool/Definition Scoring Range Reported Result	Arm 1 Results	Comparator Arm Results
	Alvisi, 2022 ⁹¹ NR	3 months MENQOL (lower score=better quality of life) Mean (95%CI change	CO₂ Laser N=23 -1.7 (-2.6, -0.7)	CO₂ Laser + Hyaluronic Acid Gel N=23 -1.6 (-2.5, -0.7) P>0.05 for change between groups
	Eftekhari, 2021 ²⁷ IRCT201907080 44143N1	3 months ICIQ-SF (MUI) (range 0 to 10 for UI outcome; higher=greater incontinence) Mean (SD) at 3 months	CO₂ Laser N=78 4.9 (3.1) Change between groups Radiofrequency vs Laser P=0.36 Radiofrequency vs Placebo P=0.002 Laser vs Placebo P=0.15	Radiofrequency N=80 4.1 (3.6) Placebo* N=79 6.1 (3.9)
Vaginal Atrophy	Page, 2022 ⁶⁶ NCT04021966	3 months VHI (range 5 to 25; 5=severe atrophy; 25=no clinical signs of atrophy) Mean (SD) change	CO₂ Laser N=29 2.90 (4.21)	Sham Laser N=29 1.24 (4.23) P>0.05 between groups
	Li, 2021 ⁵⁸ ACTRN1261600 1403426	12 months VHI (range 5 to 25; VHI<15=atrophy) Mean (95% CI) at 3, 6, and 12 months post-baseline and mean difference in change from baseline to 12 months	CO₂ Laser Arm 1: CO ₂ Laser N=42 3 months 14.1 (13.1, 15.2) N=42 6 months 14.0 (13.0, 15.0) N=38 12 months 14.3 (12.9, 15.8) Mean difference at 12 months: 0.9 (-2.2, 4.0)	Sham Laser N=41 3 months 14.2 (13.1, 15.2) N=40 6 months 14.3 (13.2, 15.3) N=40 12 months 14.7 (13.0, 16.4) Mean difference at 12 months: 1.3 (-1.4, 4.0) Mean difference between groups at 12 months: -0.4 (-4.3, 3.6); P=0.38
	Ruanphoo, 2020 ⁷⁹ TCTR201606270 02	3 months VHI (range 5 to 25; higher score=less severe atrophy) Mean (SD) at 3 months	CO₂ Laser N=44 17.45 (2.61)	Sham Laser N=44 16.08 (3.27) P<0.001 between groups

Outcome	Author, Year Trial ID	Follow-Up Measurement Tool/Definition Scoring Range Reported Result	Arm 1 Results	Comparator Arm Results
	Eftekhari, 2020 ²⁶ IRCT201609160 29835N3	6 months VHI (range 3 to 24; higher score=less atrophy) Mean (SD) at 6 months	CO₂ Laser N=25 17.36 (2.61)	Vaginal Conjugated Estrogen Cream N=25 17.96 (4.05) P=0.53 between groups
	Paraiso, 2020 ⁷¹ NCT02691936	6 months VHI NR Mean (SD) difference	CO₂ Laser N=32 0.9 (0.7)	Vaginal Conjugated Estrogen Cream N=30 1.2 (0.9) P=0.07 between groups
	Alvisi, 2022 ⁹¹ NR	3 months VHI (range 5 to 25; VHI<15=atrophy) Mean (95% CI) change	CO₂ Laser N=25 1.7 (0.3, 3.2)	CO₂ Laser + Hyaluronic Acid Gel N=25 1.9 (0.5, 3.4) P>0.05 between groups
	Alvisi, 2022 ⁹¹ NR	3 months VuHI (range 5 to 20; VuHI<8=vulvar atrophy) Mean (95% CI) change	CO₂ Laser N=25 1.7 (0.5, 2.8)	CO₂ Laser + Hyaluronic Acid Gel N=25 1.5 (0.4, 2.7) P>0.05 between groups
	Eftekhari, 2021 ²⁷ IRCT201907080 44143N1	3 months VHI (range 5 to 25; higher=less atrophy) Mean (SD) change	CO₂ Laser N=78 12.7 (4.8) Change between groups Radiofrequency vs Laser P<.0001 Radiofrequency vs Placebo P<.0001 Laser vs Placebo P<.0001	Radiofrequency N=80 20.9 (1.5) Placebo* N=79 10.5 (4.0)

Outcome	Author, Year Trial ID	Follow-Up Measurement Tool/Definition Scoring Range Reported Result	Arm 1 Results	Comparator Arm Results
Change in MBS (Dyspareunia, dryness, or itching)	Page, 2022 ⁶⁶ NCT04021966	3 months VAS (4 point; 0=not present, 3=severe) Mean (SD) change and % (95%CI) decrease	CO₂ Laser N=29 Dyspareunia domain: -0.61 (0.84) Vaginal dryness domain: -1.50 (2.12) Vaginal itching domain: -0.50 (0.71) Change in overall MBS severity: 2.86 (0.35) to 2.17 (0.93) (decrease of -23.60% [-36.10%, -11.10%])	Sham Laser N=29 Dyspareunia domain: -0.36 (0.73) Vaginal dryness domain: -0.33 (0.82) Vaginal itching domain: -1.00 (NA) Change in overall MBS severity: 2.90 (0.31) to 2.52 (0.78) (decrease of -13.20% [-22.70%, -3.73%]) P=0.13 between groups for change in overall severity; P>0.05 for all other domains Neither group reached 45% change (anticipated placebo effect for treatment of GSM)
Satisfaction with Treatment	Page, 2022 ⁶⁶ NCT04021966	3 months PGI-I (5-point Likert; 1=much worse, 5=much better) n/N (%)	CO₂ Laser N=29 Better or much better 12/29 (41.38%) No change or (much) worse 17/29 (58.62%)	Sham Laser N=29 Better or much better 10/29 (34.48%) No change or (much) worse 19/29 (65.52%)
	Ruanphoo, 2020 ⁷⁹ TCTR201606270 02	3 months 5-point Likert (1=very dissatisfied, 5=very satisfied) n/N (%)	CO₂ Laser N=39 Very satisfied or satisfied 31/39 (79.5%) Neither satisfied nor dissatisfied or lower 8/39 (20.5%)	Sham Laser N=38 Very satisfied or satisfied: 17/38 (44.7%) Neither satisfied nor dissatisfied or lower 21/38 (55.3%) P=0.002 between groups
	Paraiso, 2020 ⁷¹ NCT02691936	6 months PGI-I (5 point Likert; 1=much worse, 5=much better) and PGI-S (1=very dissatisfied, 5=very satisfied) %	CO₂ Laser N=30 Improvement rated as "better or much better" 85.8% "Satisfied or very satisfied" 78.5%	Vaginal Conjugated Estrogen Cream N=32 Improvement rated as "better or much better" 70% "Satisfied or very satisfied" 73.3% P>0.05 between groups

Outcome	Author, Year Trial ID	Follow-Up Measurement Tool/Definition Scoring Range Reported Result	Arm 1 Results	Comparator Arm Results
Composite Symptom Outcome	Ruanphoo, 2020 ⁷⁹ TCTR20160627002	3 months VAS (4 point for intensity; 0=none, 3=severe) 4 domains: dryness, irritation, soreness, and dyspareunia Mean (SD) at 3 months	CO₂ Laser N=44 1.83 (0.51)	Sham Laser N=44 2.06 (0.49) P=0.03 between groups
	Eftekhari, 2021 ²⁷ IRCT20190708044143N1	3 months VAS (0=asymptomatic; 3=severe) Included irritation, itching, dryness, dispersion, and dysuria Mean (SD) at 3 months	CO₂ Laser N=78 17.6 (12.2) Change Between Groups Radiofrequency vs Laser P=0.003 Radiofrequency vs Placebo P<0.001 Laser vs Placebo P<0.001	Radiofrequency N=80 13.5 (9.9) Placebo* N=79 23.3 (15.3)

Abbreviations: AQL-6D=Assessment of Quality of Life-6D; CI=confidence interval; CO₂=carbon dioxide; DIVA=Day-to-Day Impact of Vaginal Aging; FSDS=Female Sexual Distress Scale; FSFI=Female Sexual Function Index; FSSQ=Functional Social Support Questionnaire; GSM=genitourinary syndrome of menopause; ICIQ-OAB=International Consultation on Incontinence Questionnaire-Overactive Bladder; ICIQ-SF=International Consultation on Incontinence Questionnaire-Short Form; ICIQ-VS=International Consultation on Incontinence Questionnaire-Vaginal Symptoms; ID=identification; MBS=most bothersome symptom; MENQOL=Menopause-Specific Quality of Life; NR=not reported; PGI-I=Patient Global Impression of Improvement; PGI-S=Patient Global Impression of Severity; SD=standard deviation; UDI-6=Urogenital Distress Index; VAS=Visual Analog Scale; VHI=Vaginal Health Index

Table C.25. Detailed harms results for studies of CO₂ lasers rated low or some concerns ROB

Author, Year Total N Follow-Up Intervention Vs. Comparator	Outcome	Intervention (%)	Comparator (%)
Page, 2022⁶⁶ N=80 3 months	Any AE/TEAE	--	--
	SAEs	0/87 (0%)	0/87 (0%)
	Discontinuation due to AE	None	3.3%

Author, Year Total N Follow-Up Intervention Vs. Comparator	Outcome	Intervention (%)	Comparator (%)
CO ₂ Laser vs Sham Laser	Specific AEs	Vaginal bleeding/discharge (11.5%) Vulvovaginal pain/discomfort (2.3%) Vulvovaginal edema (0%) Dysuria/UTI (3.5%) Candidiasis/vulvovaginal itching (3.5%) Worsening of dyspareunia (0%)	Vaginal bleeding/discharge (2.3%) Vulvovaginal pain/discomfort (6.9%) Vulvovaginal edema (1.2%) Dysuria/UTI (1.2%) Candidiasis/vulvovaginal itching (1.2%) Worsening of dyspareunia (0%)
Li, 2021⁵⁸ N=85 12 months CO ₂ Laser vs Sham Laser	Any AE/TEAE	16/43 (37%)	17/42 (41%)
	SAEs	0/43 (0%)	0/42 (0%)
	Discontinuation due to AE	None	None
	Specific AEs	Number of participants with ≥1 event (37%) NOTE: % for each event not reported Vaginal pain/discomfort Spotting Lower urinary tract symptoms/infection Vaginal discharge Upper UTI after treatment	Number of participants with ≥1 event (41%) NOTE: % for each event not reported Vaginal pain/discomfort Spotting Lower urinary tract symptoms/infection Vaginal discharge Upper UTI after treatment
Salvatore, 2021⁸⁰ N=60 4 months CO ₂ Laser vs Sham Laser	Any AE/TEAE	--	--
	SAEs	0/28 (0%)	0/30 (0%)
	Discontinuation due to AE	None	None
	Specific AEs	Mild irritation during/immediately post-treatment (100%)	Mild irritation during/immediately post-treatment (0%)
Ruanphoo, 2020⁷⁹ N=88 3 months CO ₂ Laser vs Sham Laser	Any AE/TEAE	--	--
	SAEs	0/41 (0%)	0/38 (0%)
	Discontinuation due to AE	2.3%	0%
	Specific AEs	Vaginal bleeding (0%) Vaginal discharge (7.3%) Vaginitis (2.4%) Pain after procedure (7.3%) De novo dyspareunia (0%)	Vaginal bleeding (2.6%) Vaginal discharge (2.6%) Vaginitis (0%) Pain after procedure (10.5%) De novo dyspareunia (0%) P>0.05 between groups for all AEs
Eftekhari, 2020²⁶ N=50 6 months CO ₂ Laser vs Vaginal Conjugated Estrogens Cream	Any AE/TEAE	--	--
	SAEs	0/25 (0%)	0/25 (0%)
	Discontinuation due to AE	None	None
	Specific AEs	Vaginal bleeding (0%) Vaginal discharge (0%)	Vaginal bleeding (0%) Vaginal discharge (0%)
Paraiso, 2020⁷¹ N=69 6 months	Any AE/TEAE	--	--
	SAEs	None	None
	Discontinuation due to AE	0/30 (0%)	0/32 (0%)

