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DRUG EVALUATION



An overview of dehydroepiandrosterone (EM-760) as a treatment option for genitourinary syndrome of menopause

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ABSTRACT

Introduction: Dyspareunia caused by vulvovaginal atrophy is a primary symptom of genitourinary syndrome of menopause (GSM), a chronic, progressive medical condition that results from estrogen and androgen deficiency at menopause. Dehydroepiandrosterone (DHEA, prasterone) is an endogenous precursor steroid hormone that is metabolized into both androgens and estrogens that has been recently been approved by the FDA for the treatment of moderate to severe dyspareunia caused by vulvovaginal atrophy secondary to menopause.

Areas covered: This is a comprehensive drug evaluation describing the chemical composition, pharmacokinetics, metabolism, clinical efficacy and safety of dehydroepiandrosterone (prasterone) in the treatment of dyspareunia and VVA secondary to menopause. Preclinical and clinical data suggesting further potential uses, benefits, and contraindications in the genitourinary health of postmenopausal women are also considered.

Expert opinion: Intravaginal dehydroepiandrosterone (prasterone) is effective for the management of dyspareunia secondary to menopause and may be effective in the treatment of other types of sexual dysfunction that are secondary to menopause. Further studies should explore additional dosing regimens and different indications.

ARTICLE HISTORY

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Dehydroepiandrosterone (DHEA); Female androgen insufficiency; Female sexual dysfunctions (FSDs); Genitourinary syndrome of menopause (GSM); Prasterone; Vulvovaginal atrophy

1. Background

Previously known as vulvovaginal atrophy, the term genitourinary syndrome of menopause (GSM) includes a multitude of chronic, progressive signs and symptoms that are associated with deficiency in androgens and estrogens in the labia majora, labia minora, vulvar vestibule, clitoris, vagina, urethra, and bladder during the menopausal phase of life [1,2]. These symptoms affect both sexually active and inactive women, and include burning, itching, and irritation of the vaginal introitus, vaginal dryness, vaginal fissures secondary to mucosal friability, labial resorption, mucosal erythema and pallor, loss of vaginal rugae, urethral sensitivity, and sexually-associated symptoms of diminished lubrication, and vulvar, vaginal, and vestibular discomfort and pain during intercourse [3]. Additional systemic symptoms of menopause include mood swings, night sweats, and sleep disturbance, although this review focuses on localized vulvovaginal symptoms [2,4]. These symptoms can be significantly bothersome and affect the quality of life of many women in the peri- and postmenopausal periods, including not only sexual relationships, but activities of daily living as well [2,5,6]. GSM has been proven to be chronic and progressive, increasing in severity the longer a woman is past the menopausal transition, and typically does not improve without treatment [1,3,7]. The cause of GSM is the decline in the sex steroids that occur at the natural menopausal transition or surgically secondary to oophorectomy. Symptoms of GSM can also occur with the use of certain medications, including aromatase inhibitors, selective estrogen

receptor modulators, and gonadotropin releasing hormone agonists [1].

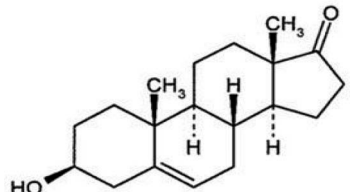
There are currently several FDA approved treatment options available to treat GSM. Systemic therapies include oral, or transdermal estrogen, and ospemifene (a selective estrogen receptor modulator). Local hormonal therapies include topical estrogens such as estradiol and conjugated equine estrogens. These vulvovaginal medications are available as creams, vaginal tablets, vagina inserts, and vaginal rings. More recently, the FDA approved Intrarosa, the intravaginal steroid precursor dehydroepiandrosterone (DHEA, Prasterone) which is converted to both androgens and estrogens in the vaginal mucosa.

Unfortunately, while these medications effectively treat GSM, they are under-prescribed and underutilized. Kingsberg et al reported that only 6% of menopausal women use vaginal estrogen therapy in the United States [8], despite the fact that that more than 50% of women will experience GSM symptoms at some point in their lives [2,3,8–11]. It is believed this may be due to a perceived lack of efficacy and high cost. However, the greatest barrier to use is fear of potential side effects including increased risks of endometrial and breast cancer, stroke, deep vein thrombosis, pulmonary embolism, and myocardial infarction. This is in spite of the fact that many studies have demonstrated that that women using local, minimally absorbed topical therapy are not at increased risk for these conditions [2,3,12–15].

