Therapies for the management of genitourinary syndrome of menopause

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Abstract

Introduction: The genitourinary syndrome of menopause is a new term that describes various menopausal symptoms and signs including not only genital symptoms (dryness, burning, and irritation) and sexual symptoms (lack of lubrication, discomfort or pain, and impaired function), but also urinary symptoms (urgency, dysuria, and recurrent urinary tract infections).

Methods: We conducted a systematic scoping review of data in women therapies with genitourinary syndrome of menopause or vulvovaginal atrophy in peer-reviewed, English-language publications in the last 20 years.

Results: The terms *vulvovaginal atrophy* and *atrophic vaginitis*, which were generally used up until recently, had a limitation because they did not cover the full spectrum of symptoms and did not imply that the symptoms are related to a decreased sex steroid level in menopause. The concept of genitourinary syndrome of menopause was recently introduced and has been gaining widespread use. Since genitourinary syndrome of menopause may have a profound negative impact on the quality of life of postmenopausal women, patients should be made aware of these problems and treated with an appropriate effective therapy. Therefore, in this review we introduce therapies for this syndrome, both local and systemic, and discuss the importance of genitourinary syndrome of menopause comprehension and the need to have an active treatment of this syndrome in postmenopausal women.

Conclusion: The increasing number of therapies for menopausal symptoms opens up new options. In addition, new products have been designed and developed by pharmaceutical companies as new possibilities for patients who did not have any treatment available and also to improve compliance.

Keywords

Genitourinary syndrome of menopause, hormone therapy, moisturizers, ospemifene, prasterone, vulvovaginal laser

Introduction

The genitourinary syndrome of menopause (GSM) is a new term that describes various menopausal symptoms and signs associated with physical changes of the vulva, the vagina, and the lower urinary tract. GSM includes not only genital symptoms (dryness, burning, and irritation) and sexual symptoms (lack of lubrication, discomfort or pain, and impaired function), but also urinary symptoms (urgency, dysuria, and recurrent urinary tract infections (UTIs)).¹ It was defined by the International Society for the Study of Women’s Sexual Health and the North American Menopause Society (NAMS) in 2013 to replace the old name of vaginal or vulvovaginal atrophy (VVA).¹

In recent online surveys in Western European countries, 80% of postmenopausal women reported vulvovaginal symptoms, with vaginal dryness being the most common one. Other symptoms included dyspareunia, vaginal irritation, itching sensation, vaginal tenderness, and vaginal bleeding or spotting during intercourse.² These symptoms are directly related to reduced circulating sex steroid levels after menopause.

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Estimated receptors (ERs; both α and β) are present in the vagina, vulva, pelvic floor muscles, endopelvic fascia, urethra, and bladder trigone during reproductive life; their levels decline with menopause and may be restored using estrogen treatment. Androgen receptors are widely distributed within the vaginal epithelium and also in the lamina propria, with a lower expression in the muscularis layer and blood vessel walls.

As a result of sex steroid deficiency after menopause, anatomic and histologic changes occur in female genital tissues, including reduced collagen and hyaluronic acid content as well as reduced elastin levels, thinned epithelium, alterations in the function of smooth muscle cells, increased connective tissue density, and fewer blood vessels. These changes reduce the elasticity of the vagina, increase vaginal pH, lead to changes in vaginal flora, diminish lubrication, and increase vulnerability to physical irritation and trauma.

GSM’s most prevalent symptom is vaginal dryness, which is also considered by patients as the most unpleasant symptom. Other high prevalence symptoms include insufficient lubrication during sexual activity and dyspareunia, as well as itching and irritation. Postcoital bleeding, reduced sexual desire, dysuria, and urinary urgency are also possible. The most prevalent signs are reduced vaginal secretion and loss of vaginal folds. Other vaginal signs potentially observed are reduced wall elasticity, paleness or erythema, fragile tissue with petechiae, loss of hymenal caruncles, and narrowed introitus. Urinary signs include urethral prolapse, prominence of urethral meatus, and frequent urinary infections.

