Energy-based interventions for genitourinary syndrome of menopause: a systematic review of randomized controlled trials and prospective observational studies

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Abstract

Importance: Hormone treatments for genitourinary syndrome of menopause (GSM) symptoms have limitations. There is interest in nonhormone therapies, including energy-based interventions. Benefits and harms of energy-based interventions are not currently well known.

Objective: The aim of this study was to assess the benefits and harms of energy-based therapies (eg, CO_2 laser, Er:YAG laser, and radiofrequency) for GSM. Outcomes of interest are the eight "Core Outcomes in Menopause" and include the following: dyspareunia, vulvovaginal dryness, vulvovaginal discomfort/irritation, dysuria, change in most bothersome symptom, quality of life, treatment satisfaction, and treatment adverse effects.

Evidence Review: Eligible studies included English language randomized controlled trials (RCT) or prospective observational studies of energy-based treatments with ≥8 weeks follow-up in postmenopausal women with ≥1 GSM symptom and studies of any design reporting adverse effects ≥12 months postintervention. Ovid/MEDLINE, Embase, and CINAHL were searched from inception to December 11, 2023 using vocabulary and natural language terms, along with free-text words. Two authors extracted data and assessed the quality of included studies.

Findings: We identified 32 unique studies (16 RCT; 1 quasi-RCT; 15 nonrandomized). Ten RCT and the quasi-RCT were rated low to moderate risk of bias (RoB) and underwent data extraction. Included studies evaluated CO_2 laser (k = 7), Er:YAG laser (k = 3), or radiofrequency and CO_2 laser (k = 1). CO_2 laser compared with sham (k = 4) may result in little to no difference in dysuria, dyspareunia, or quality of life (low certainty of evidence [COE]). CO_2 laser compared with vaginal conjugated estrogens cream (k = 2) may result in little to no difference in dyspareunia, dryness, discomfort/irritation, dysuria, or quality of life (low COE). Treatment effects on all other outcomes and effects of Er:YAG laser or radiofrequency on any outcome are very uncertain (very low COE). Studies noted few adverse events and no serious adverse events.

Conclusions and Relevance: CO_2 laser resulted in little to no difference in outcomes compared with sham or vaginal estrogen; the evidence is very uncertain on the effect of energy-based interventions versus all other comparators for all other outcomes. Adverse event reporting was limited. There is a need for further evidence assessing energy-based interventions.

Key Words: Genitourinary syndrome of menopause, Energy-based, Laser, Menopause

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Genitourinary syndrome of menopause (GSM) describes symptoms and physical changes associated with declining estrogen and androgen concentrations in the genitourinary tract after menopause. Estimates of GSM prevalence vary from 13% to 87%.[1] Core GSM therapies, including vaginal estrogens and vaginal moisturizers and lubricants, locally replace premenopausal hormones and/or secretions to reduce bothersome symptoms like vaginal dryness and dyspareunia. Limitations of hormone and topical treatments for GSM include inconsistent long-term use and concerns about potential harms for survivors of, and those at risk for, reproductive or hormone-sensitive cancers. Interest in nontraditional interventions is growing, including energy-based (EB) treatments such as laser and radiofrequency (RF) devices.[2]

Lasers and RF devices have been available as medical therapies for decades[3,4] and are used in dermatology, surgery, oncology, and ophthalmology.[4,5] The US Food and Drug Administration (FDA) has cleared EB devices for general indications in gynecology.[6] However, the safety and effectiveness of EB devices for menopausal symptoms has not been evaluated by the FDA. In 2018, the FDA issued a warning regarding lasers and other EB devices for "vaginal rejuvenation" (ie, to treat conditions and symptoms related to menopause, urinary incontinence, or sexual

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function).[7] Nevertheless, EB treatments are currently marketed to women unable or unwilling to use other therapies.[8]

The most commonly used lasers for GSM are fractional microablative carbon dioxide (CO_2) and nonablative erbium-doped yttrium aluminum garnet (Er:YAG).[2,9] Microablative lasers burn a grid of tiny holes in the surface tissue. Fractional lasers split the laser beam into columns, sparing the tissue between the columns to speed recovery. Nonablative lasers heat underlying tissue without harming surface tissue.[9,10] RF devices use electromagnetic current to generate heat due to tissue resistance to the electromagnetic current.[10]

