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## Non-hormonal strategies for treating genitourinary syndrome of menopause: a concise review

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### ABSTRACT

Genitourinary Syndrome of Menopause (GSM) is a common, chronic condition in postmenopausal women, marked by vaginal dryness, irritation and dyspareunia. It can markedly reduce life’s quality, particularly in women who cannot use hormone therapy, such as breastcancer survivors. Nonhormonal strategies therefore represent an essential therapeutic way. This narrative review examines the efficacy and safety of centralnervoussystem agents (flibanserin, bremelanotide), vaginal moisturisers and lubricants, laser and radiofrequency devices, pelvicfloor physiotherapy, dietary measures and cognitivebehavioural therapy. Overall, these interventions relieve GSM symptoms and improve sexual function with few adverse effects, although robust longterm data are still lacking. Tailored treatment plans that respect individual needs and preferences are crucial, and further research is required to confirm the generalisability of current findings across different populations.

### INTRODUCTION

Genitourinary syndrome of menopause (GSM), once called vulvovaginal atrophy, occurs when oestrogen levels fall in the vagina and lower urinary tract [1, 3]. Experts adopted the name “GSM” in 2014 to replace older terms such as “atrophic vaginitis” [4, 5].

GSM affects at least half of postmenopausal women, and some studies put the figure as high as 80 % [2, 6]. It is more likely after surgical removal of the ovaries, early menopause, smoking, heavy drinking, reduced sexual activity and cancer treatments like chemotherapy or hormoneblocking drugs [7]. Clinicians must distinguish GSM from other disorders with similar symptoms, such as lichen

sclerosus or vulvodynia [8]. GSM can seriously diminish quality of life and is a frequent, distressing sideeffect of breastcancer therapy [9, 10].

Even though GSM is common, it is often dismissed as a normal part of ageing and therefore undertreated [11]. It weakens sexual function, relationships and mental health, lowering self-esteem and limiting social interactions [12]. With women living longer, GSM has become an important public health concern [13].

Cardinal symptoms include vaginal dryness, dyspareunia and irritation, often accompanied by urinary urgency, frequency and recurrent infection [5, 11, 14-17]. Unlike vasomotor symptoms, GSM complaints tend to worsen if left untreated [18], and may appear earlier and more severely in breastcancer survivors [7]. Hypoestrogenism drives epithelial thinning, reduced collagen synthesis and an elevated vaginal pH, disrupting the microbiome [19]. Symptoms usually recur once therapy stops, so longterm management is essential [20].

Current options range from lubricants and moisturisers to local or systemic oestrogen, dehydroepiandrosterone and ospemifene [21]. For women who cannot – or prefer not to – use hormones, newer nonhormonal approaches such as energybased devices and novel topical agents have gained attention [22, 23]. This review summarises the evidence for these modalities [18]

## MATERIALS AND METHODS

This narrative review set out to summarise and critically appraise the current evidence (2015-2024) on nonhormonal interventions for genitourinary syndrome of menopause (GSM), focusing on their effectiveness, safety and impact on quality of life (**Table 1**). We searched PubMed/MEDLINE and Scopus for articles published between 1 January 2015 and 31 December 2024. The search used the following MeSH terms and freetext keywords: “genitourinary syndrome of menopause”, “vulvovaginal atrophy”, “GSM”, “VVA”, “vaginal laser”, “vaginal lubricants”, and “vaginal moisturisers/moisturization.”: “genitourinary syndrome of menopause”, “vulvovaginal atrophy”, “GSM”, “VVA”, “vaginal laser”, “vaginal lubricants”, and “vaginal moisturisers/moisturization”. Searches were restricted to human studies in English. Reference lists of key papers were handsearched to capture additional studies. Grey literature, conference

abstracts and unpublished data were not reviewed (an acknowledged limitation). Eligible studies were randomised controlled trials, prospective clinical studies or observational (crosssectional or cohort) studies that:

1. involved postmenopausal women with clinically diagnosed GSM/VVA;
2. evaluated at least one nonhormonal intervention;
3. reported patientcentred outcomes (symptoms, sexual function, urogenital scores or quality of life);
4. enrolled  $\geq 10$  participants.