Author, Year Total N Follow-Up Intervention Vs. Comparator	Outcome	Intervention (%)	Comparator (%)
CO ₂ Laser vs Vaginal Conjugated Estrogens Cream	Specific AEs	Vaginal bleeding (6.7%) Vaginal pain (3.3%) Vaginal discharge (3.3%) UTI (3.3%) Breast tenderness (0%) Migraine (0%) Abdominal cramping (0%)	Vaginal bleeding (6.3%) Vaginal pain (0%) Vaginal discharge (0%) UTI (0%) Breast tenderness (3.1%) Migraine (3.1%) Abdominal cramping (3.1%) P>0.05 between groups for all AEs
Alvisi, 2022⁹¹ N=50 3 months CO ₂ Laser vs CO ₂ Laser + Hyaluronic Acid Gel	Any AE/TEAE	--	--
	SAEs	0/25 (0%)	0/25 (0%)
	Discontinuation due to AE	None	None
	Specific AEs	None	None
Eftekhari, 2021²⁷ N=246 3 months CO ₂ Laser vs Radio-frequency	Any AE/TEAE	--	--
	SAEs	--	--
	Discontinuation due to AE	None	None
	Specific AEs	--	--

Abbreviations: AE=adverse effect; CO₂=carbon dioxide; RoB=risk of bias; SAE=serious adverse effect; TEAE=treatment-emergent adverse effect; UTI=urinary tract infection

-- NR

Table C.26. Detailed effectiveness results for studies of Er:YAG lasers rated low or some concerns ROB

Outcome	Author, Year Trial ID	Follow-Up Measurement Tool/Definition Scoring Range Reported Result	Arm 1 Results	Comparator Arm Results
Vulvovaginal dryness	Gold, 2023 ³⁷ NCT03816735	3 months EORTC SHQ-C22 Dryness n/N (%)	Er:YAG Laser N=19 Not at all: 3/19 (16%) A little: 2/19 (11%) Quite a lot: 7/19 (37%) Very much: 7/19 (37%)	Hyaluronic Acid Suppositories n=17 Not at all: 6/17 (35%) A little: 2/17 (12%) Quite a lot: 5/17 (29%) Very much: 4/17 (24%) P=0.633 between groups
Recurrent UTIs	Gold, 2023 ³⁷ NCT03816735	3 months N/A n/N (%)	Er:YAG Laser N=22 4/22 (18.2%)	Hyaluronic Acid Suppositories N=21 1/21 (4.8%) P=0.345 between groups

Outcome	Author, Year Trial ID	Follow-Up Measurement Tool/Definition Scoring Range Reported Result	Arm 1 Results	Comparator Arm Results
Overactive bladder	Chiengthong, 2023 ¹⁵ TCTR20181218002	3 months OABSS Total Score range 0 to 15; higher score=more severe symptoms Mean (SD) at 3 months Mean (95%CI) change from baseline	Er:YAG Laser N=25 6.03 (3.36) Change from baseline: -3.85 (-4.80, -2.89)	Sham Er:YAG Laser N=25 8.44 (3.39); P=0.015 between groups Change from baseline: -1.12 (-2.25, -0.01)
Dyspareunia	Gold, 2023 ³⁷ NCT03816735	3 months EORTC SHQ-C22 (Lower score=better health) Median (IQR)	Er:YAG Laser N=22 33.3 (25.0-50.0)	Hyaluronic Acid Suppositories N=21 54.2 (8.3-66.7) P=0.39 between groups
	Fidecicchi, 2023 ³³ NR	6 months VAS (10 cm; 0=no pain) Mean (SD)	Er:YAG Laser N=34 Last treatment: 4.00 (2.16) 1 month: 4.12 (1.75) 3 months: 4.47 (1.66) Change from baseline: -5.12 (2.13)	Er:YAG Laser – Hyperstack Protocol N=34 Last treatment: 2.58 (1.32) 1 month: 2.61 (0.97) 3 months: 2.59 (0.82) Change from baseline: -7.15 (1.16) P<0.05 between groups at last treatment and 1 month P<0.001 between groups at 3 months P<0.001 for difference in change from baseline
Quality of life (distress, bother, or interference of GU symptoms)	Chiengthong, 2023 ¹⁵ TCTR20181218002	3 months OAB-q (lower scores=less bother) Symptom Bother Mean (SD) at 3 months Mean (95%CI) change from baseline HRQL Median (IQR) Mean (95%CI) change from baseline	Er:YAG Laser N=25 Symptom Bother: 47.13 (16.11) Change from baseline: -8.37 (-15.98, -0.77) HRQL: 30.67 (12.00) Change from baseline: -9.41 (-16.92, -1.90)	Sham Er:YAG Laser N=25 Symptom Bother: 53.24 (19.03); P=0.2 between groups Change from baseline: -4.18 (-11.55, 3.19) HRQL: 42.67 (35.33); P=0.06 between groups Change from baseline: -4.71 (-12.73, 3.31)

Outcome	Author, Year Trial ID	Follow-Up Measurement Tool/Definition Scoring Range Reported Result	Arm 1 Results	Comparator Arm Results
	Gold, 2023 ³⁷ NCT03816735	3 months NRS for bother (0=no bother) Median (range)	Er:YAG Laser N=22 NRS Dyspareunia: 7 (1-9) NRS Dryness: 3 (0-7) NRS OAB Wet: 0 (0-0) NRS Recurrent UTIs: 0 (0-0)	Hyaluronic Acid Suppositories N=21 NRS Dyspareunia: 5 (0-8); P=0.216 between groups NRS Dryness: 2 (0-4); P=0.411 between groups NRS OAB Wet: 0 (0-3); P=0.261 between groups NRS Recurrent UTIs: 0 (0-0); P=0.206 between groups
Vaginal atrophy	Chiengthong, 2023 ¹⁵ TCTR20181218002	3 months VHI; 5 components scored 1 to 5; lower scores=less healthy tissue Mean (SD) at 3 months Mean (95%CI) change from baseline	Er:YAG Laser N=25 15.40 (3.00) Change from baseline: 6.29 (4.91, 7.67)	Sham Er:YAG Laser N=25 9.81 (4.21); P<0.001 between groups Change from baseline: 0.73 (-0.77, 2.23)
	Gold, 2023 ³⁷ NCT03816735 4	3 months VHI N/A	Er:YAG Laser N=22 VHI data not reported; VHI improved significantly in both groups (P=0.001) Between groups P=0.232	Hyaluronic Acid Suppositories N=21
Satisfaction with treatment	Gold, 2023 ³⁷ NCT03816735	3 months PGI-I (4=no change; 3=slightly better, 2=better) Median (IQR)	Er:YAG Laser N=22 3 in both groups (slightly better); interquartile range (2, 4) (better to no change); P=0.897 between groups	Hyaluronic Acid Suppositories N=21
	Gold, 2023 ³⁷ NCT03816735	3 months Zuf-8 Maximum of 32 points; higher score=higher satisfaction Median (IQR)	Er:YAG Laser N=22 20.5 (20.0-22.0)	Hyaluronic Acid Suppositories N=21 20.0 (19.0-21.0) P>0.05 between groups

Outcome	Author, Year Trial ID	Follow-Up Measurement Tool/Definition Scoring Range Reported Result	Arm 1 Results	Comparator Arm Results
Composite symptom outcome (vaginal dryness, vaginal irritation, soreness, and dyspareunia)	Chiengthong, 2023 ¹⁵ TCTR20181218002	3 months VAS (4 point-scale for each symptom 0=none, 3=severe) Median (IQR) at 3 months Mean (95%CI) change from baseline	Er:YAG Laser N=25 0 (0.33) Change from baseline: -1.25 (-1.49, -1.00)	Sham Er:YAG Laser N=25 1.0 (1.25); P=0.001 between groups Change from baseline: -0.29 (-0.57, -0.01)

Abbreviations: EORTC SHQ-C22=European Organisation For Research And Treatment Of Cancer Sexual Health Questionnaire; Er:YAG=erbium-doped yttrium-aluminum-garnet; HRQL=health-related quality of life; ID=identification; IQR=interquartile range; N/A=not applicable; NR=not reported; NRS=Numeric Rating Scale; OAB=overactive bladder; OAB-q=OAB questionnaire; OABSS=OAB Symptom Score; PGI-I=Patient Global Impression of Improvement; SD=standard deviation; UTI=urinary tract infection; VAS=Visual Analog Scale; VHI=Vaginal Health Index; ZUF-8= Zurich Satisfaction Questionnaire

Table C.27. Detailed harms results for studies of Er:YAG lasers rated low or some concerns ROB

Author, Year Total N Follow-Up Intervention Vs. Comparator	Outcome	Intervention (%)	Comparator (%)
Chiengthong, 2023¹⁴⁸ N=50 3 months Er:YAG Laser vs Sham Laser	Any AE/TEAE	--	--
	SAEs	None	None
	Discontinuation due to AE	None	None
	Specific AEs	Vaginal pain (all mild) immediately after treatment (36%) Vaginal bleeding (minimal) (4%) Vaginal abrasions (0%)	Vaginal pain (all mild) immediately after treatment (4%) Vaginal bleeding (minimal) (0%) Vaginal abrasions (0%)
Gold, 2023³⁷ N=43 3 months Er:YAG Laser vs Hyaluronic Acid Suppositories	Any AE/TEAE	--	--
	SAEs	0/22 (0%)	0/21 (0%)
	Discontinuation due to AE	None	None
	Specific AEs	None	None
Fideticchi, 2023³³ N=68 6 months Er:YAG Laser vs Er:YAG Laser Hyperstack Protocol	Any AE/TEAE	--	--
	SAEs	0/34 (0%)	0/34 (0%)
	Discontinuation due to AE	None	None
	Specific AEs	--	--

Abbreviations: AE=adverse effect; Er:YAG=erbium-doped yttrium-aluminum-garnet; RoB=risk of bias; SAE=serious adverse effect; TEAE=treatment-emergent adverse effect

-- NR

Non-Hormonal Evidence Map Characteristics

Table C.28. Characteristics of trials included in non-hormonal evidence map

Intervention Category	Author, Year PMID Country Funding	Population	Intervention Sample Size Dose, Timing, Duration Route Mean Age, Years (SD) Majority Race (%)	Comparison Sample Size Dose, Timing Duration Route Mean Age (SD) Majority Race (%)	Outcomes Reported
Education	Alavipour, 2020 ¹¹⁶ 32893512 Iran Hamadan University of Medical Sciences	Married postmenopausal women aged 40-65, with FSFI score <28	Group education on sexual dysfunction n=45 45-60 minutes, 4 sessions per month 4 weeks group sessions 55.2 (4.5) NR	Routine training n=45 NA, NA 4 weeks NA 55.0 (4.1) NR	Sexual function
	Anderson, 2015 ¹¹⁷ 25608273 Australia Cancer Council Queensland	Women aged 45-60 with a history of breast cancer with at least one moderate to severe menopausal symptom	The Pink Women's Wellness Program n=26 NA, timing and application tailored to the participant's and nurse's assessment of needs 12 weeks NA 49 (5.9) NR	Usual care n=25 NA, NA 12 weeks NA 49.8 (6.5) NR	Somatic and vasomotor, sexual dysfunction, QoL, anxiety, depression