Diagnosis is based on the presence of at least two symptoms, or one sign and one symptom, considered as unpleasant, associated with menopause and not attributable to another cause. GSM evolution is chronic and progressive. In addition, GSM diminishes quality of life significantly. However, in spite of discomfort and reduced quality of life, GSM is under-diagnosed and under-treated. The main causes of the lack of diagnosis are failure in patient-physician communication and women’s lack of awareness of GSM.

The main objective of this paper is to review the treatment options available over the 20 years for GSM. Although the term GSM is broader, all treatments have been specifically directed and studied towards VVA. Treatment options include, in addition to local and systemic hormonal therapy, lifestyle changes and non-hormonal treatments, mainly based on the use of moisturizers and lubricants. Ospemifene, the first selective estrogen receptor modulator (SERM) for VVA, prasterone, and the vaginal laser, has recently been developed for the treatment of dyspareunia and VVA. We conducted a systematic scoping review of data in women therapies with GSM or VVA in peer-reviewed, English-language publications in the last 20 years.

### Treatment

The primary goal when treating GSM is to relieve symptoms. Currently available treatment options include non-hormonal vaginal lubricants to be used during intercourse, long-acting vaginal moisturizers, systemic hormonal therapies, low-dose vaginal estrogen therapies (e.g. vaginal creams, intravaginal tablets, or intravaginal rings) and intravaginal prasterone. For women with vulvovaginal symptoms, first-line therapies include long-acting vaginal moisturizers, low-dose vaginal estrogens, or intravaginal prasterone. In a literature review, the vaginal administration of low estrogen doses demonstrated to be an effective and safe treatment in the management of postmenopausal genitourinary disorders.

Emerging treatments include ospemifene – a SERM with specific vaginal function and heat energy based treatments, such as vulvovaginal laser, which are being studied in this area.

Smoking cessation can also help relieve symptoms. Lastly, wearing looser undergarments and legwear may improve air circulation, discouraging microorganism growth. There are barriers and resistance to the use of some therapies. Healthcare professionals should initiate and encourage a frank and candid conversation about GSM and its treatment.

### Lifestyle changes

One should always keep in mind the risk factors that accelerate sex steroid deprivation and advise the patient to avoid them. There is a positive link between sexual activity and maintenance of vaginal elasticity and pliability as well as lubricative response to sexual stimulation. Sexual intercourse improves blood circulation to the vagina, and seminal fluid also contains sexual steroids, prostaglandins, and essential fatty acids, which help to maintain vaginal tissue. Vulvovaginal tissue stretching also helps to promote vaginal elasticity. Masturbation or sex devices are options for patients without a partner. Stress reduction therapy and psychological counselling may benefit women with non-organic causes of vaginal dryness.

### Local therapies

**Non-hormonal.** A number of over-the-counter vaginal lubricants (water-, silicone-, or oil-based) and moisturizers are commonly used for the treatment of postmenopausal women with vulvovaginal symptoms. The
NAMS stated that the first-line treatment for women with vulvovaginal symptoms includes non-hormonal lubricants during intercourse and a regular use of long-acting vaginal moisturizers.\textsuperscript{20} In general, lubricants may be used during sexual intercourse to reduce the friction-related irritation of the atrophic tissue.\textsuperscript{24} In addition, long-acting vaginal moisturizing agents can decrease vaginal pH to premenopausal levels, although they do not improve the vaginal maturation index (VMI).\textsuperscript{23} Two recent studies have reported that vaginal hyaluronic acid-based moisturizers are effective in relieving vulvovaginal symptoms as topical vaginal estrogens and may be considered as an alternative to estrogen-based treatment.\textsuperscript{25,26} A new SERM, ospemifene, is the only non-hormonal oral therapy for the treatment of GSM.\textsuperscript{16} New non-invasive energy-based systems such as laser and radiofrequency have opened up a new area of research and possibilities.\textsuperscript{17}