Animal or preclinical research, case reports, narrative reviews, and studies in which the intervention was exclusively hormonal were excluded. Titles, abstracts and full texts were screened by the two authors working together; all inclusion or exclusion decisions were reached by consensus. Because of the narrative design and limited team size, a formal doubleblinded screening procedure was not employed. For each included paper we extracted study design, sample size, participant characteristics, details of the nonhormonal intervention, outcome measures, followup duration and main findings. Owing to heterogeneity in study designs and endpoints, results were synthesised descriptively rather than pooled quantitatively. The review was conducted in line with the Scale for the Assessment of Narrative Review Articles (SANRA) checklist [24], which guided transparency in scope, literature search, referencing and relevance of included studies.

## RESULTS AND DISCUSSION

### *Flibanserin*

The FDA approved the central nervous system agent, flibanserin, in 2015 for treating hypoactive sexual desire disorder (HSDD) in premenopausal women [25]. Although randomized trials have shown that it can enhance sexual desire and decrease sexual distress, the drug’s side effects—including dizziness and drowsiness, along with its interactions with alcohol—have restrained its wider acceptance [26]. While flibanserin is proven effective in premenopausal women with HSDD, its application for postmenopausal women is still not widespread. Additionally, there is ongoing debate concerning the potential over-medicalization of female sexual desire, highlighting the need for

Table 1. Key characteristics of included evidence.

Intervention	Category	References	Study Description	Key Findings
Flibanserin	Central nervous system agents	Katz <i>et al.</i> (2013), Simon <i>et al.</i> (2014)	Flibanserin approved by FDA for HSDD in premenopausal women; limited use in postmenopausal women.	Increased sexual desire and reduced sexual distress; side effects limit adoption.
Bremelanotide	Central nervous system agents	Clayton <i>et al.</i> (2016), Kingsberg <i>et al.</i> (2019)	Bremelanotide approved for HSDD in premenopausal women; efficacy in postmenopausal women requires further study.	Improves desire and reduces distress; modest clinical benefit.
Hyaluronic acid	Vaginal moisturizers & lubricants	Sinha & Ewies (2013), Vale <i>et al.</i> (2019)	Studies show moisturizers like hyaluronic acid effectively relieve vaginal dryness and GSM symptoms.	Hyaluronic acid moisturizers provide lasting relief up to 2-3 days.
Lubricants	Vaginal moisturizers & lubricants	Pitsouni <i>et al.</i> (2018), Potter & Panay (2021)	Lubricants reduce friction and improve sexual comfort; shown effective in managing dyspareunia.	Effective in improving dyspareunia; less impact on sexuality scores compared to estrogens.
CO <sub>2</sub> and erbium laser	Laser therapy & radiofrequency	Behnia-Willison <i>et al.</i> (2019), Ruffolo <i>et al.</i> (2022)	CO <sub>2</sub> and erbium laser therapies improve vaginal elasticity and integrity with minimal side effects.	Short-term benefits observed; more long-term studies needed.
Radiofrequency	Laser therapy & radiofrequency	Dell'Utri <i>et al.</i> (2024), Hashim <i>et al.</i> (2018)	Radiofrequency devices like DQRF show effectiveness, though not significantly better than topical hormone treatment.	Quadripolar radiofrequency effective, but not superior to hormone treatment.
PFMT	Physical therapy	Dumoulin <i>et al.</i> (2018), Haylen <i>et al.</i> (2010)	Pelvic floor muscle training (PFMT) effective for stress urinary incontinence (SUI) in women.	Women undergoing PFMT are more likely to report cure or improvement in SUI.
Bladder retraining	Physical therapy	Greer <i>et al.</i> (2012), Newman & Wein (2013)	Bladder retraining reduces urinary leakage episodes in women with urgency urinary incontinence (UUI).	Women in PFMT groups had fewer leakage episodes compared to control groups.
Patients dietary habit	Dietary & nutritional support	Zhou <i>et al.</i> (2020), Foxman <i>et al.</i> (2000)	A Chinese study linked certain behaviours and dietary factors to recurrent urinary tract infections (RUTI) in postmenopausal women.	Wiping back-to-front, sedentary behavior, and constipation increase risk; green tea consumption linked to reduced risk.
Mindfulness-based cognitive therapy	Cognitive behavioural therapy	John <i>et al.</i> (2022)	Mindfulness-based cognitive behavioural therapy (MBCT) shown to improve quality of life and reduce menopause-related symptoms.	Significant improvement in quality of life post-intervention.

patients to make well-informed decisions regarding its use [27].

