Comparative Effectiveness Review
Number 272

Genitourinary Syndrome of Menopause: A Systematic Review

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.

Agency for Healthcare Research and Quality

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) review[1] 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 trials[2-6] (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 [CO_2] 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, CO_2 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, CO_2 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 CO_2 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
CO_2 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
CO_2 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
CO_2 laser vs. CO_2 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] ⊕◯◯◯
CO_2 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; CO_2=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:
[a]Downgraded one level for study limitations (one or more trials assessed as "some concerns" risk of bias)
[b]Downgraded one level for inconsistency (effect varied across trials)
[c]Downgraded one level for study limitations (one or more trials did not provide adequate statistical reporting)
[d]Downgraded one level for imprecision (total sample size less than OIS of 400)
[e]Downgraded one level for imprecision (SD crosses no-effect threshold)
[f]Downgraded two levels for imprecision (total sample size much less than OIS of 400)
[g]Downgraded 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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Full Report

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