This systematic review was conducted to assess the benefits and harms of EB interventions for GSM symptoms to inform clinical decision making for clinicians and women. Previous reviews[11-15] have focused on CO_2 lasers and have not used the Core Outcomes in Menopause (COMMA) framework.[16]

Key points

- **Question/Objective:** Assess effects of energy-based interventions for genitourinary syndrome of menopause (GSM).
- **Findings:** Eleven studies (n = 869) with "low" or "some concerns" risk of bias were included. Seven evaluated CO_2 laser, three Er:YAG laser, and one CO_2 laser or radiofrequency. CO_2 and Er:YAG lasers may result in little to no difference for certain GSM symptoms versus sham. Evidence is uncertain for other interventions, comparators, and outcomes. Harms reporting was limited.
- **Meaning:** Energy-based interventions are marketed to women unable or unwilling to use GSM therapies. Evidence on their effects is sparse. Additional research is needed to assess harms and determine if benefits exist.

METHODS/LITERATURE SEARCH

We searched MEDLINE, Embase, and CINAHL from database inception through December 11, 2023 (Supplemental Digital Content, http://links.lww.com/MENO/B328) supplemented by citation searches of relevant systematic reviews and original research. Protocol registered in PROSPERO (CRD42023400684).

Randomized controlled trials (RCT) and prospective observational studies with a concurrent control group were eligible if they enrolled postmenopausal women with ≥1 symptom of GSM, evaluated EB treatments, were ≥8 weeks in duration, enrolled ≥20 per arm, and reported ≥1 prespecified outcome of interest. Nonrandomized and uncontrolled studies were eligible for long-term adverse event analysis if they reported follow-up of ≥12 months. Abstracts were screened by two independent reviewers, with the assistance of DistillerSR's Artificial Intelligence System (DAISY). Articles included by any reviewer at abstract level underwent full-text review by two independent reviewers.

Risk of bias (RoB) was assessed by one author and reviewed by a second using standard tools for randomized[17] and nonrandomized studies.[18] Effectiveness and harms outcomes were extracted only from RCT or quasi-RCT deemed low or some concerns RoB; long-term harms data were extracted from nonrandomized and uncontrolled studies regardless of RoB.

Study characteristics and outcomes data were abstracted by one reviewer and overread by a second. Outcomes of interest included the eight COMMA outcomes[16]: not all studies reported all COMMA outcomes; we present data as reported by authors.

We narratively summarized outcomes for each intervention/comparator group. We were unable to perform meta-analysis of results due to variability in populations, interventions, comparisons, and outcomes. Extracted results include change from baseline to follow-up means and between-group statistical testing. Certainty of evidence (COE) for COMMA outcomes was determined using the GRADE approach and was based on statistical significance.[19]

RESULTS

This review is part of a larger review assessing all treatments for GSM.[20] The overall search identified 11,993 unique articles; 32 EB treatment studies (34 publications) met inclusion criteria (Fig. 1). Of the 32 studies, 16 were RCT, one was a quasi-randomized study, and 15 were noncontrolled. The noncontrolled studies were all rated critical or serious RoB and used only for assessment of long-term (≥12 months) harms. Of the 16 RCT, six were rated high RoB and did not undergo outcomes extraction or further analyses.[21-27] Five were rated low RoB,[28-32] and another five were rated some concerns RoB[33-37]; the quasi-randomized study was rated moderate RoB.[38]