**Lubricants.** Vaginal lubricants work by reducing the friction associated with thin, dry genital tissue. They come in liquid or gel form and are applied to the vagina and vulva (and, if desired, to the partner’s penis) right before sex.\textsuperscript{23} Lubricants are not absorbed into the skin, are immediate-acting, and provide a temporary relief from vaginal dryness and related pain during sex. They are particularly appropriate for women whose vaginal dryness is an issue only or primarily during sex.\textsuperscript{12,20}

A wide variety of lubricants are commercially available, either as water-, silicone-, or oil-based products. Water-based lubricants have the advantage of being non-staining. Oil-based lubricants (such as petroleum jelly and baby oil) should be avoided, as they can cause vaginal irritation and are associated with high rates of latex condom breakage that can lead to sexually transmitted infections.\textsuperscript{27} One of the main concerns is related to the fact that some lubricants contain one of the most popular existing preservatives – parabens. Parabens are easily absorbed by the human body. In light of the literature, which classifies parabens as a group of endocrine disrupting chemicals, we need to perform an accurate assessment of their influence on the human endocrine system and the impact of chronical use.\textsuperscript{28}

**Moisturizers.** Like lubricants, vaginal moisturizers reduce the painful friction that sex can cause as a result of vaginal atrophy. Additionally, moisturizers, unlike lubricants, are absorbed into the skin and cling to the vaginal lining in a way that mimics natural secretions. Another difference is that moisturizers are applied regularly, not just before sex, and their effects are more long-term, lasting for up to three or four days. Some moisturizers have an applicator to help place the product into the vagina.\textsuperscript{12,23}

Because moisturizers maintain vaginal moisture and acidity, they are particularly appropriate for women who are bothered by symptoms of vaginal dryness (such as irritation and burning) that are not limited to sexual activity. Some women who regularly use moisturizers still use a lubricant as needed before sex, for additional lubrication and comfort, but latex condoms should be avoided. For both moisturizers and lubricants, women need to experiment with several products to find the one that proves best for them.\textsuperscript{23}

Vaginal semisolid products are frequently used to treat vaginal infections and atrophy-related symptoms of menopause. Formulation composition and the methods for their characterization, especially those developed regarding the target epithelia, are key tools to predict in vivo results at early stages of product development. The aim of this area is to improve traditional characterization methods by using physiological parameters in order to construct predictive tools to characterize a new ideal vaginal semisolid formulation.\textsuperscript{25}

Regarding hyaluronic acid, which is a natural polysaccharide, it can be said that it is an important part of the extracellular matrix of the skin and cartilage. This substance is able to preserve a large amount of water molecules and it has a key role due to properties like formation and preservation of extracellular inflation, skin moistening in case of inflammation, and preservation of water equilibrium.\textsuperscript{23,25} In addition, it proves largely effective in the treatment of skin diseases due to preservation of tissue consistency, facilitating cellular migration in cases of inflammation as well as tissue improvement and the regeneration process. Various prospective observational studies carried out on hyaluronic acid have shown that this compound has been well tolerated without side effects among patients. Complications have only been observed when applied in the form of parenteral jelly by creating susceptibility at injection sites such as mild inconveniences, redness, oedema, and cyanosis.\textsuperscript{25,26} However, these are studies with a low number of cases and a short duration. Therefore, new studies are needed to compare different types of moisturizers and demonstrate long-term safety.

According to a research by Palacios et al.\textsuperscript{12} on vaginally administered products, a periodic evaluation of the advantages, disadvantages, effects, and benefits perceived by prescribers and users can help to improve the habits and conditions of its prescription and use, and as a result of this, adherence and effectiveness.