Intervention Category	Author, Year PMID Country Funding	Population	Intervention Sample Size Dose, Timing, Duration Route Mean Age, Years (SD) Majority Race (%)	Comparison Sample Size Dose, Timing Duration Route Mean Age (SD) Majority Race (%)	Outcomes Reported
	Chao, 2022 ¹¹⁸ 35597057 Taiwan Ministry of Science and Technology	Women aged 50-65 experiencing genitourinary symptoms	Supervision of intervention (educational materials and pelvic floor muscle training and yoga information) n=50 NA, group practice sessions weekly (mo. 1-2), 2x monthly (mo. 3-6), monthly (mo. 7-12) 12 months group education + group practice sessions 57.1 (5.3) NR	Unsupervised n=41 NA, monthly (mo1-6), every 2 months (mo 7-12) 12 months group education + call with RA 56.7 (5.0) NR	Frequency, urgency, nocturia, dryness, itching, irritation, dyspareunia, QoL
	Ganz, 2000 ¹¹⁹ 10880548 United States Government	Disease-free, female breast cancer patients, between 8 months and 5 years after the diagnosis of stage I or II disease with at least one moderate-severe symptom under investigation	Comprehensive menopausal assessment (CMA) n=37 NA, tailored to each woman's needs and preferences 6 months NA 54.6 (6.4) White (97)	Usual care n=39 NA, NA 6 months NA 54.5 (5.5) White (82)	Difficulty with bladder control, vaginal dryness, genital itching/ irritation, dyspareunia, QoL
	Naeij, 2019 ¹²⁰ 30531440 Iran Mazandaran University of Medical Sciences	Postmenopausal women aged 44-55 with FSFI score <26.5	Midwife-based counseling education program n=26 4 70-minute sessions, every 10 days 40 days single-couple in-person sessions 51.5 (3.3) NR	Routine care n=26 NA, NA 40 days NA 50.7 (2.5) NR	Sexual function, desire, pain

Intervention Category	Author, Year PMID Country Funding	Population	Intervention Sample Size Dose, Timing, Duration Route Mean Age, Years (SD) Majority Race (%)	Comparison Sample Size Dose, Timing Duration Route Mean Age (SD) Majority Race (%)	Outcomes Reported
	Schover, 2013 ¹²¹ 24225972 United States Government (National Cancer Institute) and UT MD Anderson Cancer Center Support Grant	Women 1-7 years post- diagnosis of breast or gynecological cancer, off active treatment other than hormone therapy, score <26.5 of FSFI	Self-help (access to website) + counseling n=36 3 counseling sessions, guiding women through website, NA 12 weeks NA 52 (9) NR	Self-help (access to website) n=36 NA, NA 12 weeks NA 54 (9) NR	Sexual desire, arousal, lubrication, orgasm, satisfaction, and pain, emotional distress, QoL, adverse events
Natural Products	Abedi, 2018 ¹²² 29696061 Yaralizadeh, 2016 ¹²³ 26617271, Iran Ahvaz Jundishapur University of Medical Sciences	Postmenopausal women aged 45-65 with FSFI score <26	Fennel vaginal cream n=30 5g, NR 8 weeks vaginal 53.7 (3.6) NR	Placebo n=30 NA, NR 8 weeks vaginal 52.9 (3.4) NR	Vaginal dryness, itching and burning, dyspareunia, arousal, lubrication, orgasm, sexual satisfaction and pain

Intervention Category	Author, Year PMID Country Funding	Population	Intervention Sample Size Dose, Timing, Duration Route Mean Age, Years (SD) Majority Race (%)	Comparison Sample Size Dose, Timing Duration Route Mean Age (SD) Majority Race (%)	Outcomes Reported
	Afshar, 2020 ¹²⁴ NA Iran None	Postmenopausal women aged 41-54 with sexual dysfunction	Foeniculum vulgare, Melissa officinalis Extract, and Nigella saliva n=27 100 mg (M. officinalis extract (300 mg), fennel fruit extract (300 mg), and N. sativa fresh seed powder (400 mg)), daily 8 weeks oral 46.9 (4) NR	Placebo n=21 NA, daily 8 weeks oral 47.5 (6.3) NR	Sexual dysfunction
	Ahmadizad, 2022 ¹²⁵ 36618834 Iran Academia	Postmenopausal women with symptoms of vaginal atrophy	Estrogen (Stromarine 2%) n=41 0.625 mg, daily for 2 weeks, then without for 10 days, then daily for 2 weeks Vaginal 53 (2.1) NR	Licorice cream (2%) n=41 NR, daily for 2 weeks, then without for 10 days, then daily for 2 weeks Vaginal 53.8 (2.2) NR	Sexual desire, arousal, lubrication, dyspareunia
	Alizadeh, 2023 ¹²⁶ 36640148 Iran Tabriz University of Medical Sciences	Menopausal women aged 45-60 with a score of ≥ 6 from the second three questions of the Questionnaire for Urinary Incontinence Diagnosis (QUID)	Nigella sativa L. seed oil (black seed oil) n=30 2-3 drops, 2x/day 8 weeks topically, beneath the navel 54.4 (2.0) NR	Placebo n=30 2-3 drops, 2x/day 8 weeks topically, beneath the navel 53.3 (3.1) NR	Urge urinary incontinence, sexual function, adverse events

Intervention Category	Author, Year PMID Country Funding	Population	Intervention Sample Size Dose, Timing, Duration Route Mean Age, Years (SD) Majority Race (%)	Comparison Sample Size Dose, Timing Duration Route Mean Age (SD) Majority Race (%)	Outcomes Reported
	Arjmand, 2023 ¹²⁷ 36826518 Iran	Postmenopausal women aged 50-80 with incontinence or nocturia more than once at night.	Vitamin D n=48 50,000 IU, NR 8 weeks Oral 58 (5) NR	Placebo n=49 NA, NR 8 weeks Oral 57 (5) NR	Urinary incontinence, frequency and severity, nocturia frequency and severity, impact of urinary symptoms on daily life
	Azari, 2023 ¹²⁸ 37122641 Iran Tabriz University of Medical Sciences	Sexually-active postmenopausal women with VVA and overactive bladder aged 45-56 yrs	Vitamin E n=36 100 IU Nightly for 1 week then 2x/week for 7 weeks 8 weeks Vaginal All participants: 54.4 (1.84) NR	Conjugated estrogen cream n=36 0.3 mg Nightly for 1 week then 2x/week for 7 weeks 8 weeks Vaginal	Overactive bladder, vulvovaginal atrophy, adverse events
	Beerepoot, 2012 ¹²⁹ 22782199 Netherlands Netherlands Organization for Health Research and Development	Postmenopausal women with a history of recurrent symptomatic UTIs	Lactobacillus rhamnosus GR-1 and Lactobacillus reuteri RC-14 n=125 10 ⁹ colony-forming units, 2x daily and 1 placebo capsule at night 12 months oral 63.2 (8.6) NR	Trimethoprim-sulfamethoxazole n=127 480 mg, 1 tablet at night and 1 placebo capsule twice daily 12 months oral 65.4 (8.3) NR	Recurrent UTI, adverse events

Intervention Category	Author, Year PMID Country Funding	Population	Intervention Sample Size Dose, Timing, Duration Route Mean Age, Years (SD) Majority Race (%)	Comparison Sample Size Dose, Timing Duration Route Mean Age (SD) Majority Race (%)	Outcomes Reported
	Bosak, 2022 ¹³⁰ 32995326 Bosak, 2020 ¹³¹ 35400624, Iran Deputy of Research at AJUMS, Ahvaz	postmenopausal women aged 45-65 with vaginal atrophy symptoms and dyspareunia	Chamomile vaginal gel n=32 1g, 1g daily for 2 weeks then 1g 2x/week for 10 weeks 12 weeks vaginal 53 (3.4) NR	Conjugated estrogen vaginal cream n=32 1g, 1g daily for 2 weeks then 1g 2x/week for 10 weeks 1g daily for 2 weeks, 1g 2x daily for 10 weeks 12 weeks vaginal 53.8 (3.2) NR Placebo vaginal gel n=32 1g, 1g daily for 2 weeks then 1g 2x/week for 10 weeks 12 weeks vaginal 53.7 (2.0) NR	Sexual function, desire, arousal, dyspareunia, adverse events
	Bottari, 2012 ¹³² 23241929 Italy NR	Postmenopausal women with presence of sexual dysfunction aged 45-55	Lady Prelox n=40 20 mg Pycnogenol, 200 mg L-arginine, 200 mg L- citrulline, 50 mg Rosvita, 4 tablets, 2x daily 8 weeks oral 50.1 (3.1) NR	Placebo n=43 NA, 4 tablets, 2x daily 8 weeks oral 51.2 (2.3) NR	Sexual desire, arousal, pain

Intervention Category	Author, Year PMID Country Funding	Population	Intervention Sample Size Dose, Timing, Duration Route Mean Age, Years (SD) Majority Race (%)	Comparison Sample Size Dose, Timing Duration Route Mean Age (SD) Majority Race (%)	Outcomes Reported
	Capobianco, 2014 ¹³³ 24057079 Italy NR	Postmenopausal women with symptoms of urinary stress incontinence, vaginal atrophy, and histories of recurrent urinary tract infections.	Lactobacillus Acidophili + Estriol + pelvic floor muscle training (PFMT) and electrical stimulation n=68 50 mg lyophilisate with at least 100 million live bacteria + estriol (30 mcg), once daily for 2 weeks and then two ovules once weekly 6 months Vaginal 59.1 (2.4) NR	Estriol + PFMT and electrical stimulation n=68 estriol 1 mg, once daily for 2 weeks and then two ovules once weekly 6 months Vaginal 58.5 (4.4) NR	Vaginal dryness, dyspareunia
	Carmignani, 2015 ¹³⁴ 25423326 Brazil Foundation	Postmenopausal women aged 40-60 with complaints of urogenital according to the MRS urogenital subscale (dryness, bladder problems and sexual problems)	1. Soy isoflavone n=20 45 mg, 2x daily 16 weeks Oral 52.9 (3.5) White (40)	2. Estradiol n=20 1 mg, 2x daily 16 weeks Oral 53.3 (4.5) White (65) 3. Placebo 16 weeks Oral 50.9 (3.4) White (70)	Vaginal dryness, urinary symptoms, dysuria, vaginal atrophy, sexual symptoms, adverse events

Intervention Category	Author, Year PMID Country Funding	Population	Intervention Sample Size Dose, Timing, Duration Route Mean Age, Years (SD) Majority Race (%)	Comparison Sample Size Dose, Timing Duration Route Mean Age (SD) Majority Race (%)	Outcomes Reported
	Chang, 2012 ¹³⁵ 21887807 United States NR	Postmenopausal women with score >20 on KMI	EstroG-100 (Cynanchum wilfordii, Phlomis umbrosa and Angelica gigas) n=31 257.05mg, 1 tablet, 2x daily 12weeks oral 53.2 (5.7) White (total sample=91)	Placebo n=33 NA, one tablet twice a day 12weeks oral 54.1 (5.9) NR	Vaginal dryness, depression, adverse events
	Chen, 2018 ¹³⁶ 30405741 China National Science and Technology Support Program and the National Science Foundation of China	Postmenopausal women aged 45-65 with at least one VVA symptom	Modified erzhi granules n=39 10g, 1 bag daily taken twice 12 weeks NR 59.7 (3.5) NR	Placebo n=36 NA, 1 bag daily taken twice 12 weeks NR 58.5 (4.5) NR	Vaginal pain, itching, burning, sexual function
	Chung, 2021 ¹³⁷ 33216632 South Korea NR	Premenopausal women diagnosed with gynecologic cancer >20 years of age, who underwent at least bilateral salpingo-oophorectomy and were experiencing menopausal symptoms after surgery	Korean red ginseng n=30 500mg, 2 capsules 3x daily 12 weeks oral 49.4 (4.9) NR	Placebo n=29 NA, 2 capsules 3x daily 12 weeks oral 48.6 (5.0) NR	Urinary symptoms, vaginal dryness, sexual dysfunction, anxiety, depression