Article highlights

- Dyspareunia caused by vulvovaginal atrophy is a primary symptom of menopause. Intravaginal DHEA (prasterone) is effective for the management of dyspareunia secondary to menopause
- Intravaginal DHEA (prasterone) is effective for the management of dyspareunia secondary to menopause
- Intravaginal DHEA (prasterone) is effective for the management of dyspareunia secondary to menopause
- Intravaginal DHEA (prasterone) is effective for the management of dyspareunia secondary to menopause
- Exogenous prasterone is metabolized in the same manner as endogenous DHEA
- There is current evidence suggesting that intravaginal DHEA (prasterone) is effective in treating additional symptoms in women with GSM, such as decreased lubrication, decreased sexual desire, decreased sexual satisfaction, decreased ability to achieve orgasm, and pain.

Box 1. Drug summary box.

Drug name	Dehydroepiandrosterone (EM-760)
Phase	Launched
Indication	Dyspareunia in postmenopausal women; GSM
Pharmacology description	Endogenous steroid that converts to active androgens and/or estrogens
Route of administration	Intravaginally
Chemical structure	

Pivotal trial(s) [33,34,35,37]

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While the management of women with postmenopausal symptoms initially included androgens in the form of animal ovarian extracts that contained both androgens and estrogens, the role of androgens in the genitourinary function of women was generally neglected until the early 2000s [16], with the majority of healthcare providers favoring estrogen-based products [anonymous]. This is likely due to a combination of the following: a lack of understanding of understand of the role of androgens in female physiology, a fear of potential androgenic side effects (acne, hirsutism, and clitoromegaly), and the availability of FDA approved estrogen medications [17,18]. However, over the past two decades, research has shown that androgens are as important to the genitourinary health of women as estrogens, and a deficiency in androgens can result in significantly bothersome structural and functional changes of the vulva and vagina [2,4,19,20]. Despite this, there is a knowledge gap among many health care providers of the importance of androgens in the treatment of genitourinary conditions [2].

Androgens and estrogens are steroid hormones derived from cholesterol with a diverse range of actions throughout the whole body, though they are especially important in the genitourinary organs [19]. Steroid hormones bind to hormone receptors that are primarily intracellular or nuclear but can

also be on the plasma membrane coupled to proteins within the cell [21]. Binding of hormones to receptors results in a downstream cascade of signal transduction that leads to modulation of gene expression within the cell through activation and inhibition of a multitude of transcription complexes that alter protein production [21]. Steroid hormones specifically lead to the production of proteins such as collagen, which is vital to the structural and functional integrity of the cell and tissues, and mucin, which is important for the health of the urogenital mucosa and during sexual function [4,22].

Androgens are sex steroids produced by the adrenal glands, ovaries, testis, placenta, brain, and skin. The primary androgens are dehydroepiandrosterone sulfate (DHEA-S), DHEA, androstenedione, testosterone, and dihydrotestosterone (DHT), with DHEA-S and DHEA being the most prevalent in serum [20]. DHEA-S, DHEA, and androstenedione are pro-hormones that are converted to the active androgens testosterone and DHT in peripheral tissues [19,20,23].

DHEA is a naturally occurring C-19 adrenal steroid derived from cholesterol and is an established precursor for the sex steroids estrogen and androgen [24]. It is secreted primarily by the zona reticularis of the adrenal cortex in humans. The secretion of DHEA is controlled by pituitary factors, most noted adrenocorticotrophin (ACTH). The adrenal cortex synthesizes DHEA daily from cholesterol and secretes 75-90% of the body's DHEA, with the majority of the remainder being produced by the ovaries [24]. The secretion and the blood levels of the adrenal steroid dehydroepiandrosterone (DHEA) decrease profoundly with age [25,26].