New ideas involving the combination of hydration and lubrication properties are emerging. An example is a non-hormonal gel that acts as a moisturizer and as a lubricant thanks to its strong hydrating properties, also enhancing and accelerating the repair of the atrophic or injured cervicovaginal mucosa. Already approved in
Europe as a medical device, this product is based on niosomes containing hyaluronic acid, β-glucan, alpha-glucan oligosaccharide, Coriolus versicolor, Asian Centella, Azadirachta indica (also known as neem), and Aloe vera. Encapsulation in niosomes allows for a more penetrating capability of the components, which have shown hydrating, repairing, anti-inflammatory, effect as well as their ability to preserve the balance of vaginal microbiota.25

This type of products that are prepared using an innovative formula based on natural ingredients and developed through Niosomal and Phytosomal biotechnology – which facilitates the penetration of the active ingredients into the vaginal epithelium – represents the new moisturizers approach. They have moisturizing and restorative properties for the vaginal mucosa and are indicated for the improvement of the symptoms and signs that make up the genitourinary syndrome.

Vulvovaginal laser. Physical methods such as laser in the non-ablative, ablative, and microablative forms have been used with the purpose of rejuvenating the skin of the face, neck, and body. The laser has been used in medicine for 40 years, but its vaginal and vulvar use is recent and based on three concepts. The first is water absorption coefficient by the vagina’s lamina propria (90% of which is made of water), since the laser is captured by the water. The second is the fractioned application of energy, which allows burnt tissue to be immediately covered by healthy tissue, prevents pain, and involves a rapid recovery – the constant application of the laser would cause injuries that would delay recovery. The third concept is the laser’s thermal effect – the heat transmitted to the water stimulates collagen-producing fibroblasts.17

The laser causes a small ablation of around 30 μm of tissue. A natural protection is then formed, with a coagulation of around 20 μm. Last comes neocollagenesis, since all heat transmitted to the whole lamina stimulates fibroblasts.29

Laser effects are developed in three stages. In the first stage, which lasts for about two or three days, a light oedema is produced and chemical mediators are released – these mediators have not been properly studied yet. The second stage is proliferation, with new collagen formation and neovascularization. This stage lasts for about 30 days, so the interval among sessions should be one month at least. The third stage is remodeling. It lasts for 30–40 days and includes collagen fibre maturation, neovascularization, and increase in lubrication and vaginal acidity. Once this stage is over, the vaginal mucosa will have regained its physiology and functionality.30

There are different types and ranges of laser devices. The most important thing is for the device selected to be approved by the FDA and the European agency.

The use of laser for GSM treatment has been evaluated by observational studies with satisfactory results,29,30 even though there is a lack of long-term efficacy and safety data.17,30 In a 14-study meta-analysis with 542 participants, the intravaginal laser significantly improved GSM symptoms, urinary incontinence, and quality of life, but evidence was of low or very low quality.31 Neocollagenesis is achieved with few sessions, but collagenitis is not avoided.

The microablative fractional carbon dioxide (CO2) laser is usually administered in three sessions at five- to six-week intervals, but benefits have been suggested to be wider with up to five sessions.32 Its regenerative mechanism activation effects are first observed 1 h after the session, with blood vessel, papilla, and collagen formation in the connective tissue, as well as thickening and desquamation of the mucosal epithelial cells.33 In various recent studies, an improvement of GSM signs and symptoms has been noted,34–37 including sexual dysfunction38 and urinary incontinence,39 with a follow-up of up to 24 months.37 In addition, the CO2 laser has been compared with intravaginal estril in a randomized, double-blind, placebo-controlled study.40 The study included 45 women with GSM randomly distributed in three treatment groups: fractional CO2 vaginal laser and estril cream placebo, estril cream and laser placebo, and laser and estril cream. After 20 weeks, vaginal dryness decreased in all groups (p < 0.001 for all), but in those groups treated with laser and estril or just with laser, burning and dyspareunia were also significantly reduced. Sexual function improved significantly only in the laser- and estril-treated group. However, in the group treated just with laser, sex-associated pain increased (p = 0.04).40 On the other hand, the microablative fractional CO2 laser has been demonstrated to increase the prevalence of lactobacillus from 30 to 79% after three laser therapies at monthly intervals in postmenopausal women.41

Er:YAG (erbium, yttrium, aluminium, garnet) laser has been compared with 0.5 mg estril intravaginal ovules in 50 women with GSM. Symptoms improved significantly with both treatments, but the improvement was larger in the laser-treated group. Only laser effects were maintained for 12 and up to 18 months later.42