Intervention Category	Author, Year PMID Country Funding	Population	Intervention Sample Size Dose, Timing, Duration Route Mean Age, Years (SD) Majority Race (%)	Comparison Sample Size Dose, Timing Duration Route Mean Age (SD) Majority Race (%)	Outcomes Reported
	Farshbaf-Khalili, 2022 ¹³⁸ 35719707 Iran Grant: Tabriz University Medical Sciences	Postmenopausal women aged 40-60 with a score between 15-42 on Greene climacteric scale	Curcumin n=26 500 mg (total 1000mg/d), 2x/day 8 weeks oral 52.0 (2.5) NR	Vitamin E n=27 500 mg (total 400 IU/d), 2x/day 8 weeks oral 52.5 (3.2) NR Placebo n=28 500 mg microcrystalline cellulose, 1x/day 8 weeks oral (capsule) 52.1 (2.7) NR	Sexual symptoms, depression, adverse events
	Golmakani, 2019 ¹³⁹ 29971469 Iran Mashhad University of Medical Sciences	Postmenopausal women with genitourinary syndrome of menopause aged 40-65	Vitamin E vaginal suppository n=30 100 IU, daily for first 2 weeks, then 2x weekly for 10 weeks 12 weeks Vaginal NR (reports ranges) NR	Conjugated estrogen vaginal cream n=30 0.5g, daily for first 2 weeks, then 2x weekly for 10 weeks 12 weeks vaginal NR NR	Sexual function, desire, arousal

Intervention Category	Author, Year PMID Country Funding	Population	Intervention Sample Size Dose, Timing, Duration Route Mean Age, Years (SD) Majority Race (%)	Comparison Sample Size Dose, Timing Duration Route Mean Age (SD) Majority Race (%)	Outcomes Reported
	Hafizi, 2021 ¹⁴⁰ 33708258 Iran NR	Married postmenopausal women aged 45-60 with FSFI score ≤26	Jazar (mix of fennel, Vitex and carrot seeds) n=43 500 mg, 2x/day 8 weeks oral 52.4 (4.2) NR	Placebo n=41 500 mg, 2x/day 8 weeks oral 54.5 (3.8) NR	QoL, adverse events
	Hidalgo, 2005 ⁴¹ 43041746 Ecuador NR	Postmenopausal women aged >40 with Kupperman Index score ≥15	Red clover n=60 80 mg, daily 90 days Oral NR NR	Placebo n=60 80 mg, daily 90 days Oral NR NR	Dyspareunia, vaginal dryness, low libido
	Kamronrithisorn, 2020 ¹⁴¹ 32967068 Thailand None	Postmenopausal women with vulvovaginal atrophy (VVA)	Vitamin D n=40 20,000 IU, 2 capsules/week 12 weeks oral 60.0 (5.8) NR	Placebo n=40 NA, 2 capsules/week 12 weeks oral 58.3 (6.3) NR	Dryness, pain, itching, and dyspareunia
	Karimi, 2021 ¹⁴² 34745918 Iran NR	Married postmenopausal women aged 45-65 with dyspareunia and symptoms of vaginal atrophy	Squill oil n=30 3 mL, 2-3x/week, 5 min before intercourse 4 weeks vaginal 53.5 (2.2) NR	Placebo n=30 3 mL, 2-3x/week, 5 min before intercourse 4 weeks applied directly to clitoris and vaginal opening 51.7 (4.5) NR	Dyspareunia, arousal, satisfaction, orgasm

Intervention Category	Author, Year PMID Country Funding	Population	Intervention Sample Size Dose, Timing, Duration Route Mean Age, Years (SD) Majority Race (%)	Comparison Sample Size Dose, Timing Duration Route Mean Age (SD) Majority Race (%)	Outcomes Reported
	Karimi, 2023 ¹⁴³ 37044017 Iran NR	Postmenopausal women aged 45-60 who were diagnosed with vaginal atrophy (per the vaginal assessment scale) and had sex in the past 6 months	Nettle vaginal cream n=42 5% nettle, 1g cream Nightly x 2 wks then 2x/week for 6 weeks 8 weeks Vaginal 54.1 (3.3) NR	Base cream n=42 1g cream Nightly x 2 wks then 2x/week for 6 weeks 8 weeks Vaginal 52.6 (3.1) NR	Vaginal dryness, itching, burning, dyspareunia
	Keshavarzi, 2019 ¹⁴⁴ 30729333 Iran NR	Married women with stage 1 or 2 breast cancer, aged <50 receiving tamoxifen, Vaginal Maturation Index ≤52	Vitamin D n=32 1000 IU, daily 8 weeks Vaginal 43.7 (3.9) NR	Vitamin E n=32 1 mg, daily 8 weeks Vaginal 44.1 (4.6) NR placebo n=32 NA, daily 8 weeks Vaginally 42.0 (6.3) NR	Genitourinary atrophy
	Khayatan, 2019 ¹⁴⁵ NA Iran NR	Postmenopausal women aged 45-65 with dyspareunia	Red clover vaginal cream n=38 NR, daily 8 weeks vaginal 56.2 (3.6) NR	Placebo n=38 NR, daily 8 weeks vaginal 56.1 (3.6) NR	Dyspareunia

Intervention Category	Author, Year PMID Country Funding	Population	Intervention Sample Size Dose, Timing, Duration Route Mean Age, Years (SD) Majority Race (%)	Comparison Sample Size Dose, Timing Duration Route Mean Age (SD) Majority Race (%)	Outcomes Reported
	Kianitalaei, 2022 ¹⁴⁶ NA Iran University/Hospital for thesis	40-65 yr women with complaints of VVA	Alcea (marshmallow botanical) n=30 125 mg suppository, Nightly for 2 weeks + every other night for 6 weeks 8 weeks total vaginal 56.6 (5.5) NR	Placebo n=30 suppository, Nightly for 2 weeks + every other night for 6 weeks 8 weeks total vaginal 54.6 (5.9) NR	Vaginal dryness, irritation, itching, dyspareunia, bleeding, adverse events
	Kim, 2021 ¹⁴⁷ 34399063 South Korea Pulmuone, Inc	Postmenopausal women aged 40-60 experiencing moderate or severe menopausal symptoms (Kupperman Menopausal Index score >20)	Standardized Soy and Hop Extract n=40 95 mg, 2x daily 12 weeks oral 54.7 (3.7) NR	Placebo n=41 NA, 2x daily 12 weeks oral 54.3 (3.7) NR	Vaginal dryness, adverse events
	Larmo, 2014 ¹⁴⁸ 25104582 Finland Government (Tekes – the Finnish Funding Agency for Innovation)	Postmenopausal women aged 55-75 experiencing moderate- severe symptoms of vaginal dryness, itching or burning	Sea buckthorn oil n=57 3g, 3 capsules 2x daily 3 months oral 64 (5) NR	Placebo n=59 NA, 3 capsules 2x daily 3 months oral 62 (5) NR	Dryness, burning, itching, pain

Intervention Category	Author, Year PMID Country Funding	Population	Intervention Sample Size Dose, Timing, Duration Route Mean Age, Years (SD) Majority Race (%)	Comparison Sample Size Dose, Timing Duration Route Mean Age (SD) Majority Race (%)	Outcomes Reported
	Le Donne, 2011 ¹⁴⁹ 20577750 Italy NR	Postmenopausal women with vaginal atrophy symptoms	Genistein n=31 97mcg, 15 continuous days/month 3 months Vaginal suppository 57.8 (4.7) NR	Hyaluronic acid n=31 NA, 15 continuous days/month 3 months Vaginal suppository 59.7 (3.4) NR	Dryness, itching, dyspareunia
	Lima, 2014 ¹⁵⁰ 24856055 Brazil NR	Postmenopausal women aged >45 with symptoms of vaginal dryness, pain, soreness, burning or dyspareunia	Soy isoflavone (<i>Glycine max</i> (L.) Merr.) n=30 1 g gel containing 0.04g soybean extract, daily 12 weeks vaginal 59.2 (4.8) NR	Placebo n=30 12 weeks vaginal 59.9 (2.9) NR	Vaginal dryness, soreness, burning, dyspareunia
	Lima, 2013 ¹⁰⁹ 23312487 Brazil None	Postmenopausal women aged >45 with symptoms of vaginal dryness, pain, soreness, burning or dyspareunia	Soy isoflavone (<i>Glycine max</i> (L.) Merr.) n=30 1 g gel containing 0.05g soybean extract, daily 12 weeks vaginal 57 (SD NR) NR	Conjugated estrogen cream n=30 0.5 g of 0.625 mg CEE/g cream, daily 12 weeks vaginal 56 (SD NR) NR 3. Placebo n=30 12 weeks vaginal 57 (SD NR) NR	Vaginal dryness, soreness, burning, dyspareunia, adverse events

Intervention Category	Author, Year PMID Country Funding	Population	Intervention Sample Size Dose, Timing, Duration Route Mean Age, Years (SD) Majority Race (%)	Comparison Sample Size Dose, Timing Duration Route Mean Age (SD) Majority Race (%)	Outcomes Reported
	Loripoor, 2023 ¹⁵¹ 36650842 Iran Vice-Chancellor for Research and Student Research Committee of Rafsanjan University of Medical Sciences	Married postmenopausal women 50-65 yrs, FSFI <19	Palm pollen n=45 1 capsule, daily 4 weeks oral 56.6 (4.4) NR	Placebo n=44 54 capsule, daily 4 weeks oral 55.6 (4.8) NR	Sexual function
	Mainini, 2020 ¹⁵² 33100948 Italy NR Prospective cohort study	Menopausal women with a history of recurrent UTIs	Nutraceutical compound (inulin, D-mannose, cranberry, bearberry, Olea europaea, Orthosiphon, Lactobacillus acidophilus) n=48 2 g inulin, 500 mg D- mannose, 200 mg cranberry, 200 mg bearberry, 100 mg Olea europaea, 10 mg Orthosiphon, 10 billion CFU Lactobacillus acidophilus, 10 day course per month 12 months oral 53.0 (5.8) NR	None n=46 NA, NA 12 months NA 54.1 (4.5) NR	Recurrent UTI, QoL, adverse events