While in the past emphasis has been placed on the role of estrogen in the treatment of GSM, it is now widely accepted that the labia majora, labia minora, vulvar vestibule, vestibular glands, vaginal mucosa, clitoris and urethra are also dependent on androgens for optimal health and function [2,4,19]. Distinct from, though complimentary to the actions of estrogens, androgens have been shown to enhance vaginal blood flow, smooth muscle contraction, and vulvar and vaginal lubrication [1]. DHEA, the precursor of both androgens and estrogens, begins to decrease between ages 30-35, and continues to decrease thereafter with advancing age. In women of postmenopausal age, DHEA production has decreased by an average of 60% [19,25-27]. In the absence of adequate levels of sex steroids, the mucosa of the vagina and vulva can atrophy, fuse, and become irritated, erythematous and friable [28]. Due to a loss of surface epithelial proliferation, the vaginal mucosa cannot produce rugae and becomes smooth [4]. The mucosa loses elasticity and lubrication and can become inflamed [29]. The vaginal introitus narrows, and with the structural changes, pelvic organs can prolapse. Due to a loss of the native lactobacilli and decreased lactic acid, the vaginal pH becomes less acidic, and is predisposed to colonization and infection secondary to non-native bacterial and fungal species [4].

2. Chemistry

The chemical name of prasterone (dehydroepiandrosterone, DHEA) is 3 β -Hydroxy-5 α -androst-17-one corresponding to the molecular formula C₁₉H₂₈O₂. The active substance has a relative molecular mass 288.43 g/mol. It is a steroid, which

consists of three six-membered rings and one five-membered ring. Prasterone displays stereoisomerism due to the presence of six chiral centers. The active substance displays polymorphism. The active substance is a white to yellowish white non-hygroscopic powder, practically insoluble in water, soluble in methanol, freely soluble in isopropanol and dichloromethane. The product is stable under long term storage, at conditions of 25 degrees C [29].

3. Pharmacokinetics

In a study conducted in postmenopausal women, administration of the Intrarosa vaginal insert once daily for 7 days resulted in a mean prasterone C_{max} and area under the curve from 0 to 24 hours (AUC 0–24) at Day 7 of 4.4 ng/mL and 56.2 ng·h/mL, respectively, which were significantly higher than those in the group treated with placebo. The C_{max} and AUC 0–24 of the metabolites testosterone and estradiol were also slightly higher in women treated with the Intrarosa vaginal insert compared to those receiving placebo [30]. In two primary efficacy trials, daily administration of Intrarosa vaginal insert for 12 weeks increased mean serum C_{trough} of prasterone and its metabolites testosterone and estradiol by 47%, 21% and 19% from baseline, respectively. This comparison based on C_{trough} may underestimate the magnitude of increase in prasterone and metabolites' exposure because it does not take into account the overall concentration-time profile following administration of Intrarosa [30].

4. Metabolism

Exogenous prasterone is metabolized in the same manner as endogenous DHEA. Human steroidogenic enzymes (eg, hydroxysteroid dehydrogenases, 5- α -reductases and aromatases) transform prasterone into androgens and estrogens (testosterone, androstenedione, estradiol, estrone, and DHT) [23].

5. Pharmacodynamics

The mechanism of action of DHEA administered intravaginally is based on the hypothesis of intracrinology [23]. This suggests that DHEA, an inactive compound by itself, is converted in peripheral tissues (vaginal cells) under the action of specific enzymes into sex steroids and then inactivated locally thus avoiding an increase of systemic exposure to sex steroids [23].

6. FDA approval

In November 2016, prasterone (Intrarosa, Amag Pharmaceuticals, Waltham, MA) was approved by the U.S. Food and Drug Administration (FDA) for the treatment of moderate to severe dyspareunia, a symptom of vulvar or vaginal atrophy, secondary to menopause [30]. Intrarosa is a vaginal suppository containing 6.5mg endogenous prasterone which is inserted once daily. The FDA approval was based on two 12-week randomized, double-blinded, placebo-controlled efficacy trials, including 255 (trial 1) and 558 (trial 2) postmenopausal women respectively. It has not been studied in pregnant, lactating, or premenopausal women [30].