An overview of the included RCT/quasi-RCT rated low, or some concerns RoB can be found in Table 1. Studies were small (10 studies had <100 participants each) and short in duration (10 were ≤6 months). Only one was conducted in the United States.[31] Mean age ranged from 56-64 years. Only two studies reported race; both were >90% White. Symptom inclusion criteria varied (nine included women with vulvovaginal symptoms, and none required study participants to have a combination of vulvovaginal, urinary, and sexual symptoms). Baseline symptom severity was only reported in two studies (rated as moderate to severe). Nine studies required hormone therapy be discontinued prior to enrollment, seven required nonhormone therapies be discontinued prior to enrollment, and four excluded prior EB treatment. Three studies reported the percentage of participants who used prior hormone therapy (range: 17%-80%). The 10 RCT investigated CO_2 laser (k = 7) or Er:YAG laser (k = 3) interventions. One of the CO_2 laser RCT was a three-arm trial that evaluated CO_2 lasers versus RF or placebo. For CO_2 laser RCT, comparators included sham laser (k = 4),[28,29,33,34] vaginal conjugated estrogens cream (CEC) (k = 2),[30,31] or RF or placebo (k = 1, with three arms; the placebo was not described).[35] Interventions included three 30-40 watts treatments, 4-6 weeks apart. For Er:YAG laser RCT, comparators included sham laser (k = 1),[32] hyaluronic acid (HA) suppositories (k = 1),[37] or an Er:YAG laser hyperstack protocol (k = 1).[36] Interventions included one to three monthly treatments, with two modes or protocols used per treatment, ranging from 6-20 J/cm^2. The quasi-randomized study compared CO_2 laser with CO_2 laser plus HA gel, and used 3 monthly 15 watts treatments.[38] Detailed study characteristics and results are in Supplemental Tables 1-8 (http://links.lww.com/MENO/B328). COE is reported in Table 2.

Dyspareunia

Seven RCT (n = 927)[28-31,33,36,37] and one quasi-randomized study (n = 50)[38] assessed the effect of an EB intervention on dyspareunia at 3-12 months. Dyspareunia was measured using a