### Bremelanotide

In 2019, the FDA approved bremelanotide, a drug that acts on melanocortin-4 receptors, specifically aimed at treating hypoactive sexual desire disorder (HSDD) in premenopausal women [28]. This approval was based on promising results from clinical trials that noted increases in satisfying sexual events among users. The drug has also shown a clinically significant improvement in sexual desire and a reduction in the distress caused by a lack of sexual desire [29]. Common side effects associated with bremelanotide include nausea, facial flushing, and headaches, affecting approximately 39.9%, 20.4%, and 11% of users, respectively [30].

As the second medication of its kind approved by the FDA for HSDD, bremelanotide represents a significant advancement in the treatment options available for this condition [31, 32]. However, its precise role in the overall treatment strategy for HSDD remains unclear, as the clinical guidelines for HSDD were last updated in 2017, before bremelanotide's approval [33]. Clinical trials have found the drug to have a statistically significant impact on elements of sexual desire and the distress associated with it, though the overall clinical benefits are considered modest [34].

Bremelanotide is administered via a subcutaneous injection and is designed to be used on an as-needed basis, about 45 minutes before anticipated sexual activity. It does not interact significantly with other drugs or with alcohol, making it a relatively safe option for most users [35]. However, due

to its effects on blood pressure and the potential for causing postural hypotension, it is recommended that doses do not exceed one in a 24-hour period, and no more than eight doses should be used within a month [29].

Despite its approval and the benefits it offers, the effectiveness of bremelanotide in postmenopausal women has yet to be thoroughly studied, indicating an area for further research to determine its utility across a broader demographic.

### **Moisturizers and lubricants**

Vaginal moisturizers and lubricants present a viable non-hormonal alternative for women who prefer not to use or are unable to use estrogen treatments [36]. These products, including those based on hyaluronic acid, have proven effective in alleviating symptoms of vaginal dryness and genitourinary syndrome of menopause (GSM), offering clinical benefits that can persist for two to three days [37]. The effectiveness of these moisturizers and lubricants is attributed to their ability to hydrate the vaginal area, normalize the acid-base balance, and promote collagen synthesis. Additionally, the bioactive compounds such as hyaluronic acid in these gels aid in the repair of epithelial tissues [31]. A study from 1994 demonstrated that vaginal moisturizers could match the effectiveness of local estrogen treatments in relieving vaginal dryness, though they did not affect the vaginal epithelial maturation index, a measure of tissue health [38]. More recent research supports these findings, showing that products like Replens<sup>®</sup> and aloe-based gels can emulate the effects of estrogen on the vaginal mucosa, enhancing tissue condition without the associated risks [39, 40]. Furthermore, it has been found that hyaluronic acid can beneficially alter the composition of vaginal microbiota, promoting a healthier vaginal environment [41].

Conversely, vaginal lubricants are specifically formulated to minimize friction during sexual activity, thus enhancing comfort. Although vaginal estrogens have been shown to more significantly improve sexual function scores, lubricants have also been recognized for their effectiveness in reducing discomfort associated with dyspareunia, making them a useful option for immediate symptom relief during intercourse [42]. Regarding bioactive moisturisers, a retrospective study of 172 postmenopausal women treated once daily for 12 weeks with a purified bovine colostrum gel (Monurelle Biogel) reported marked symptom relief. Vaginal Health Index scores

rose from a mean  $\pm$  SD of  $12.5 \pm 3.7$  to  $19.3 \pm 3.5$ , the proportion of women having regular intercourse increased from 59 % to 84 %, and total FSFI scores improved accordingly. Voiding diary data showed significant reductions in daytime frequency, urgency, nocturia and incontinence events, mirrored by better UDI6 and OABQ scores; 83 % of participants rated their overall condition as “much” or “very much” improved. Adverse events were minimal, suggesting that biocolostrum gels could be a safe, multisymptom option for GSM management. [43].