The first studies with solid state vaginal laser (SSVL) have been recently published, with SSVL applied to 80 GSM women in four sessions every 15–20 days. Vaginal dryness, vaginal cytology, and sexual function symptoms improved in most women, as well as urinary incontinence cases.43
Additionally, various studies on the use of the laser in breast cancer patients developing severe GSM owing to chemotherapy have been published. The laser’s beneficial effects on these patients have been noted both with the CO₂ ablative laser 44 and with the Er:YAG laser.45,46

In spite of the progress made in the last years, we need further evidence regarding the use of the vulvovaginal laser, and further research should be carried out on how to improve collagen (mainly type 3 over type 1), vaginal physiology, and the impact of heat on elastin. Well-defined protocols should be developed, and a method to determine how to select patients according to symptom evaluation, patient motivation, and the possibilities of the device per se should be established. Anyway, the use of the laser to treat the pelvic floor, including GSM, is becoming higher and more widespread.

**Hormonal**

**Local estrogens.** Systemic estrogen therapy is preferred if vasomotor symptoms are also present, whereas local vaginal estrogen therapy (vaginal estrogen ovules or tablets, creams, or a vaginal ring) is preferred when genitourinary symptoms are the only complaint.14,47 Local estrogen preparations as a short-term therapy can improve the clinical signs and symptoms of GSM.48

Studies on the effectiveness of vaginal estrogens have reported subjective outcomes, including improvement in vulvovaginal symptoms and lower urinary tract symptoms such as dysuria, urinary urgency, frequency, nocturia, SUI, and UTI.48 These studies have also demonstrated objective outcomes including decreased vaginal pH, increased number of vaginal lactobacilli, favourable shifts in vaginal and urethral cytology, improved gross vaginal mucosal appearance, and favourable changes in urine culture results.48,49 In a recent review, topical estrogen administration has been concluded to be effective for the treatment of VVA and seems to reduce complaints of overactive bladder, including GSM, is becoming higher and more widespread.

In its 2013 report on vaginal atrophy, the NAMS recommended local estrogens for VVA with moderate or intense symptoms.20 In its 2017 hormone therapy (HT) report, it recommends local estrogens over systemic hormonal therapy as a first-line treatment for GSM without vasomotor symptoms, including cases with unpleasant symptoms not improving with treatments without medical prescription.47

Local estrogens (estradiol, estriol, and promestriene) are considered as an effective and safe treatment for GSM. They are more effective than placebo regarding GSM signs and symptoms.1 They do not require combined administration with progestogens or periodic endometrial controls.51 They come in cream, ovules, tablets, and vaginal rings, with different estrogens and doses. In a 2006 Cochrane review, all presentations were concluded to be effective compared with placebo, and treatment was determined to be safe.52 In the update published in 2016, 30 clinical studies with over 6200 women were included. No statistically significant differences were found in the efficacy and safety of the various presentations assessed (cream, pessary, tablets, and ring).53

The application of creams, ovules, and tablets is recommended at night for the user’s comfort. Creams and ovules are used two to three times a week. However, the silicone intravaginal ring releases estradiol gradually for at least 90 days, which makes it easy to use and a well-accepted method. Only 3% of users refer discomfort.54

The absorption of local estrogens is very low, but they may cause some systemic adverse effects such as vaginal bleeding or breast tension.18 This is why their efficacy and safety have been studied at very low doses, with a 0.005%55 or even 0.0003%56,57 hormone concentration. Five hundred and seventy-five women with moderate or intense GSM participated in a randomized, double-blind, placebo-controlled study. The application of an estradiol vaginal cream at 0.003% twice a week was effective and well tolerated to improve vaginal signs and symptoms.56 In another study with a similar design, 550 women with GSM and dyspareunia as the main symptom used an estradiol vaginal cream at 0.003% applied three times a week, or placebo over 12 weeks. The low-dose estradiol cream relieved dyspareunia, improved vaginal cytology, and reduced pH (p < 0.001 for the three parameters as compared to placebo). Vaginal dryness and irritation also improved (p < 0.01). Estradiol effects started to be noticeable from the fourth week of treatment.57