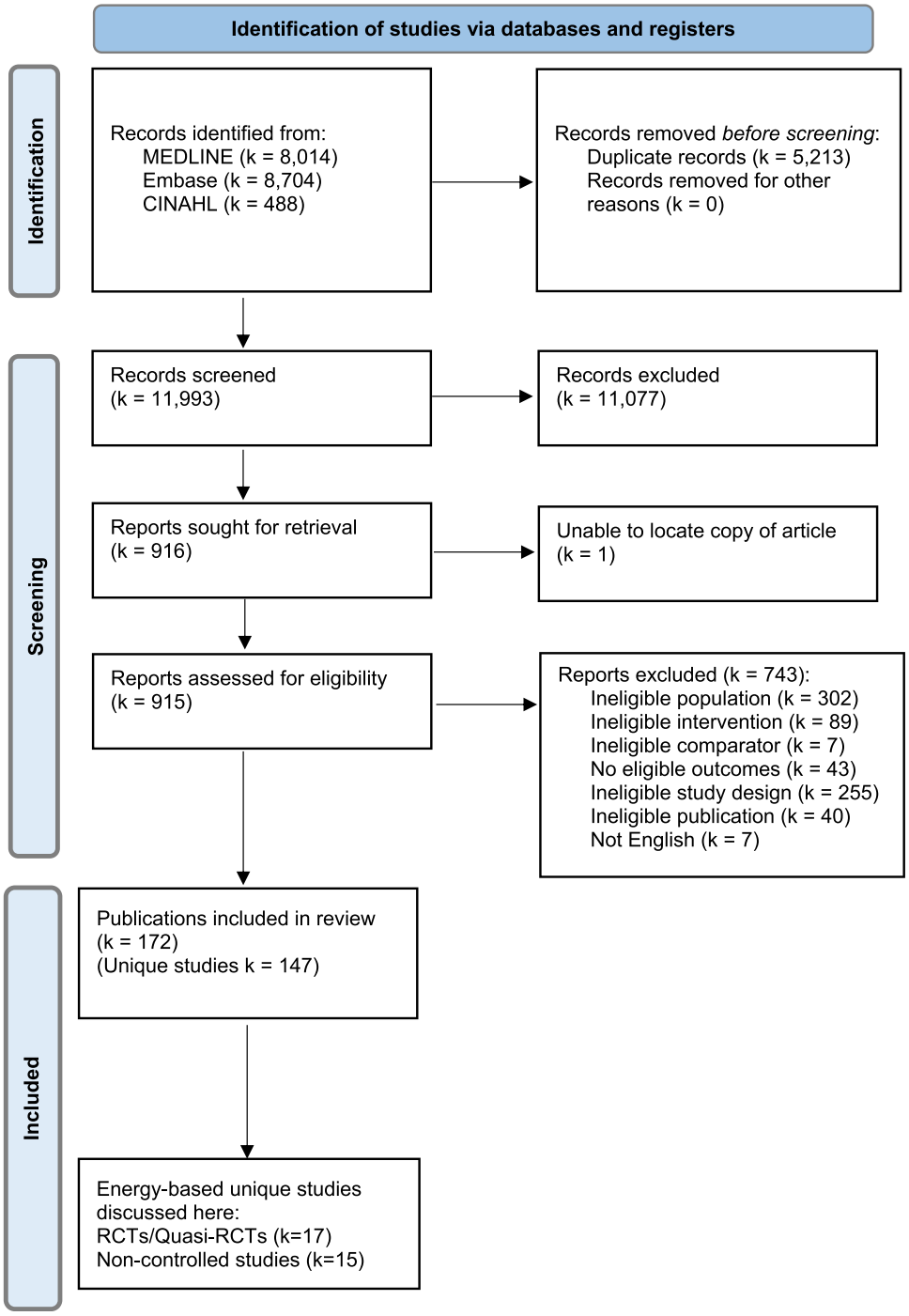

FIG. 1. Literature flow diagram.

10- or 100-point Visual Analog Scale (VAS), the Female Sexual Function Index pain domain, and the European Organization for Research and Treatment of Cancer Sexual Health Questionnaire. CO_2 laser may result in little to no difference versus vaginal CEC (low COE). The evidence is very uncertain on the effect of CO_2 laser versus sham, CO_2 laser versus CO_2 laser plus HA gel, Er:YAG laser versus HA suppositories, and Er:YAG laser versus an Er:YAG laser hyperstack protocol on dyspareunia (very low COE).

Vulvovaginal dryness/lubrication

Vulvovaginal dryness was assessed using a 10- or 100-point VAS, the Female Sexual Function Index lubrication domain, International Consultation on Incontinence Modular Questionnaire (ICIQ) Vaginal Symptoms, and European Organization for Research and Treatment of Cancer Sexual Health Questionnaire at 3-12 months. In the seven RCT (n = 455)[28-31,33,34,37] and one quasi-randomized study (n = 50)[38] that assessed the effect of EB

TABLE 1. Overview of eligible energy-based intervention studies

Category	Characteristics	CO_2 Laser vs Sham Laser (k = 4)	CO_2 Laser vs Vaginal CEC (k = 2)	CO_2 Laser vs Laser + HA Gel (k = 1)	CO_2 Laser vs Radiofrequency vs Placebo (k = 1)	Er:YAG Laser vs Sham Laser (k = 1)	Er:YAG Laser vs HA Suppositories (k = 1)	Er:YAG Laser VEL vs Er:YAG Hyperstack Laser (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	6
	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	1	0	2
	Sexual	2	0	0	1	0	1	0	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 or high-risk for cancer	0	0	0	0	0	1	1	2
	Treatment naïve/washout period	4	2	1	0	0	1	1	9
Length of follow-up	3 mo	1[a]	1	1	0	1	1	1	6
	4 mo	1	0	0	0	0	0	0	1
	6 mo	1	1	0	0	0	0	0	2
	≥12 mo	1	0	0	0	0	0	0	1
Outcomes reported[b]	Dyspareunia	3	2	1	1	0	1	1	9
	Dryness	4	2	1	0	0	1	0	8
	Discomfort/irritation	3	1	1	0	0	0	0	5
	Dysuria	3	1	1	0	0	0	0	5
	Change in MBS	1	0	0	0	0	0	0	1
	QoL	3	1	1	1	1	1	0	8
	Treatment satisfaction	2	1	0	0	0	1	0	4
	Adverse effects	4	2	1	1	1	1	1	10
Location	United States	0	1	0	0	0	0	0	1
	Europe	2	0	1	0	0	1	1	5
	Asia	1	0	0	0	1	0	0	2
	Australia	1	0	0	0	0	0	0	1
	Middle East	0	1	0	1	0	0	0	2

AE, adverse events; CEC, conjugated estrogen cream; CO_2, carbon dioxide; Er:YAG, erbium-doped yttrium aluminum garnet laser; HA, hyaluronic acid; hx, history; QoL, quality of life; s/p, status post; VEL, vaginal erbium laser; VVA/GSM, vulvovaginal atrophy/genitourinary syndrome of menopause.