7. Clinical efficacy

The first efficacy trial (trial 1) included 255 generally healthy postmenopausal women ages 40 to 75 years, with a mean age of 58.6 years, who reported moderate to severe dyspareunia as their most bothersome symptom of vulvar and vaginal atrophy [31]. Objectively, the women had less than or equal to 5% superficial cells on vaginal smear and a vaginal pH > 5. The women were randomized in a 1:1:1 ratio between three treatment groups who received daily prasterone 6.5mg (n = 87), a comparator vaginal insert (n = 87), or placebo (n = 81). The women treated with prasterone reported significantly improved dyspareunia from baseline to Week 12 as compared to women treated with placebo (SD 0.99 vs 0.95 p = 0.0132). They also reported a significant difference in superficial cells, parabasal cells, and vaginal pH (SD 5.49 vs. 2.69, p < 0.0001; SD 42.50 vs. 28.22, p < 0.001; SD 1.00 vs. 0.69, p < 0.001) [31]. Additionally, endometrial biopsies remained atrophic at all stages of monitoring [31].

The second efficacy trial included 558 generally healthy postmenopausal women between ages 40 to 80 years, with a mean age of 59.5, reporting moderate to severe dyspareunia as their most bothersome symptom of vulvovaginal atrophy [32]. Objectively, they had less than or equal to 5 vaginal superficial cells and a vaginal pH > 5. The women were randomized in a 2:1 ratio to receive prasterone 6.5mg daily or placebo. The primary endpoints were similar to those of trial 1 [32]. Women treated with prasterone reported significantly improved dyspareunia from baseline to Week 12 compared to women treated with placebo (SD 1.00 vs 1.02 p = 0.0002). They also reported a significant difference in superficial cells, parabasal cells, and vaginal pH (SD 10.32 vs. 3.33, p < 0.0001; SD 36.26 vs. 29.58, p < 0.001; SD 0.94 vs. 0.74, p < 0.001) [32].

The efficacy and safety of intravaginal prasterone on moderate-severe dyspareunia and signs of vulvovaginal atrophy was confirmed in a 52-week open-label phase III trial [33]. Five-hundred and twenty-one postmenopausal women applied 0.5% (6.5mg) DHEA daily, and the severity of symptoms, along with the objective health of the vagina was examined. Improvement in pain at sexual activity was observed both in women who had dyspareunia as their most bothersome symptom (n = 183), along with women who had moderate to severe dyspareunia that was not their most bothersome symptom (n = 240), with a 1.70 severity unit (66.1% from baseline) decrease in dyspareunia in women who had dyspareunia as their most bothersome symptom (p < 0.0001 versus baseline) [33]. There was also improvement in pain at sexual activity in women who had moderate to severe symptoms of vulvovaginal atrophy that were not their most bothersome symptom (n = 57, p < 0.0001 versus baseline). Continued improvement in dyspareunia for an additional 0.33 severity units (19.4%) was observed in women who continued treatment from 12 to 52 weeks [33]. Objectively, there was significant improvement in vaginal secretions, color of the vaginal mucosa, epithelial integrity, and epithelial surface thickness (p < 0.001 versus baseline) [33]. Endometrial biopsies were completed at screening and at week 52, or upon discontinuation in women who applied intravaginal DHEA for at least 12 weeks, with the endometrium of all women remaining atrophic [34].

Additional clinical trials have since confirmed that prasterone is effective in the treatment of dyspareunia secondary to

menopause, with a recent review of 12 randomized, controlled trials concluding that intravaginal DHEA (prasterone) is safe and effective treatment for menopausal vulvovaginal atrophy and dyspareunia in most women [35]. Several trials compared prasterone 6.5mg to 10 µg estradiol (E2) and 0.3 mg conjugated equine estrogens (CEEs) cream. These trials concluded that intravaginal prasterone was as effective as intravaginal estrogens in the treatment of vulvovaginal atrophy and dyspareunia, with intravaginal prasterone having a stronger effect on vaginal dryness as compared to twice weekly CEEs. There was no statistical significance on vaginal dryness when CEEs were applied daily [34].