Intervention Category	Author, Year PMID Country Funding	Population	Intervention Sample Size Dose, Timing, Duration Route Mean Age, Years (SD) Majority Race (%)	Comparison Sample Size Dose, Timing Duration Route Mean Age (SD) Majority Race (%)	Outcomes Reported
	Markland, 2019 ¹⁵³ 30578542 United States Government (NIH); National Institute of Diabetes and Digestive and Kidney Diseases	Postmenopausal women aged >50 with predominant urgency urinary incontinence (UUI)	Vitamin D3 n=28 50,000 IU, weekly 12 weeks oral 61.4 (7.1) Black/African American (57.1)	Placebo n=28 NA, weekly 12 weeks oral 59.5 (9.2) Black/African American (82.1)	% change in frequency of UUI, QoL, side effects
	Manonai, 2007 ¹⁵⁴ 17415017 Thailand Institute of Thai Traditional Medicine, Ministry of Public Health	Healthy, nonhysterectomized, postmenopausal women aged 45-60 with urogenital symptoms and at least 2 symptoms of vaginal atrophy	Pueraria mirifica n=51 20, 30, or 50 mg, daily 24 weeks oral 53.2 (3.4) NR	Placebo n=20 NA, daily 24 weeks oral 53.2 (3.8) NR	Urge incontinence, frequency, dryness, dyspareunia, breast tenderness
	Mazaladeh, 2020 ¹⁵⁵ 32984113 Iran None	Postmenopausal women with vaginal atrophy symptoms	Fenugreek vaginal cream n=30 5%, NR 8 weeks topical 54.1 (4.4) NR	Placebo n=30 NA, NR 8 weeks topical 55.1 (4.6) NR	Vaginal atrophy, vaginal dryness, dyspareunia
	Postigo, 2016 ¹⁵⁶ 26902700 Brazil Government	Postmenopausal women who experienced sexual dysfunction after menopause	Tribulus Terrestris n=30 250mg, 3x daily 90 days oral 56 (5.8) White (53.3)	Placebo n=30 1 tablet, 3x daily 90 days oral 54 (5.1) White (60)	Sexual desire, arousal

Intervention Category	Author, Year PMID Country Funding	Population	Intervention Sample Size Dose, Timing, Duration Route Mean Age, Years (SD) Majority Race (%)	Comparison Sample Size Dose, Timing Duration Route Mean Age (SD) Majority Race (%)	Outcomes Reported
	Radnia, 2023 ¹⁵⁷ 37122641 Iran None	Postmenopausal women with GSM who had been referred to one of two clinics in 2021. Off hormones for 12 weeks. (GSM criteria NR)	Vitamin D/E combined n=32 Vitamin D 1000IU + Vitamin E IU per dose (2 g of drug total) Daily x 2 wks then 3x/wk for 10 wks Vaginal 54.5 (NR) NR	Conjugated estrogen cream n=32 0.625g/dose Daily x 2 wks then 3x/wk for 10 wks Vaginal 53.0 (NR) NR	Dysuria, urinary frequency, urge incontinence, vaginal symptoms, sexual function and dyspareunia
	Ribeiro, 2018 ¹⁵⁸ 30531444 Brazil Foundation	Postmenopausal women aged 40-60 with symptoms estrogen deprivation according to the MRS	1. Soy isoflavone n=20 150 mg, NR 16 weeks Oral 53 (3.4) White (57.9)	2. Soy isoflavone + probiotic n=20 150 mg, NR + one packet, NR 16 weeks oral 52.2 (3.4) White (50) 3. Estradiol n=20 1 mg, NR 16 weeks Oral 52 (3.4) White (78.9)	Vaginal dryness, urinary symptoms, sexual symptoms, adverse events

Intervention Category	Author, Year PMID Country Funding	Population	Intervention Sample Size Dose, Timing, Duration Route Mean Age, Years (SD) Majority Race (%)	Comparison Sample Size Dose, Timing Duration Route Mean Age (SD) Majority Race (%)	Outcomes Reported
	Sadeghi, 2020 ¹⁵⁹ 32257873 Iran NR	Postmenopausal women with symptoms of vaginal atrophy	Licorice vaginal cream n=35 2%, daily at bedtime 8 weeks vaginal 56.4 (4.3) NR	Placebo n=35 NA, daily at bedtime 8 weeks vaginal 56.2 (4.7) NR	Vaginal dryness, soreness, burning or itching, dyspareunia
	Safary, 2020 ¹⁶⁰ 32640956 Iran Tabriz University of Medical Sciences	Postmenopausal women aged >45 with atrophic vaginitis	Fenugreek vaginal cream n=30 0.5g, 2x week 12 weeks vaginal 57.1 (5.4) total sample NR	Conjugated estrogens n=30 0.3mg, NR 12 weeks vaginal NR NR	Vaginal dryness, itching, burning, and abnormal vaginal discharge, dyspareunia
	Sritonchai, 2020 ¹⁶¹ 32972635 Thailand Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok	Postmenopausal women aged 50-70 with at least one symptom of GSM	Pueraria mirifica n=30 0.5 g, daily for 2 weeks, then 3x per week 12 weeks Vaginal 57.4 (5.7) NR	Placebo n=30 NA, daily for 2 weeks, then 3x per week 12 weeks Vaginal 57.3 (5.9) NR	Urinary urgency, dysuria, recurrent UTI, dryness, burning, irritation, sexual discomfort or pain, adverse events
	Suwanvesh, 2017 ¹⁶² 27749740 Thailand Faculty of Medicine Ramathibodi Hospital, Mahidol University	Women aged 45-70 with at least symptom of estrogen deprivation	Pueraria mirifica gel n=41 0.5g, daily for 2 weeks, then 3x per week 12 weeks Vaginal 56.4 (4.4) NR	Conjugated equine estrogen cream n=41 0.5g, daily for 2 weeks, then 3x per week 12 weeks Vaginal 55.7 (5.2) NR	Dryness, soreness, irritation, dyspareunia

Intervention Category	Author, Year PMID Country Funding	Population	Intervention Sample Size Dose, Timing, Duration Route Mean Age, Years (SD) Majority Race (%)	Comparison Sample Size Dose, Timing Duration Route Mean Age (SD) Majority Race (%)	Outcomes Reported
	Vahedpoorfard, 2023 ¹⁶³ 37101856 Iran Kashan University of Medical Sciences	Postmenopausal women with vaginal atrophy who complained of postmenopausal symptoms	Hop extract n=30 NR, daily for 7 days then 2x/wk for up to, or for an additional 8 weeks Vaginal NR	Estradiol n=30 0.625mg Two 28-day cycles: 21 day treatment then 7days off each cycle Vaginal NR	Sexual function, dyspareunia, adverse events
	Vale, 2021 ¹⁶⁴ 34142638 Brazil Brazilian Council for Scientific and Technological Development	Postmenopausal women reporting symptoms of female sexual dysfunction	Tribulus terrestris n=26 94 mg, 3x daily 90 days NR 56 (5.3) NR	Tribulus terrestris n=26 280 mg, 1x daily 90 days NR NR NR	Sexual desire, arousal, pain
	Warinsiriruk, 2022 ¹⁶⁵ 35550707 Thailand Faculty of Medicine Rmathibodi Hospital, Mahidol University, Bangkok	postmenopausal women aged 50-40 with at least one symptom of GSM	Pueraria mirifica gel n=36 0.5 g, daily for 21 days, then stop for 7 days 12 weeks vaginal 57.5 (7.9) NR	Placebo n=36 NA, daily for 21 days, then stop for 7 days 12 weeks vaginal 58.1 (5.2) NR	Urinary urgency, frequency, dysuria, recurrent UTI, vaginal dryness, burning, irritaiton, sexual discomfort/pain

Intervention Category	Author, Year PMID Country Funding	Population	Intervention Sample Size Dose, Timing, Duration Route Mean Age, Years (SD) Majority Race (%)	Comparison Sample Size Dose, Timing Duration Route Mean Age (SD) Majority Race (%)	Outcomes Reported
	Yang, 2012 ¹⁶⁶ 23304198 China National Science Foundation of China	Women age 45-55 diagnosed with menopausal syndrome and with Traditional Chinese Medicine (TCM)-pattern diagnosis of kidney deficiency	1. TCM psychotherapy (PSY) + Chinese herbal medicine (CHM, (Gengnianningxin capsule or Bushen oral liquid) n=105 >1 hour TCM PSY weekly; 4 capsules CHM 3x/day 12 weeks individual and group sessions/oral 49.8 (2.9) NR 2. TCM PSY + Placebo CHM n=104 >1 hour TCM PSY weekly; 4 capsules placebo 3x/day 12 weeks individual and group sessions/oral 50.2 (2.8) NR	3. CHM n=111 4 capsules CHM, 3x/day 12 weeks oral 49.5 (2.9) NR 4. Placebo CHM n=104 4 capsules placebo, 3x/day 12 weeks oral CHM placebo 49.7 (2.9) NR	Sexual symptoms, psychological symptoms, adverse events

Intervention Category	Author, Year PMID Country Funding	Population	Intervention Sample Size Dose, Timing, Duration Route Mean Age, Years (SD) Majority Race (%)	Comparison Sample Size Dose, Timing Duration Route Mean Age (SD) Majority Race (%)	Outcomes Reported
Mind and Body Practices	Ahmed, 2020 ¹⁶⁷ NA Egypt None	Postmenopausal women aged 55-65 with overactive bladder	<p>1. Transcutaneous tibial nerve stimulation (TNS) + anti Muscarinic drugs n=20 NA, 3 sessions/week + control drug 12 weeks NA 60.3 (3.7) NR</p> <p>2. Percutaneous TNS + anti Muscarinic drugs n=20 NA, 3 sessions/week + control drug 12 weeks NA 61.0 (2.5) NR</p>	<p>3. Control (anti Muscarinic drugs only) n=20 10mg, 1x daily 12 weeks oral 60.1 (3.1) NR</p>	Overactive bladder, QoL

Intervention Category	Author, Year PMID Country Funding	Population	Intervention Sample Size Dose, Timing, Duration Route Mean Age, Years (SD) Majority Race (%)	Comparison Sample Size Dose, Timing Duration Route Mean Age (SD) Majority Race (%)	Outcomes Reported
	D'Alessandro, 2022 ¹⁶⁸ 35251438 Brazil None	Breast cancer patients undergoing the hormonal-blockage phase of treatment (tamoxifen) and experiencing climacteric-like symptoms	True-acupuncture (manual) n=20 NA, 20 min/1x weekly 10 weeks NA 48.6 (NR) NR	Sham-acupuncture n=20 NA, 20 min/1x weekly 10 weeks NA 51.6 (NR) NR Wait-list control n=20 NA, NA 10 weeks NA 50.8 (NR) NR	"menopause syndrome" genitourinary domains, depression

Intervention Category	Author, Year PMID Country Funding	Population	Intervention Sample Size Dose, Timing, Duration Route Mean Age, Years (SD) Majority Race (%)	Comparison Sample Size Dose, Timing Duration Route Mean Age (SD) Majority Race (%)	Outcomes Reported
	Duijts, 2012 ¹⁶⁹ 23045575 Netherlands NR	Women <50 with primary breast cancer, diagnosed when premenopausal, experiencing menopausal symptoms	CBT n=109 six weekly group sessions of 90 minutes each + A booster session was held 6 weeks after completion of the program 12 weeks 48.2 (5.7) NR physical exercise n=104 individually tailored, home-based, selfdirected exercise program of 2.5 to 3 hours per week 12 weeks 47.7 (5.6) NR	CBT+ physical exercise n=106 12 weeks 49.0 (4.9) NR Wait-list control n=103 12 weeks 47.8 (6.0) NR	Urinary symptoms, sexual functioning, distress, QoL
	Hummel, 2017 ¹⁷⁰ 28240966 Netherlands The Netherlands Cancer Institute	women with a history of breast cancer aged 18-65 and a diagnosis of sexual dysfunction	Internet-based CBT n=84 NA, weekly 24 weeks therapist guided sessions 51.6 (7.7) NR	wait-list control (booklet and phone call with sexologist) n=85 NA, NA 24 weeks NA 50.5 (6.8) NR	Sexual function, desire, arousal, distress, QoL, psychological distress