[a]Page[28] follow-up time reported here as 3 months postbaseline (outcomes assessed before active laser group cross-over to sham laser).

[b]Genital or vulvovaginal signs/symptoms include dryness, irritation, pain, soreness, urethral caruncle, urethral prolapse, vaginal atrophy; urinary symptoms include dysuria, nocturia, overactive bladder, recurrent urinary tract infections, urinary frequency, urge incontinence, urinary urgency; sexual symptoms include dyspareunia, bleeding associated with sexual activity, decreased arousal, low libido, orgasmic dysfunction, sexual desire, sexual function; QoL outcomes include distress, bother, or interference of GSM symptoms, anxiety, depression, partner satisfaction; adverse effects includes side effects, systemic AE, safety outcomes.

TABLE 2. Certainty of evidence statements for COMMA effectiveness outcomes

Intervention vs Comparator	Dyspareunia	Dryness	Discomfort/Irritation	Dysuria	Change in MBS	Quality of Life	Treatment Satisfaction
	Certainty of Evidence # Studies: k # Enrollees (n): Effect Direction	Certainty of Evidence # Studies: k # Enrollees (n): Effect Direction	Certainty of Evidence # Studies: k # Enrollees (n): Effect Direction	Certainty of Evidence # Studies: k # Enrollees (n): Effect Direction	Certainty of Evidence # Studies: k # Enrollees (n): Effect Direction	Certainty of Evidence # Studies: k # Enrollees (n): Effect Direction	Certainty of Evidence # Studies: k # Enrollees (n): Effect Direction
CO_2 laser vs sham laser	Very low ⊕◯◯◯ Uncertain 3 (205): ↑ 1 study ↔ 1 study ? 1 study	Very low ⊕◯◯◯ Uncertain 4 (293): ↑ 1 study ↔ 1 study ? 2 studies	Very low ⊕◯◯◯ Uncertain 3 (205): ↑ 1 study ↔ 1 study ? 1 study	Low ⊕⊕◯◯ May result in little to no difference 3 (205): ↔ 2 studies ? 1 study	Low ⊕⊕◯◯ May result in little to no difference 1 (60): ↔ 1 study	Low ⊕⊕◯◯ May result in little to no difference 3 (205): ↔ 2 studies ? 1 study	Very low ⊕◯◯◯ Uncertain 2 (148): ? 2 studies
CO_2 laser vs vaginal conjugated estrogens cream	Low ⊕⊕◯◯ May result in little to no difference 2 (119): ↔ 1 study ? 1 study	Low ⊕⊕◯◯ May result in little to no difference 2 (119): ↔ 1 study ? 1 study	Low ⊕⊕◯◯ May result in little to no difference 1 (69): ↔ 1 study	Low ⊕⊕◯◯ May result in little to no difference 1 (69): ↔ 1 study	NR	Low ⊕⊕◯◯ May result in little to no difference 1 (69): ↔ 1 study	Very low ⊕◯◯◯ Uncertain 1 (69): ? 1 study
CO_2 laser vs CO_2 laser plus HA gel	Very low ⊕◯◯◯ Uncertain 1 (50): ↔ 1 study	Very low ⊕◯◯◯ Uncertain 1 (50): ↔ 1 study	Very low ⊕◯◯◯ Uncertain 1 (50): ↔ 1 study	Very low ⊕◯◯◯ Uncertain 1 (50): ↔ 1 study	NR	Very low ⊕◯◯◯ Uncertain 1 (50): ↔ 1 study	NR
CO_2 laser vs radiofrequency, placebo	NR	NR	NR	NR	NR	Very low ⊕◯◯◯ Uncertain 1 (246): ? 1 study	NR
Er:YAG laser vs sham laser	NR	NR	NR	NR	NR	Low ⊕⊕◯◯ May result in little to no difference 1 (50): ↔ 1 study	NR
Er:YAG laser vs HA suppositories	Very low ⊕◯◯◯ Uncertain 1 (43): ? 1 study	Very low ⊕◯◯◯ Uncertain 1 (43): ? 1 study	NR	NR	NR	Very low ⊕◯◯◯ Uncertain 1 (43): ? 1 study	Very low ⊕◯◯◯ Uncertain 1 (43): ? 1 study
Er:YAG laser vs Er:YAG hyperstack	Very low ⊕◯◯◯ Uncertain 1 (68): ↑ 1 study	NR	NR	NR	NR	NR	NR
Radiofrequency vs CO_2 laser, placebo	NR	NR	NR	NR	NR	Very low ⊕◯◯◯ Uncertain 1 (246): ? 1 study	NR

Direction of effect.