Local estrogens and vaginal moisturizers were compared in a randomized, double-blind, placebo-controlled study carried out in more than 300 women with GSM and moderate or intense vulvovaginal symptoms. After 12 weeks of treatment, no statistically significant differences were found in dyspareunia or vaginal dryness between 10 μg intravaginal estradiol tablets, a moisturizing gel, and placebo. Nevertheless, the over 50% decrease in symptom intensity was more frequent with estradiol (70%) than with the moisturizing gel (54%).58 Although vaginal estrogen therapy is generally safe for most symptomatic women with GSM, the treatment is contraindicated in some women with undiagnosed vaginal or uterine bleeding, and controversial in women with estrogen-dependent neoplasia (e.g. breast cancer or endometrial cancer).57
Therefore, local estrogens are not adequate for all women with GSM (Table 1). If there are contraindications, difficulties in use, or rejection, other therapeutic options should be explored.

**Dehydroepiandrosterone (DHEA).** Recently, there has been a great clinical development in the use of intravaginal DHEA in the treatment of GSM. This new treatment introduces the concept of intracrinology. The vaginal tissue-specific enzymes transform DHEA into the appropriate small amounts of estrogens and androgens for a strictly intracellular and local action, which prevents biologically significant changes in serum sex steroids from occurring.

DHEA as compared to placebo is an effective treatment improving symptoms of vaginal atrophy – dyspareunia, burning, itching, and dryness. Objective parameters of vaginal atrophy, namely pH and VMI, improved as compared to baseline and placebo. There were significant improvements in libido and dyspareunia with the intravaginal use of DHEA. In November 2016, prasterone was approved by the Food and Drug Administration (FDA) for intravaginal application in the treatment of GSM with moderate to severe symptoms. This new drug application involves the use of prasterone vaginal inserts for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause. In Europe, the same contraindications still exist as for local estrogens (Table 1).

**Table 1. Contraindications, difficulties, and rejection causes of local estrogens.**

<table>
<thead>
<tr>
<th>Relative contraindications</th>
<th>Difficulties in use</th>
<th>Rejection causes</th>
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<tbody>
<tr>
<td>History of breast cancer, endometrial cancer, or melanoma</td>
<td>Obesity</td>
<td>Discomfort</td>
</tr>
<tr>
<td>Acute hepatic disease or altered hepatic function</td>
<td>Arthritis</td>
<td>Complex therapeutic regimen</td>
</tr>
<tr>
<td>Porphyria</td>
<td>Parkinson’s disease</td>
<td>Concerns over adverse effects</td>
</tr>
<tr>
<td>Endometriosis</td>
<td>Residual disability following stroke</td>
<td>Interference with sexual spontaneity</td>
</tr>
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Source: Based on Nappi et al.

**Systemic therapies**

**HT.** The primary role of menopausal HT is to relieve vasomotor symptoms (hot flashes, night sweats, and sleep disruption), prevent or reverse the GSM (including vaginal atrophy), prevent bone loss and fractures, and improve quality-of-life issues such as fatigue due to deprivation of sleep and mood changes.

Systemic hormone treatment is indicated in GSM associated with vasomotor symptoms impacting quality of life. However, it is not effective in all GSM cases, and up to 26% of women still have GSM symptoms. According to a 2017 Cochrane review, if menopausal symptoms cannot be tolerated, this treatment could be used in the short term or at low doses, considering risks and benefits. Systemic HT can increase the risk of breast cancer and thromboembolic disease.

**Osipemifene.** Due to concerns about the potential stimulating effects of systemic estrogens on breast and endometrial tissues and long-term adverse effects, SERMs have been developed with the aim of bringing about positive effects on targeted tissues with minimal negative effects on other tissues.