### **Oral nutraceuticals and dietary support**

A six-month prospective series followed 98 reproductive age women who had recurrent postcoital urinary tract infections. Participants took an oral formulation containing hyaluronic acid, chondroitin sulphate, curcumin and quercetin (two tablets daily for one month, then one tablet daily for five months). Symptom scores for dysuria, frequency and pelvic pain fell significantly, quality of life and sexual function indices improved, and only 7% experienced microbiologically confirmed recurrence. No serious adverse events were reported, suggesting that this nutraceutical combination may offer a safe, nonantibiotic option for UTI prophylaxis while supporting sexual health [44].

### **Laser therapy and radiofrequency devices**

CO<sub>2</sub> and erbium laser therapies are emerging as promising options for managing genitourinary syndrome of menopause (GSM) and stress urinary incontinence (SUI). These therapies work by inducing photothermal reactions that improve local blood flow and the integrity of mucous membranes [45]. Short-term studies, particularly up to 12 weeks, indicate that these laser treatments are safe and effective, with Erbium: YAG laser treatments improving vaginal elasticity and epithelial integrity while presenting minimal side effects [46]. A specific study from 2014 on women aged 33-56 with symptomatic atrophic vaginitis demonstrated significant improvements in pelvic floor elasticity and subjective symptoms after two months of treatment [47]. Additionally, laser therapy has shown to benefit high-risk postmenopausal populations, as evidenced by outcomes from studies such as those conducted by Ruffolo and Marceau [47, 48]. Despite these encouraging results, the effectiveness and safety of laser therapies in the long term remain to be conclusively determined due to the absence of larger, well-designed studies and adequate

control groups. The encouraging aspect is the minimal occurrence of serious side effects, suggesting a good safety profile but highlighting the need for more comprehensive research [48].

Importantly, a recent narrative review of nine studies evaluated fractional CO<sub>2</sub> laser in breast, ovarian, endometrial and cervical cancer survivors with therapy-induced VVA. Across studies, VHI and FSFI scores improved consistently, with only minor, transient adverse events reported, supporting laser treatment as an effective, well-tolerated option when oestrogen is contraindicated [49]. On another side, radiofrequency (RF) treatment, an alternative energy-based therapy, uses concentrated electromagnetic waves to heat deeper tissues without targeting melanin specifically. This induces collagen contraction, neocollagenesis, and neovascularization, which help restore vaginal mucosa elasticity and moisture. Clinical improvements have been observed in urinary incontinence measures and significant enhancements in vaginal health scores [50, 51]. The newest among RF treatments, the low-energy dynamic quadripolar radiofrequency (DQRF) device, has been evaluated in a prospective parallel cohort study. Although effective, DQRF has not shown superior clinical outcomes compared to topical hormone treatments, which are less expensive and more convenient. However, DQRF could be considered when topical estrogens are ineffective, not tolerated, or contraindicated, suggesting a selective use in certain therapeutic scenarios [16, 52, 53].

### *Pelvic floor physical therapy*

Pelvic floor physiotherapy is an effective treatment to improve the trophism of the vaginal tissues, which is essential for the overall health of the female reproductive system. This type of therapy helps to strengthen and tone the pelvic floor muscles, thus directly supporting the structure of the vaginal tissues. Through specific exercises, such as muscle contractions and relaxations guided by a specialised physiotherapist, blood circulation in the pelvic area is improved. This increased blood flow brings more nutrients and oxygen to the tissues, facilitating cell regeneration and increasing the elasticity and overall health of the vaginal mucosa. In addition, regular stimulation through physiotherapy helps prevent atrophy and maintain the functionality of vaginal tissues, offering substantial benefits for the prevention and treatment of symptoms associated with conditions such as urinary incontinence and pelvic organ prolapse. A specific