Intervention Category	Author, Year PMID Country Funding	Population	Intervention Sample Size Dose, Timing, Duration Route Mean Age, Years (SD) Majority Race (%)	Comparison Sample Size Dose, Timing Duration Route Mean Age (SD) Majority Race (%)	Outcomes Reported
	Meng, 2016 ¹⁷¹ 27760084 China Science Project of Jiangsu Province Hospital	Postmenopausal women aged 40-60 with menopausal symptoms	Gua sha therapy + conventional treatment (Qingxin Zishen Tang [Gou Teng (Uncaria rhychophylla) 15 g, Lian Zixin (Lotus plumule) 5 g, Huang Lian (Coptis chinensis) 3 g, Zi Beichi (Arabic cowry shell) 10 g, Huai Shanyao (Rhiizoma dioscoreae) 10 g, Shan Zhuyu (Dogwood) 10 g, Tai Zishen (Radix pseudostellariae)]) 15 g]) n=40 NA, 1 session per week + 2x daily drink 8 weeks NA + oral (drink) 50.4 (2.7) NR	Conventional treatment n=40 2x daily (am/pm) 8 weeks oral (drink) 51.0 (2.8) NR	Recurrent UTI, sexual complantes, QoL

Intervention Category	Author, Year PMID Country Funding	Population	Intervention Sample Size Dose, Timing, Duration Route Mean Age, Years (SD) Majority Race (%)	Comparison Sample Size Dose, Timing Duration Route Mean Age (SD) Majority Race (%)	Outcomes Reported
	Mojtehed, 2022 ¹⁷² 36524136 Iran Thesis grant, source NR	Married postmenopausal women aged 50-60, mild to moderate anxiety on Beck Anxiety Scale, FSFI <28	1. Aromatherapy + mindfulness-based intervention (MBI) n=33 2-3 drops aroma + 8 sessions MBI, 3x/day aroma; 1x/wk for 8 wks MBI 8 weeks rubbed on forearm and inhaled, in-person group MBI sessions 55.3 (3.3) NR 2. Aromatherapy (lavandula angustifolia Mill and Citrus bergamia) + routine care (RC) n=33 2-3 drops aroma + RC, 3x/day aroma 8 weeks rubbed on forearm and inhaled + RC 54.7 (3.2) NR	3. MBI + placebo n=33 8 sessions, 1x/week 8 weeks in-person group MBI sessions 56.0 (3.2) NR 4. RC + placebo n=33 NA, 3x/day placebo drops to forearm and inhaled 8 weeks rubbed on forearm and inhaled 56.6 (4.3) NR	Sexual function, anxiety, depression, adverse events

Intervention Category	Author, Year PMID Country Funding	Population	Intervention Sample Size Dose, Timing, Duration Route Mean Age, Years (SD) Majority Race (%)	Comparison Sample Size Dose, Timing Duration Route Mean Age (SD) Majority Race (%)	Outcomes Reported
	van Driel, 2019 ¹⁷³ 30222235 Netherlands C&W de Boer Foundation	Women who had undergone risk reducing salpingo-oophorectomy before age 52 years and reported at least two moderate-to-severe menopausal symptoms in the two preceding weeks	MBSR n=34 NA, weekly sessions of 2.5 hours each, a silent retreat evening lasting 4 hours, and a commitment to performing mindfulness exercises at home for 30–45 minutes for 6 days of the week using instructions provided on an MP3 player 8 weeks NA 47 (5) NR	Usual care n=32 NA, NA 8 weeks NA 48.5 (5.4) NR	Sexual desire, arousal, pain, distress, QoL
Pharmaceutical	Agarwal, 2015 ¹⁷⁴ 25861202 India NR	Postmenopausal women aged 45-55 with psychosomatic and sexual symptoms	Gabapentin + calcium n=25 900 mg/day + 500 mg, 300 mg 3x daily + 1x daily 6 months oral 46.2 (6.6) NR	Calcium n=25 500 mg, 1x daily 6 months oral 45.8 (6.8) NR	Dryness, dyspareunia, anxiety, depression
	Goetsch, 2015 ¹⁷⁵ 26215946 United States OHSU Knight Cancer Institute	Estrogen-deficient breast cancer survivors with severe penetrative dyspareunia	4% aqueous lidocaine n=23 NA, 3 minutes 6 months applied as a compress to the vulvar vestibule just before vaginal penetration 56.6 (8.2) White (91.3)	Saline n=23 NA, 3 minutes 6 months applied as a compress to the vulvar vestibule just before vaginal penetration 54.0 (9.2) White (87)	Pain, quality of sexual life

Intervention Category	Author, Year PMID Country Funding	Population	Intervention Sample Size Dose, Timing, Duration Route Mean Age, Years (SD) Majority Race (%)	Comparison Sample Size Dose, Timing Duration Route Mean Age (SD) Majority Race (%)	Outcomes Reported
	Green, 2006 ¹⁷⁶ 17085151 United States NR	Postmenopausal women aged >40 with a history of urge urinary incontinence	Aprepitant n=61 160mg, 1x daily 8 weeks oral 65.1 (11.0) White (90.2)	Placebo n=64 NA, 1x daily 8 weeks oral 64.5 (8.8) White (92.2)	Urgency, incontinence, adverse events
	Kinjo, 2023 ¹⁷⁷ 36822245 Japan NR	Postmenopausal women with treatment-naive overactive bladder	Vibegron n=102 50mg, daily 12 weeks Oral 71.1 (10.8) NR	Mirabegron n=97 50mg, daily 12 weeks Oral 71.5 (12.6) NR	Overactive bladder, QoL, drug-related adverse events
	Rios-Espinosa, 2022 ¹⁷⁸ 35997971 Mexico None	Postmenopausal women clinically diagnosed with vasomotor syndrome (VMS) or GSM; MRS score >17	Citalopram n=49 20 mg, daily 6 months oral 53.9 (NR) NR	Fluoxetine n=42 20 mg, daily 6 months oral 54.1 (NR) NR	Bladder problems, dryness, sexual problems, QoL

Intervention Category	Author, Year PMID Country Funding	Population	Intervention Sample Size Dose, Timing, Duration Route Mean Age, Years (SD) Majority Race (%)	Comparison Sample Size Dose, Timing Duration Route Mean Age (SD) Majority Race (%)	Outcomes Reported
	Zhong, 2011 ¹⁷⁹ 22289552 China NR	Postmenopausal women with recurrent UTIs	Low-dose daily antibiotic prophylaxis n=42 50 mg/day furantoin; 200/40 mg/day sulphamethazine–trimethoprim (SMZ–TMP); 200 mg/day norfloxacin; 125 mg/day ciprofloxacin; 500 mg/day amoxicillin; 250 mg/day cefaclor; or 250 mg/day cefuroxime., 1x daily 12 months oral 62.8 (7.3) NR	Intermittent patient-initiated single-dose antibiotic prophylaxis n=41 50 mg/day furantoin; 200/40 mg/day SMZ–TMP; 200 mg/day norfloxacin; 125 mg/day ciprofloxacin; 500 mg/day amoxicillin; 250 mg/day cefaclor; or 250 mg/day cefuroxime., take a single-dose antibiotic every time they were exposed to conditions predisposing to UTI – such as, sexual intercourse, travelling, working or walking for a long time, emiction holdback, diarrhea or constipation 12 months oral 62.3 (7) NR	Recurrent UTI, adverse events

Abbreviations: AJUMS=Ahvaz Jundishapur University of Medical Sciences; CBT=cognitive behavioral therapy; CEE=conjugated equine estrogen; CHM=Chinese herbal medicine; FSFI=Female Sexual Function Index; g=grams; GSM=genitourinary syndrome of menopause; IU=international units; KMI=Kupperman Menopausal Index; MBI=mindfulness-based intervention; MBSR=mindfulness-based stress reduction; mg=milligrams; mL=milliliters; MRS=Menopause Rating Scale; NA=not applicable; NR=not reported; PFMT=pelvic floor muscle training; PMID=PubMed ID; PSY=psychotherapy; QoL=quality of life; RA=research assistant; SD=standard deviation; SMZ–TMP=sulphamethazine–trimethoprim; TCM=traditional Chinese medicine; TNS=transcutaneous nerve stimulation; UTI=urinary tract infection; UUI=urgency urinary incontinence; VVA=vulvovaginal atrophy

Table C.29. Measures used in non-hormonal intervention studies

Category	Measure	# Times Used
Urinary	Brief Symptom Inventory-18 (BSI-18) ¹²¹	1
	Functional Assessment of Cancer Treatment–Endocrine Symptoms (FACT-ES) ^{169, 170}	2
	Genitourinary atrophy self-assessment tool (Lester 2012 ref) ¹⁴⁴	1
	Incontinence Impact Questionnaire ¹⁷⁶	1
	Incontinence-QoL (I-QoL) ^{126, 176}	2
	Indevus Urgency Severity Scale ¹⁵³	1
	International Consultation on Incontinence Questionnaire-Overactive Bladder (ICIQ-OAB) ¹⁵³	1
	International Consultation on Incontinence Questionnaire-Urinary Incontinence (ICIQ-UI) ^{126, 153}	2
	International Consultation on Incontinence Questionnaire-Short Form (ICIQ-SF) ¹⁵⁸	1
	Overactive bladder symptom and HRQoL questionnaire (Coyne 2002 ref) ¹⁶⁷	1
	Overactive Bladder Symptom Score (OABSS) (Homma 2006 ref) ^{128, 177}	2
	Questionnaire for Urinary Incontinence Diagnosis (QUID) ¹²⁶	1
	Taiwan Teacher Bladder Survey - Lower urinary tract symptoms (LUTS) subscale ¹¹⁸	1
	Urge Urogenital Distress Inventory (UUDI) ¹⁷⁶	1
Sexual	Abbreviated +D13 Sexual Function Questionnaire (ASFQ) ¹³⁹	1
	Female Intervention Efficacy Index (FIEI) questionnaire ¹⁵⁶	1
	Female Sexual Distress Scale (FSDS) ^{170, 173, 175}	3
	Female Sexual Function Index (FSFI) ^{116, 120, 170, 172, 180, 122, 125, 126, 163, 173, 124, 132, 136, 140, 151, 157, 164}	17
	Marinoff dyspareunia scale ¹⁴²	1
	Menopausal Sexual Interest Questionnaire (MSIQ) ¹²¹	1
	QS-F (Scale for Quality of Sexual Function) ¹⁶⁴	1
	Sabbatsberg Sexual Self-Rating Scale ¹⁴²	1
	Sexual Activity Questionnaire (SAQ) ^{169, 170}	2
	Sexual Function Questionnaire (SF-Q) ¹⁷⁵	1
	Sexual Quotient—female version (SQ-F) ¹⁵⁶	1
Psychological or QoL	Beck Anxiety Inventory (BAI) ¹⁷²	1
	Beck Depression Inventory (BDI-II) ^{168, 172}	2
	Hospital Anxiety and Depression Scale (HADS) ^{169, 170}	2
	Menopause-specific QoL (MENQoL) ^{126, 140, 166, 171, 173}	5
	Quality of Life in Adult Cancer Survivors (QLACS) ¹²¹	1
	Quality of Life Index (from AUA, for BPH, Barry 1992 ref) ¹⁷⁷	1
	SF-36 ^{117-119, 169, 170}	5
Mixed (tool measured more than one category)	Breast Cancer Prevention Trial Symptom Checklist ¹¹⁹	1
	Bristol Female Lower Urinary Tract Symptoms Questionnaire (BFLUTS) ¹⁶⁹	1
	Cancer Rehabilitation Evaluation System (CARES) ¹¹⁹	1
	Clinical interview questionnaire (Davila 2003 ref) ¹⁶²	1
	Functional Assessment of Cancer Therapy—Breast (FACT-B) ¹¹⁷	1
	Greene climacteric scale (GCS) ^{117, 138}	2
	GSM-specific questionnaire (Portman, 2014 ref) ^{161, 165}	2
	Kupperman Index (KI) ^{41, 135, 136, 147, 166, 171}	6
	Menopause Rating Scale (MRS) ^{134, 137, 158, 168, 178}	5
	Numeric Rating Scale (Dworkin 2008 ref) ¹⁷⁵	1