8. Safety and tolerability

Adverse reactions were studied in five trials, including the four placebo-controlled, 12-week clinical trials and one 52-week open label non-comparative clinical trial. In all clinical trials, vaginal discharge was the most common adverse side effect, with greater than or equal to 5.72% of women reporting vaginal discharge in the four 12-week trials as compared to 3.55% in the placebo group, and 14.2% of women reporting vaginal discharge in the 52-week trial [30]. In addition to vaginal discharge, the 52-week open-label trial had an adverse effect of abnormal Pap smears in 11 out of 521 women, with 10 cases of atypical cells of undetermined significance (ASCUS) and 1 case of low-grade squamous intraepithelial lesions (LSIL) [33]. Multiple studies investigating systemic absorption of prasterone that show no significant increase in serum androgen and estrogen levels outside of normal postmenopausal range following intravaginal administration [36,37].

9. Conclusion

The clinical data reviewed indicates that intravaginal prasterone is effective in the treatment of dyspareunia secondary to vulvovaginal atrophy in women with GSM, with current evidence suggesting that it is also effective in treating additional symptoms experienced in women with GSM, such as decreased lubrication, decreased sexual desire, decreased sexual satisfaction, decreased ability to achieve orgasm, and pain. Given that serum androgen and estrogen levels remained within normal postmenopausal range following intravaginal prasterone administration, intravaginal prasterone may be safe for use in patients with contraindications to oral hormone replacement, but additional studies are needed. Future studies should explore the efficacy of intravaginal prasterone in conditions outside of GSM, including hypoactive sexual dysfunction disorder and female sexual arousal disorder.

10. Expert opinion

10.1. Menopausal symptoms and conditions other than dyspareunia

While prasterone is FDA approved for the treatment of moderate to severe dyspareunia secondary to GSM it has also been shown to be effective in treating/improving other signs and symptoms of GSM including vaginal dryness, vaginal pH, vaginal mucosal

maturation, and vaginal lubrication [38,39]. Even more interestingly, Bouchard and colleagues evaluated 154 women who reported vaginal dryness, decreased lubrication, and dyspareunia who used daily intravaginal prasterone 6.5mg for a total of 52 weeks. Their sexual dysfunction symptoms were evaluated using the female sexual function index (FSFI) questionnaire. Compared to baseline, there was a statistically significant increase in desire, arousal, lubrication, orgasm, sexual satisfaction, and decreased pain (28%, 49%, 115%, 51%, 41% and 108% respectively, $p < 0.0001$ for all parameters) at 52 weeks, as well as an increase in the total FSFI score from 13.4 ± 0.62 at baseline to 21.5 ± 0.82 (+60%, $p < 0.0001$) [38]. It was hypothesized that these benefits might be secondary to prasterone-derived androgens stimulating an increase in local nerve density [38]. Alternatively, it has been shown that decreased sexual desire, decreased arousal, decreased orgasm, and dyspareunia are inter-related [38]. Therefore, it is possible that the improvement in sexual function may be solely due to long-term improvement in dyspareunia. Further studies are underway to evaluate the improvement in sexual function in women using prasterone.

10.2. In women with contraindications to systemic estrogen

Multiple studies have proven that use of localized use of prasterone does not lead to a significant change in serum androgen or estrogen levels, as prasterone is converted to androgens and estrogens peripherally and inactivated intracellularly [36,37]. In one study of 733 women treated with low dose (6.5mg) intravaginal prasterone, serum DHEA, estrogen and androgen levels and their metabolites were followed for a 7-day period, with serum levels taken at 10 intervals in a 24-hour period on the first day and again after 7 days. Serum DHEA and inactive metabolites rose slightly but remained in the normal postmenopausal range, while serum androgens, estrogens, and their metabolites remained static, also within the normal postmenopausal range. This indicates that there is no statistically significant systemic absorption when prasterone is administered intravaginally, suggesting that intravaginal prasterone may be a novel therapy for women with dyspareunia and symptoms of vulvovaginal atrophy with contraindications to systemic estrogen use, in whom is currently contraindicated [37]. Similarly, intravaginal prasterone is likely safe in women with contraindications to systemic hormone replacement secondary to uterine cancer as well. In 668 non-hysterectomized women treated with 12 weeks or greater with intravaginal prasterone, including 389 women treated for one year, the endometrium remained atrophic and inactive in all women [40].