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

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

↔: No statistically significant difference between groups.

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

AE, adverse event; CEC, conjugated estrogens cream; CO_2, carbon dioxide; Er:YAG, erbium-doped yttrium aluminum garnet laser; HA, hyaluronic acid; MBS, most bothersome symptom; NR, not reported; QoL, quality of life.

interventions on vulvovaginal dryness, CO_2 laser may result in little to no difference on vulvovaginal dryness compared with vaginal CEC (low COE), but the evidence is very uncertain on the effect of CO_2 laser versus sham laser, CO_2 laser versus CO_2 laser plus HA gel, and Er:YAG laser versus HA suppositories on vulvovaginal dryness (very low COE).

Vulvovaginal discomfort/irritation

In a time span ranging from 3-12 months, four RCT (n = 274)[28,29,31,33] and one quasi-randomized study (n = 50)[38] assessed the effect of EB interventions on vulvovaginal discomfort/irritation using a 10- or 100-point VAS. CO_2 laser may result in little to no difference on vulvovaginal discomfort compared with vaginal CEC. The evidence is very uncertain on the effect of CO_2 laser versus sham laser and CO_2 laser versus CO_2 laser plus HA gel on vulvovaginal discomfort (very low COE).

Dysuria

Dysuria was measured using a 10-point or 100-point VAS. With follow-up ranging from 3-12 months, four RCT (n = 274)[28,29,31,33] and one quasi-randomized study (n = 50)[38] assessed the effect of EB interventions on dysuria and found that CO_2 laser versus sham laser and CO_2 laser versus vaginal CEC may result in little to no difference in dysuria. The evidence is very uncertain on the effect of CO_2 laser versus CO_2 laser plus HA gel on dysuria (very low COE).

Change in MBS

One RCT (n = 60) assessed the effect of CO_2 laser versus sham laser using a 4-point VAS at 3 months.[28] CO_2 laser may result in little to no difference in MBS versus sham laser (low COE).

Quality of life

Seven RCT (n = 613)[28,29,31-33,35,37] and one quasi-randomized study (n = 50)[38] assessed the effect of EB interventions on quality of life (QoL) using ICIQ Overactive Bladder, Functional Social Support Questionnaire, Assessment of Quality of Life-6D, Urinary Distress Inventory Short Form, Day-to-Day Impact of Vaginal Aging Questionnaire, Female Sexual Distress Scale, Menopause-Specific Quality of Life, ICIQ short form, Overactive Bladder questionnaire, Health-Related Quality of Life, and Numeric Rating Scale from 3-12 months. CO_2 laser versus sham laser, CO_2 laser versus vaginal CEC, and Er:YAG laser versus sham laser may result in little to no difference in QoL (low COE). The evidence is very uncertain on the effect of CO_2 laser versus CO_2 laser plus HA gel, CO_2 laser versus RF or placebo, Er:YAG laser versus HA suppositories, and RF versus CO_2 laser or placebo (very low COE).

Treatment satisfaction

Treatment satisfaction was assessed by four RCT (n = 260)[28,31,34,37] using Patient Global Impression of Improvement, a 5-point Likert scale, and Zuf-8 from 3-6 months. The evidence is very uncertain on the effect of CO_2 laser versus sham, CO_2 laser versus vaginal CEC, and Er:YAG laser versus HA suppositories on treatment satisfaction (very low COE).