	Study-specific or author written checklist or questionnaire ^{41, 109, 118, 122, 127, 129, 130, 133, 140, 145, 148-150, 154, 155, 159, 160, 174}	18
	Vaginal Health Index (VHI) ¹²⁸	1
	Vulvovaginal Atrophy Questionnaire (Simon, 2008 ref) ¹²⁸	1

Appendix D. FDA Information for Included Interventions

Table D.1. Summary of findings of FDA warning labels for interventions of interest

Drug Name (Dose/Route)	Black Box Warnings	Indications	Contraindications	Additional Warnings
Ospemifene (Osphena) 60 mg once daily orally	<p>Endometrial Cancer OSPHEA is an estrogen agonist/antagonist with tissue selective effects. In the endometrium, OSPHEA has estrogen agonistic effects. There is a potential increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens. Adequate diagnostic measures, including directed and random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding.</p> <p>Cardiovascular Disorders In the clinical trials for OSPHEA (duration of treatment up to 15 months), the incidence rates of thromboembolic and hemorrhagic stroke were 1.13 and 3.39 per thousand women years, respectively in the OSPHEA 60 mg treatment group and 3.15 and 0 with placebo. The incidence of DVT was 2.26 per thousand women years (2 reported cases) in the OSPHEA 60 mg treatment group and 3.15 per thousand women years (1 reported case) with placebo. OSPHEA should be prescribed for the shortest duration consistent with treatment goals and risks for the individual woman.</p>	<ul style="list-style-type: none"> • Treatment of moderate to severe dyspareunia • Treatment of moderate to severe vaginal dryness 	<ul style="list-style-type: none"> • Undiagnosed abnormal genital bleeding • Known or suspected estrogen-dependent neoplasia • Active DVT, pulmonary embolism (PE), or a history of these conditions • Active arterial thromboembolic disease (for example, stroke and myocardial infarction [MI]), or a history of these conditions • Hypersensitivity (for example, angioedema, urticaria, rash, pruritus) to OSPHEA or any ingredients • Known or suspected pregnancy 	<ul style="list-style-type: none"> • Venous Thromboembolism: Risk of DVT and pulmonary embolism • Known, suspected, or history of breast cancer • Severe Hepatic Impairment-- • Do not use estrogens or estrogen agonist/antagonist concomitantly with OSPHEA. • Do not use fluconazole concomitantly with OSPHEA. Fluconazole increases serum concentrations of OSPHEA. • Do not use rifampin concomitantly with OSPHEA. Rifampin decreases serum concentration of OSPHEA

	<p>There is a reported increased risk of stroke and deep vein thrombosis (DVT) in postmenopausal women (50 to 79 years of age) who received daily oral conjugated estrogens (CE) [0.625 mg]-alone therapy over 7.1 years as part of the Women's Health Initiative (WHI).</p>			
<p>Estrogen ring (ESTRING) Vaginal ring which contains a drug reservoir of 2 mg estradiol and releases approximately 7.5 mcg per 24 hours over 90 days</p>	<p>Endometrial Cancer Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding.</p> <p>Cardiovascular and Other Risks Estrogens with or without progestins should not be used for the prevention of cardiovascular disease or dementia. <u>Estrogen Alone</u> Increased risks of stroke and DVT in postmenopausal women (50 to 79 years of age) during 6.8 years and 7.1 years, respectively, of treatment with daily oral conjugated estrogens (CE 0.625 mg) relative to placebo. Increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 5.2 years of treatment with daily CE 0.625 mg alone <u>Estrogen Plus Progestin Therapy</u> Increased risks of MI, stroke, invasive breast cancer, pulmonary emboli, and DVT in postmenopausal women (50 to 79 years of age) during 5.6 years of treatment with daily oral CE 0.625</p>	<ul style="list-style-type: none"> • Treatment of moderate to severe urogenital symptoms due to postmenopausal atrophy of the vagina (e.g., dryness, burning, pruritus and dyspareunia) and/or the lower urinary tract (e.g., urinary urgency and dysuria) 	<ul style="list-style-type: none"> • Undiagnosed abnormal genital bleeding. • Known, suspected, or history of cancer of the breast. • Known or suspected estrogen-dependent neoplasia. • Active deep vein thrombosis, pulmonary embolism or a history of these conditions. • Active or recent (within the past year) arterial thromboembolic disease (for example, stroke and myocardial infarction). • Known liver dysfunction or disease. • Known hypersensitivity to any of the ingredients in ESTRING. • Known or suspected pregnancy. 	<ul style="list-style-type: none"> • 2 to 4-fold increase in the risk of gallbladder disease. • May lead to severe hypercalcemia in patients with breast cancer and bone metastases. • Retinal vascular thrombosis has been reported in patients receiving estrogens. <u>Estrogen Alone Therapy</u> <ul style="list-style-type: none"> • Increased risk of stroke and DVT. • Increased risk of endometrial cancer. • Increased risk of breast cancer. <u>Estrogen Plus Progestin Therapy</u> <ul style="list-style-type: none"> • Increased risk of stroke, DVT, pulmonary embolism, and MI. • Clinical surveillance is important, though adding progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia. • Increased risk of breast cancer. • Increased risk of ovarian cancer.

	<p>mg combined with medroxyprogesterone acetate (MPA 2.5 mg), relative to placebo. Increased risk of developing probable dementia during 4 years of treatment with daily CE 0.625 mg combined with MPA 2.5 mg, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women. In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and MPA and other combinations and dosage forms of estrogens and progestins.</p>			
<p>Estrogen cream (Premarin) 0.5 to 2 g intravaginally 21 days on/7 days off for Treatment of Atrophic Vaginitis and Kraurosis Vulvae 0.5 g intravaginally 21 days on/7 days off for Treatment of Moderate to Severe Dyspareunia, a Symptom of Vulvar and Vaginal Atrophy, due to Menopause 0.5 g 2x/week for Treatment of Moderate to Severe Dyspareunia, a Symptom of Vulvar and Vaginal Atrophy, due to Menopause</p>	<p><u>Estrogen-Alone Therapy</u> There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens. Estrogen-alone therapy should not be used for the prevention of cardiovascular disease or dementia. The Women's Health Initiative (WHI) estrogen-alone substudy reported increased risks of stroke and deep vein thrombosis (DVT). The WHI Memory Study (WHIMS) estrogen-alone ancillary study of WHI reported an increased risk of probable dementia in postmenopausal women 65 years of age and older. <u>Estrogen Plus Progestin Therapy</u> Estrogen plus progestin therapy should not be used for the prevention of cardiovascular disease or dementia. The WHI estrogen plus progestin substudy reported increased risks of stroke, DVT, pulmonary embolism (PE), and myocardial infarction (MI).</p>	<p>Treatment of Atrophic Vaginitis and Kraurosis Vulvae Treatment of Moderate to Severe Dyspareunia, a Symptom of Vulvar and Vaginal Atrophy, due to Menopause</p>	<p>Undiagnosed abnormal genital bleeding Known, suspected, or history of breast cancer Known or suspected estrogen-dependent neoplasia Active DVT, PE, or a history of these conditions Active arterial thromboembolic disease (for example, stroke and MI), or a history of these conditions Known anaphylactic reaction or angioedema to PREMARIN Vaginal Cream Known liver dysfunction or disease Known protein C, protein S, or antithrombin deficiency or other known thrombophilic disorders Known or suspected pregnancy</p>	<p>Estrogens increase the risk of gallbladder disease Discontinue estrogen if severe hypercalcemia, loss of vision, severe hypertriglyceridemia or cholestatic jaundice occurs Monitor thyroid function in women on thyroid replacement therapy</p>

	<p>The WHI estrogen plus progestin substudy reported increased risks of invasive breast cancer.</p> <p>The WHIMS estrogen plus progestin ancillary study of WHI reported an increased risk of probable dementia in postmenopausal women 65 years of age and older.</p>			
<p>Oxytocin (Prepidil Gel) Dinoprostone 0.5 mg/3 g (2.5 mL gel)</p>	<p>FOR HOSPITAL USE ONLY</p> <p>Dinoprostone, as with other potent oxytocic agents, should be used only with strict adherence to recommended dosages. Dinoprostone should be administered by physicians in a hospital that can provide immediate intensive care and acute surgical facilities.</p> <p>Women aged 30 years or older, those with complications during pregnancy and those with a gestational age over 40 weeks have been shown to have an increased risk of postpartum disseminated intravascular coagulation. In addition, these factors may further increase the risk associated with labor induction. Therefore, in these women, use of dinoprostone should be undertaken with caution. Measures should be applied to detect as soon as possible an evolving fibrinolysis in the immediate post-partum phase.</p> <p>The Clinician should be alert that the intracervical placement of dinoprostone gel may result in inadvertent disruption and subsequent embolization of antigenic tissue causing in rare circumstances the development of</p>	<p>PREPIDIL Gel is indicated for ripening an unfavorable cervix in pregnant women at or near term with a medical or obstetrical need for labor induction.</p>	<p>Patients in whom oxytocic drugs are generally contraindicated or where prolonged contractions of the uterus are considered inappropriate, such as:</p> <ul style="list-style-type: none"> cases with a history of cesarean section or major uterine surgery cases in which cephalopelvic disproportion is present cases in which there is a history of difficult labor and/or traumatic delivery grand multiparae with six or more previous term pregnancies cases with non-vertex presentation cases with hyperactive or hypertonic uterine patterns cases of fetal distress where delivery is not imminent in obstetric emergencies where the benefit-to-risk ratio for either the fetus or the mother favors surgical intervention <p>Patients with hypersensitivity to prostaglandins or constituents of the gel.</p> <p>Patients with placenta previa or unexplained vaginal bleeding during this pregnancy.</p> <p>Patients for whom vaginal delivery is not indicated, such as vasa previa or active herpes genitalia.</p>	<p><u>General Precautions</u> During use, uterine activity, fetal status, and character of the cervix (dilation and effacement) should be carefully monitored either by auscultation or electronic fetal monitoring to detect possible evidence of undesired responses, e.g., hypertonus, sustained uterine contractility, or fetal distress. In cases where there is a history of hypertonic uterine contractility or tetanic uterine contractions, it is recommended that uterine activity and the state of the fetus should be continuously monitored. The possibility of uterine rupture should be borne in mind when high-tone myometrial contractions are sustained. Feto-pelvic relationships should be carefully evaluated before use of PREPIDIL Gel.</p> <p>Caution should be exercised in administration of PREPIDIL Gel in patients with:</p> <ul style="list-style-type: none"> asthma or history of asthma glaucoma or raised intraocular pressure <p>Caution should be taken so as not to administer PREPIDIL</p>