Given that there is no statistically significant systemic absorption, a potential use of intravaginal prasterone may be in patients with contraindications to systemic estrogen replacement who have symptoms of vulvovaginal atrophy secondary to GSM, such as women with a current or past history of breast, ovarian, and uterine cancer, hypercoagulability, a history of deep vein thrombosis or pulmonary embolism, systemic lupus erythematosus, liver disease, and coagulopathies, among others. For example, one study in women with breast cancer reported as many as 63% ($n = 158$) of patients taking endocrine therapy had bothersome urogenital symptoms, however, only 27% ($n = 68$) of those

patients utilizing some form of treatment [41]. In another study in breast cancer patients taking aromatase inhibitors, as many as 73.9% ($P < 0.05$) of women reported decreased lubrication, and 56.5% of women reported dyspareunia ($p < 0.05$) [42]. Given that prasterone is converted only in the vaginal mucosa to both estrogens and androgens, intravaginal prasterone may mitigate vaginal symptoms of hormonal deficiency, such as dyspareunia secondary to vulvovaginal atrophy, in patients in whom oral estrogens are contraindicated.

At the time of submission, there are two clinical trials investigating prasterone use for vulvovaginal atrophy in postmenopausal cancer patients with vulvovaginal atrophy. The first trial, that was completed as of August 2013, is a randomized, double blind, placebo-controlled phase III trial by Alliance for Clinical Trials in Oncology investigating the efficacy of two daily doses of intravaginal prasterone in treatment the most bothersome symptom of vulvovaginal atrophy (dyspareunia or vaginal dryness) in 464 female breast and gynecologic cancer survivors [43]. The second trial is a placebo-controlled, double blind, randomized Phase III clinical trial by Endoceutics Inc. and AMAG Pharmaceuticals, Inc. investigating the effect of prasterone on symptoms of vulvovaginal atrophy in women with breast cancer under treatment with an aromatase inhibitor is recruiting 500 women beginning in June 2019 [44]. Data is pending at this time for both clinical trials, however, they should identify whether prasterone is effective in treating symptoms of vulvovaginal atrophy in breast and gynecologic cancer survivors as a whole, and in breast cancer patients treated with aromatase inhibitors.

10.3. Prasterone in comparison to other therapies

In addition to prasterone as an intravaginal therapy, there are alternative oral and topical treatments for the treatment of dyspareunia and vulvovaginal atrophy in postmenopausal women, including local estrogens therapies (LETs), and selective estrogen receptor modulators. With hypogonadism as the etiology of the cellular changes that lead to vulvovaginal atrophy and dyspareunia, replacing hormones locally, through the use of creams, ointments, and oil-based compounds, has been a mainstay of treatment for postmenopausal women. Previous evidence and treatment modalities have focused mainly on replacement of estrogens, with the importance of including oral and topical androgen replacement only becoming studied extensively in the past several years [2]. Both systemic and local hormone replacement therapies (HRTs) have been shown to be efficacious in increasing the thickness of the vaginal mucosa, reducing the pH of the vagina, increasing vaginal maturation index, increasing vaginal mucosa rugae, and improving the symptoms of GSM [45]. Local HRT preparations are made with a variety of doses of conjugated estrogens, estradiol, and estriol, and have been shown to have limited systemic absorption and an insignificant effect on serum estrogen levels [2,3,13]. However, there is increasing evidence that the combination of estrogen and androgens are superior to estrogens in improving vulvovaginal atrophy and dyspareunia [2]. Unfortunately, there are no FDA approved combination estrogen and androgen preparations so patients must obtain these medications from compounding

pharmacies. This option is sub-optimal as quality control cannot be assured and frequently these medications are not covered by insurance policies.

Ospemifene is an oral selective estrogen receptor modulator that was approved by the FDA in 2013 in the treatment of moderate to severe dyspareunia and vulvovaginal atrophy secondary to menopause. There has been sufficient evidence that ospemifene has a comparable effect to vaginal estrogens in improving vaginal atrophy, with Ospemifene showing significant increase in the percentage of surface cells of the vaginal epithelium and a decrease in the percentage of parabasal cells and a decrease in vaginal pH [45,46]. Multiple studies have shown that ospemifene has no significant impact on the proliferation of the endometrium. However, the FDA approved package insert contains a boxed warning for agonism of endometrial tissue. Additionally, a post hoc safety analysis suggesting that ospemifene has no significant impact on the breast, bone, and cardiovascular health in comparison to placebos [46–48]. In comparison to local estrogen therapies, ospemifene was shown to have greater treatment regimen adherence and a lower mean outpatient medical care costs compared to patients utilizing local estrogen therapies [49].