Various studies have investigated the use of SERMs for the treatment of vulvovaginal symptoms in menopausal women. While raloxifene and tamoxifen have no estrogen agonist effect on the vagina, lasofoxifene and osipemifene demonstrate a positive impact on vaginal tissue in postmenopausal women. Although several studies have found that lasofoxifene results in significant improvements in vaginal pH and VMI, the clinical development of this SERM is on hold.

Osipemifene is the only SERM approved by the FDA for the treatment of moderate to severe dyspareunia, and in Europe, the European Medical Agency has approved it for the treatment of vulvar and vaginal atrophy in postmenopausal women who are not eligible for local vaginal estrogen therapy.
daily dose. After 12 weeks of treatment, ospemifene improves dryness, dyspareunia, and irritation, as well as the signs of dryness, paleness, petechiae, friability, and mucosal redness. It also improves the signs and symptoms of the vulvar vestibule, as well as sensitivity in this area. All these effects are combined with an improved sexual function. In addition, ospemifene could prove beneficial for urinary tract disorders associated with GSM. In over 100 GSM women presenting with hyperactive bladder syndrome or stress urinary incontinence, ospemifene reduced urinary symptoms \(^{(p < 0.0001,)}\), which was associated with an increase in quality of life and an improvement in sexual function.

The combined analysis of safety data from six randomized, double-blind, placebo-controlled studies of up to 52 weeks demonstrated that ospemifene is well tolerated at a 60mg/day dose. Most adverse effects were mild or moderate, appearing between weeks 4 and 12 of treatment. Breast cancer and cardiovascular adverse effect incidence were low and similar to those noted with placebo. Ospemifene is not an agonist of breast ERs, so it is safe regarding breast cancer. It can be administered in women with breast cancer history having completed treatment (including adjuvant therapy). Ospemifene does not act on the endometrium either, so it does not increase the risk of hyperplasia or endometrial cancer. Post-marketing safety data in the United States demonstrated that, over a two-year analysis period, no additional adverse effects were noted, and venous thromboembolism risk did not increase.

According to an indirect comparison based on a bibliographic review, 60mg/day ospemifene has an efficacy, safety, and tolerability equal to or higher than those of vaginal estrogens.

Ospemifene contraindications are the same as those for estrogen therapy, i.e. personal history of venous thromboembolism, unexplained vaginal bleeding, breast cancer under active treatment (including adjuvant therapy) or suspected, and estrogen-dependent cancers such as endometrial cancer. Safety in endometrial hyperplasia cases has not been studied.

**Nutraceuticals.** Data on the efficacy of these therapies are scarce and dubious. The evidence regarding phytoestrogens such as soy isoflavones is also insufficient. In a 12-week randomized, double-blind, placebo-controlled study with over 350 participants, various medicinal herb preparations and soy were compared with a systemic estrogen treatment. Estrogens significantly improved vaginal dryness and cytology as compared to placebo \((p < 0.05)\). However, no significant differences were found for herb preparations and soy as compared to placebo. Nevertheless, it has been recently published that nutraceuticals containing equol could be effective in modulating postmenopausal symptoms, particularly vaginal symptoms, and could be well accepted by those women who usually do not wish to use HT or cannot use it for medical reasons.

**Conclusion**

The treatment goal is to make symptoms disappear or improve as much as possible. And there are many options for this. One should always recommend lifestyle changes. So far the treatments are directed exclusively to VVA. The term GSM is a more clinical and diagnostic concept.

There are local treatments, such as lubricants and moisturizers, with local estrogens, and finally with new methods based on heat energy such as the laser. On the other hand, there are also effective systemic treatments such as menopause HT and ospemifene.

The clinical data obtained using a small dose of intravaginal DHEA (prasterone) confirm the mechanisms of local intracrinology which avoid biologically significant changes in serum E2 and testosterone. Safety and efficacy add a new first-line treatment option.

As previously described, there are many treatments that have proven effective for GSM. However, there are very few face-to-face studies that can recommend one treatment or another. We have mentioned the recommendations from the related companies, which also underline the importance of individualization and patient’s preference.

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