	<p>Anaphylactoid Syndrome of Pregnancy (Amniotic Fluid Embolism).</p>			<p>Gel above the level of the internal os. Careful vaginal examination will reveal the degree of effacement which will regulate the size of the shielded endocervical catheter to be used. That is, the 20 mm endocervical catheter should be used if no effacement is present, and the 10 mm catheter should be used if the cervix is 50% effaced. Placement of PREPIDIL Gel into the extraamniotic space has been associated with uterine hyperstimulation.</p> <p>As PREPIDIL Gel is extensively metabolized in the lung, liver, and kidney, and the major route of elimination is the kidney, PREPIDIL Gel should be used with caution in patients with renal and hepatic dysfunction.</p> <p><u>Patients With Ruptured Membranes</u> Caution should be exercised in the administration of PREPIDIL Gel in patients with ruptured membranes. The safety of use of PREPIDIL Gel in these patients has not been determined.</p> <p><u>Drug Interactions</u> PREPIDIL Gel may augment the activity of other oxytocic agents and their concomitant use is not recommended. For the sequential use of oxytocin following PREPIDIL Gel administration, a dosing</p>
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				<p>interval of 6–12 hours is recommended.</p> <p><u>Carcinogenesis, Mutagenesis, Impairment of Fertility</u> Carcinogenic bioassay studies have not been conducted in animals with PREPIDIL Gel due to the limited indications for use and short duration of administration. No evidence of mutagenicity was observed in the Micronucleus Test or Ames Assay.</p> <p><u>Pregnancy</u> Prostaglandin E2 produced an increase in skeletal anomalies in rats and rabbits. No effect would be expected clinically, when used as indicated, since PREPIDIL Gel is administered after the period of organogenesis. PREPIDIL Gel has been shown to be embryotoxic in rats and rabbits, and any dose that produces sustained increased uterine tone could put the embryo or fetus at risk. See statements under General Precautions.</p> <p><u>Pediatric Use</u> Safety and effectiveness in pediatric patients have not been established.</p>
DHEA (Intrarosa) 6.5 mg prasterone vaginal insert once daily	None	INTRAROSA is a steroid indicated for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause.	Undiagnosed abnormal genital bleeding: Any postmenopausal woman with undiagnosed, persistent or recurring genital bleeding should be evaluated to determine the cause of the bleeding before consideration of treatment with INTRAROSA.	<p><u>Current or Past History of Breast Cancer</u> Estrogen is a metabolite of prasterone. Use of exogenous estrogen is contraindicated in women with a known or suspected history of breast cancer. INTRAROSA has not</p>

				been studied in women with a history of breast cancer.
Raloxifene (Evista) Daily 60 mg oral tablet	<p>INCREASED RISK OF VENOUS THROMBOEMBOLISM AND DEATH FROM STROKE</p> <p>Increased risk of deep vein thrombosis and pulmonary embolism have been reported with EVISTA. Women with active or past history of venous thromboembolism should not take EVISTA.</p> <p>Increased risk of death due to stroke occurred in a trial in postmenopausal women with documented coronary heart disease or at increased risk for major coronary events. Consider risk-benefit balance in women at risk for stroke.</p>	<p>Treatment and prevention of osteoporosis in postmenopausal women.</p> <p>Reduction in risk of invasive breast cancer in postmenopausal women with osteoporosis.</p> <p>Reduction in risk of invasive breast cancer in postmenopausal women at high risk for invasive breast cancer.</p>	<p>Active or past history of venous thromboembolism, including deep vein thrombosis, pulmonary embolism, and retinal vein thrombosis.</p> <p>Pregnancy, women who may become pregnant, and nursing mothers.</p>	<p>Venous Thromboembolism:</p> <p>Increased risk of deep vein thrombosis, pulmonary embolism, and retinal vein thrombosis. Discontinue use 72 hours prior to and during prolonged immobilization.</p> <p>Death Due to Stroke:</p> <p>Increased risk of death due to stroke occurred in a trial in postmenopausal women with documented coronary heart disease or at increased risk for major coronary events. No increased risk of stroke was seen in this trial. Consider risk-benefit balance in women at risk for stroke.</p> <p>Cardiovascular Disease:</p> <p>EVISTA should not be used for the primary or secondary prevention of cardiovascular disease.</p> <p>Premenopausal Women: Use is not recommended.</p> <p>Hepatic Impairment: Use with caution.</p> <p>Concomitant Use with Systemic Estrogens: Not recommended.</p> <p>Hypertriglyceridemia: If previous treatment with estrogen resulted in hypertriglyceridemia, monitor serum triglycerides.</p>

Appendix E. PCORI® Methodology Standards Checklist

Contract No.	75Q80120D00008				
Task Order No.	75Q80122F32006				
EPC	Minnesota				
Project Title	Genitourinary Syndrome of Menopause: A Systematic Review				
Standard Category	Abbrev.	Standard	Is This Standard Applicable to This SR?	List Pages of the SR Report Where You Address This Standard	Notes
Cross-Cutting Standards for PCOR					
Standards for Formulating Research Questions	RQ-1	Identify gaps in evidence	Yes	1-2	--
	RQ-2	Develop a formal study protocol	Yes	3	--
	RQ-3	Identify specific populations and health decision(s) affected by the research	Yes	1-2	--
	RQ-4	Identify and assess participant subgroups	Yes	1	--
	RQ-5	Select appropriate interventions and comparators	Yes	5-6, 8-10	--
	RQ-6	Measure outcomes that people representing the population of interest notice and care about	Yes	10-11	--
Standards Associated with Patient-Centeredness	PC-1	Engage people representing the population of interest and other relevant stakeholders in ways that are appropriate and necessary in a given research context	Yes	iv-vi	--
	PC-2	Identify, select, recruit, and retain study participants representative of the spectrum of the population of interest and ensure that data are collected thoroughly and systematically from all study participants	N/A	N/A	--
	PC-3	Use patient-reported outcomes when patients or people at risk of a condition are the best source of information for outcomes of interest	N/A	N/A	--
	PC-4	Support dissemination and implementation of study results	Yes	99-100	--
Standards for Data Integrity and Rigorous Analyses	IR-1	A priori, specify plans for data analysis that correspond to major aims	Yes	8-11	--
	IR-2	Assess data source adequacy	Yes	8-11	--
	IR-3	Describe data linkage plans, if applicable	N/A	--	--
	IR-4	Document validated scales and tests	N/A	--	--
	IR-5	Provide sufficient information in reports to allow for assessments of the study's internal and external validity	Yes	Appendix C. Evidence Tables	--
	IR-6	Masking should be used when feasible	N/A	--	--

	IR-7	In the study protocol, specify a data management plan that addresses, at a minimum, the following elements: collecting data, organizing data, handling data, describing data, preserving data, and sharing data.	Yes	5-11	--
Standards for Preventing and Handling Missing Data	MD-1	Describe methods to prevent and monitor missing data	N/A	--	--
	MD-2	Use valid statistical methods to deal with missing data that properly account for statistical uncertainty due to missingness	N/A	--	--
	MD-3	Record and report all reasons for dropout and missing data, and account for all patients in reports	N/A	--	--
	MD-4	Examine sensitivity of inferences to missing data methods and assumptions, and incorporate into interpretation	N/A	--	--
Standards for Heterogeneity of Treatment Effect (HTE)	HT-1	State the goals of HTE analyses, including hypotheses and the supporting evidence base	N/A	--	--
	HT-2	For all HTE analyses, provide an analysis plan, including the use of appropriate statistical methods	N/A	--	--
	HT-3	Report all prespecified HTE analyses and, at minimum, the number of post-hoc HTE analyses, including all subgroups and outcomes analyzed	N/A	--	--
Standards for Specific Study Designs and Methods					
Standards for Data Registries	DR-1	Requirements for the design of registries	N/A	--	--
	DR-2	Documentation and reporting requirements of registry materials, characteristics, and bias	N/A	--	--
	DR-3	Adapting established registries for PCOR	N/A	--	--
	DR-4	Documentation requirements when using registry data	N/A	--	--
Standards for Data Networks as Research-Facilitating Structures	DN-1	Requirements for the design and features of data networks	N/A	--	--
	DN-2	Selection and use of data networks	N/A	--	--
Causal Inference Standards	CI-1	CI-I: Specify the causal model underlying the research question ***CROSS-CUTTING STANDARD***	N/A	--	--
	CI-2	Define and appropriately characterize the analysis population used to generate effect estimates	N/A	--	--
	CI-3	Define with the appropriate precision the timing of the outcome assessment relative to the initiation and duration of exposure	N/A	--	--

	CI-4	Measure potential confounders before start of exposure and report data on potential confounders with study results	N/A	--	--
	CI-5	Report the assumptions underlying the construction of propensity scores and the comparability of the resulting groups in terms of the balance of covariates and overlap	N/A	--	--
	CI-6	Assess the validity of the instrumental variable (i.e. how the assumptions are met) and report the balance of covariates in the groups created by the instrumental variable	N/A	--	--
Standards for Adaptive and Bayesian Trial Designs	AT-1	Specify planned adaptations, decisional thresholds, and statistical properties of those adaptations	N/A	--	--
	AT-2	Specify the structure and analysis plan for Bayesian adaptive randomized clinical trial designs	N/A	--	--
	AT-3	Ensure that clinical trial infrastructure is adequate to support planned adaptation(s) and independent interim analyses	N/A	--	--
	AT-4	When reporting adaptive randomized clinical trials, use the CONSORT statement, with modifications	N/A	--	--
Standards for Studies of Medical Tests	MT-1	Specify the clinical context and key elements of the medical test	N/A	--	--
	MT-2	Assess the effect of factors known to affect performance and outcomes	N/A	--	--
	MT-3	Focus studies of medical tests on patient-centered outcomes, using rigorous study designs with a preference for randomized controlled trials	N/A	--	--
Standards for Systematic Reviews	SR-1	Adhere to National Academy of Medicine (NAM) standards for systematic reviews of comparative effectiveness research, as appropriate	N/A	--	--
Standards on Research Designs Using Clusters	RC-1	Specify whether the study objectives, the interventions, and the primary outcomes pertain to the cluster level or the individual level	N/A	--	--
	RC-2	Justify the choice of cluster randomization	N/A	--	--
	RC-3	Power and sample size estimates must use appropriate methods to account for the dependence of observations within clusters and the degrees of freedom available at the cluster level	N/A	--	--
	RC-4	Data analyses must account for the dependence of observations within clusters regardless of its magnitude	N/A	--	--
	RC-5	Stratified randomization should be used when feasible	N/A	--	--

Standards for Studies of Complex Interventions	SCI-1	Fully describe the intervention and comparator and define their core functions	N/A	--	--
	SCI-2	Specify the hypothesized causal pathways and their theoretical basis.	N/A	--	--
	SCI-3	Specify how adaptations to the form of the intervention and comparator will be allowed and recorded	N/A	--	--
	SCI-4	Plan and describe a process evaluation	N/A	--	--
	SCI-5	Select patient outcomes informed by the causal pathway	N/A	--	--
Standards for Qualitative Methods	QM-1	State the qualitative approach to research inquiry, design, and conduct	N/A	--	--
	QM-2	Select and justify appropriate qualitative methods sampling strategy	N/A	--	--
	QM-3	Link the qualitative data analysis, interpretations, and conclusions to the study question	N/A	--	--
	QM-4	Establish trustworthiness and credibility of qualitative research	N/A	--	--
Standards for Mixed Methods Research	MM-1	Specify how mixed methods are integrated across design, data sources, and/or data collection phases	N/A	--	--
	MM-2	Select and justify appropriate mixed methods sampling strategy	N/A	--	--
	MM-3	Integrate data analysis, data interpretation, and conclusions	N/A	--	--
Standards for Individual Participant-Level Data Meta-Analysis (IPD-MA)	IPD-1	Specify the research question(s) that will be addressed through the IPD-MA and describe the specific information it will provide that other approaches would not	N/A	--	--
	IPD-2	Describe the proposed governance structure for the IPD-MA in the protocol and study reports	N/A	--	--
	IPD-3	Use systematic, reproducible methods to identify studies for inclusion in the IPD-MA	N/A	--	--
	IPD-4	Specify the design and planned analyses of the IPD-MA in a protocol, document any changes, and report significant amendments and modifications	N/A	--	--

Appendix F. Appendix References

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