case study further illustrates the effectiveness of this therapy [54]: a 77-year-old woman with severe symptoms of vulvovaginal atrophy (VVA), despite the use of local oestrogen therapy, participated in a clinical trial that incorporated pelvic floor muscle training (PFM) into her treatment regimen. Prior to surgery, during local oestrogen therapy, the patient presented with symptoms of VVA as evidenced by the ICIQ-Vaginal Symptoms and ICIQ-Female Sexual Matters questionnaires related to female sexual problems, as well as physical signs of VVA during the PFM dynamometric evaluation. After a 12-week PFM training programme, the patient reported a significant reduction in symptoms of vaginal dryness and dyspareunia, and an improvement in quality of sexual life. Although some signs of VVA remained unchanged, there was an improvement in PFM tone and elasticity at post-treatment evaluation. These results emphasise the importance and effectiveness of pelvic floor muscle training in improving some symptoms and signs of VVA, suggesting the need for further research to confirm these findings and to explore the mechanisms by which this intervention acts on VVA. Surgical correction can complement conservative pelvic floor measures in selected women. In a cohort of 151 patients with stage  $\geq$  II rectocele who underwent vaginal native tissue repair, the objective cure rate reached 88 % at a median 64-month follow-up, with marked reductions in defaecatory dysfunction, dyspareunia and prolapse-related bother; quality of life indices and the proportion of women engaging in regular intercourse improved significantly, and no serious intraoperative events occurred [55].

### *Cognitive behavioural therapy*

Menopause can often bring about both psychological and somatic disturbances in women, impacting their overall quality of life. Research indicates that psychological and behavioural interventions can effectively alleviate these menopausal symptoms [56]. To explore this further, a randomized double-blind study was conducted at a tertiary care hospital in Chennai, Tamil Nadu, focusing on the impact of Mindfulness-Based Cognitive Therapy (MBCT) on the quality of life in postmenopausal women. The study involved 50 women who had reached menopause. These participants were evenly divided into two groups: an intervention group and a control group, each consisting of 25 women. The intervention group received MBCT once a week over eight one-hour sessions, whereas the control

group did not receive any intervention. The effectiveness of the MBCT was assessed using several instruments including a demographic questionnaire, Kupperman's Index, and a menopause-related quality of life questionnaire. These tools were administered to both groups before the intervention, immediately after, and two weeks following the completion of the sessions. The analysis revealed significant improvements in all assessed domains, including vasomotor and psychological symptoms, for the intervention group compared to the control group after 10 weeks. This suggests that mindfulness-based interventions like MBCT can significantly enhance the quality of life by reducing the severity of menopause-related symptoms [57-65].

## CONCLUSIONS AND CLINICAL RECOMMENDATIONS

Non-hormonal treatments for Genitourinary Syndrome of Menopause (GSM) represent an essential component of therapeutic care, particularly for women who cannot or prefer not to use hormonal therapies, such as cancer survivors or those with contraindications. Options including vaginal moisturizers and lubricants, centrally acting agents, energy-based therapies (laser and radiofrequency), pelvic floor physiotherapy, dietary supplements, and cognitive-behavioural therapy have demonstrated variable but promising efficacy in alleviating GSM symptoms and improving sexual and urinary function. Most are well tolerated, though robust long-term data and standardized outcome metrics remain limited.

These interventions should be viewed as part of a patient-centred approach that prioritizes safety, symptom relief, and quality of life. While some treatments, such as lubricants and moisturizers, can be recommended as first-line options for mild symptoms, others (*e.g.*, laser/RF therapy or physiotherapy) may be suitable for persistent or multidimensional symptoms, particularly when hormonal therapy is contraindicated.

- First-line therapy for mild GSM symptoms should include vaginal moisturizers and lubricants, with preference given to products containing bioactive ingredients like hyaluronic acid.
- Patients with contraindications to estrogen (*e.g.*, breast cancer survivors) may benefit from energy-based devices, physiotherapy, or dietary support, pending individual risk-benefit assessment.

- Pelvic floor muscle training should be considered in women with concurrent pelvic floor dysfunction or incontinence.
- Clinicians should evaluate psychological and sexual distress, incorporating cognitive-behavioural strategies or referral to specialists when indicated.
- Shared decision-making is critical: patients should be informed of the benefits, limitations, and current evidence for each non-hormonal option.
- Follow-up and symptom monitoring are essential to assess efficacy and tailor ongoing management.

## COMPLIANCE WITH ETHICAL STANDARDS

### *Authors' contribution*

D.D.N., R.M.: Conceptualization. D.V., M.R., F.M.C.: Data curation. A.C., M.F.: Formal analysis. I.M.: Investigation. C.V.: Methodology. D.D.N., G.N.: Project administration. P.F., D.D.N., R.M.: Writing – original draft. D.V., N.I., M.R., F.M.C., A.C., M.F., I.M., C.V., D.D.N., G.N.: Writing – review & editing.

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N/A.

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