Adverse effects

No serious adverse effects (AE) were reported in RCT or quasi-randomized studies of any of the EB interventions studied, including CO_2 and Er:YAG laser, RF, and comparators, including sham laser, CEC, CO_2 laser plus HA gel, and HA suppositories. Among the 15 noncontrolled and retrospective studies, eight reported no AE[39-47]; one reported no AE lasting longer than 1 year.[48] Five reported no serious AE or no treatment-related AE but provided no detail about any nonserious events.[39-43,49] One reported no study withdrawals due to AE.[47]

DISCUSSION

We systematically reviewed the evidence for effectiveness and harms of EB interventions for GSM. Studies employed heterogeneous inclusion criteria and used inconsistent, nonvalidated outcome measures. Nearly all trials included fewer than 100 women, followed participants for 6 months or fewer, and were conducted outside the United States. Intervention protocols varied, and few studies evaluated nonablative CO_2 lasers, Er:YAG lasers, or RF devices.

Across 11 studies of CO_2 laser, Er:YAG laser, and RF, we found no benefit of, or insufficient evidence for, EB therapies relative to any comparator for any GSM symptom. We found some GSM outcomes for CO_2 laser may not be significantly different than outcomes for CEC. However, we do not consider these treatments equivalent. The two small trials[30,31] comparing CO_2 laser with CEC reported inconsistent results and demonstrated minimal effectiveness of both interventions for some outcomes; one trial was stopped early and did not achieve its prespecified noninferiority targets, and the other did not report statistical comparisons of change over time between study arms. Harms reporting for most interventions was limited, and studies were not powered to evaluate infrequent but serious harms.

Our findings confirm and expand on other systematic reviews, although study inclusion criteria and methodology for quality assessment and data synthesis varied.[12-15,50-52] Authors identified similar concerns about the available evidence, such as inconsistent participant selection criteria, varied comparators, unvalidated subjective outcome measures, nonrandomized studies, small sample sizes, and short follow-up periods. Two authors noted the need for greater detail on laser settings and intensity to clarify the total amount of energy being delivered.[51,52]

These results have implications for clinicians who provide healthcare for postmenopausal women. The American Urogynecologic Society recently updated their Clinical Consensus Statement on vaginal energy devices.[9,53] They noted inadequate evidence on participant eligibility criteria; level of training of clinicians; efficacy of treatment on vulvovaginal atrophy, vaginal dryness, or menopausal dyspareunia; long-term safety; and optimal treatment regimens.[9] The American Urogynecologic Society also cited limitations regarding variations in treatment protocols, lack of educational and credentialing standards for providers, variations in symptoms and severity, and lack of validated tools to assess outcomes.[7,9] The Menopause Society (formerly The North American Menopause Society) released a position statement in 2020 stating that there is a need for more sham-controlled trials in order to better understand the safety and efficacy of EB interventions.[54]

Further research in GSM treatments should consider consistent definitions of symptom presence and severity, more diverse populations, subgroups of interest, and consistent outcome reporting. Future research needs specific to EB treatments include studying the range of EB treatments, how they are implemented, the combination of EB treatments with other interventions (such as moisturizer), and different dosing protocols and schedules. We found no studies of hybrid lasers, few studies of Er:YAG lasers, and only one study of RF devices. The only study of ultrasound systems was rated as high RoB.[23] To improve understanding of the safety profile of EB devices, future research should include longer follow-up periods, improved reporting of reasons for study dropout, and assessment of a statistical difference in AE severity and frequency between treatment arms.

Registries for reporting of AE could supplement short-term data from intervention studies. The FDA maintains the Manufacturer and User Facility Device Experience database. Participants, physicians, and manufacturers voluntarily report AE; reports are unverified and may lack detail. Several studies have reported findings from searching the Manufacturer and User Facility Device Experience database. Four reviews identified between 39 and 130 complaints; pain was the most common complaint.[3,55-57] Adverse effects may be difficult to distinguish from persistence of initial symptoms due to a lack of treatment effect.

Our review is subject to several limitations. We used statistical, rather than clinical, differences to determine COE, in part due to the lack of validated measures of clinically meaningful differences for the relevant outcomes. We focused on randomized clinical trials to most accurately assess the causal effects of EB treatments of GSM. Studies using other designs (eg, observational reports) may provide additional information, especially for rare but serious harms.

CONCLUSIONS

Limited evidence suggests CO_2 lasers may result in little to no difference in selected GSM symptoms versus sham or CEC. Evidence for other types of EB interventions and outcomes is insufficient. Harms reporting was limited though most studies did not find serious or frequent harms. Prior to wider use, research is needed to assess benefits and harms.

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