Prasterone is an intravaginal, local therapy similar to many local estrogen therapies, but has not been compared in a randomized, controlled trial with alternative local and oral therapies [50]. Prasterone does not have box warnings related to systemic absorption and endometrial or mammary tissue proliferation. Multiple ongoing studies are investigating the safety of prasterone for use in postmenopausal patients with breast and gynecologic cancers. The data show that intravaginal prasterone is an effective treatment option for postmenopausal women with moderate to severe dyspareunia and vulvovaginal atrophy. Further double-blind, randomized, controlled trials are needed to compare intravaginal prasterone to alternative systemic and local treatment options.

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References

Papers of special note have been highlighted as either of interest (*) or of considerable interest (***) to readers.

- Portman DJ, Goldstein SR, Kagan R. The treatment of moderate to severe dyspareunia with intravaginal prasterone therapy: a review. *Climacteric*. 2019;21(1):65–72.
- Simon JA, Goldstein I, Kim NN, et al. The role of androgens in the treatment of genitourinary syndrome of menopause (GSM): International Society for the Study of Women's Sexual Health (ISSWSH) expert consensus panel review. *Menopause*. 2018;25(7). DOI:10.1097/GME.0000000000001138.
- This article contains the pathophysiologic and treatment guidelines of a recent consensus panel review highlighting the importance of androgens in the treatment of GSM. Prasterone is one of the first steroid hormone precursor treatment options for patients with GSM, and addresses local estrogen and androgen deficiencies simultaneously**
- Gandhi J, Chen A, Dagur G, et al. Genitourinary syndrome of menopause: an overview of clinical manifestations, pathophysiology, etiology, evaluation, and management. *Am J Obstet Gynecol*. 2016;215:704–711.
- Traish AM, Vignozzi L, Simon JA, et al. Role of androgens in the genitourinary structure and function: implications in the genitourinary syndrome of menopause (GSM). *Sex Med Rev*. 2018;6:558–571.
- Simon JA, Kokot-Kierepa M, Goldstein J, et al. Vaginal health in the United States: results from the vaginal health: insights, views & attitudes survey. *Menopause*. 2013;20:1043–1048.
- DiBonaventura M, Luo X, Moffatt M, et al. The association between vulvovaginal atrophy symptoms and quality of life among postmenopausal women in the United States and western Europe. *J Womens Health (Larchmt)*. 2015;24:713–722.
- Portman DJ, Gass ML. Vulvovaginal atrophy terminology consensus conference panel. Genitourinary syndrome of menopause: new terminology for vulvovaginal atrophy from the International Society for the Study of Women's Sexual Health and The North American Menopause Society. *Menopause*. 2014;21:1063–1068.
- World 2020 Website, 2017. [cited 2017 Aug 24]. Available from <https://www.populationpyramid.net/world/2020>
- Kingsberg SA, Krychman M, Graham S, et al. The women's EMPOWER survey: identifying women's perceptions on vulvar and vaginal atrophy and its treatment. *J Sex Med*. 2017;14:413–424.
- Barlow DH, Cardozo LD, Francis RM, et al. Urogenital aging and its effect on sexual health in older British women. *J Obstet Gynaecol*. 1997;104:87–91.
- Barlow D, Samsioe G, van Geelen JM. A study of European women's experience of the problems of urogenital ageing and its management. *Maturitas*. 1997;27:239–247.
- Kyvernitakis I, Kostev K, Hars O, et al. Discontinuation rates of menopausal hormone therapy among postmenopausal women in the post-WHI study era. *Climacteric*. 2015;18:737–742.
- Kyvernitakis I, Kostev K, Hars O, et al. Persistency with estrogen replacement therapy among hysterectomized women after the Women's Health Initiative study. *Climacteric*. 2015;18:826–834.
- Portman D, Shulman L, Yeaw J, et al. One-year treatment persistence with local estrogen therapy in postmenopausal women diagnosed as having vaginal atrophy. *Menopause*. 2015;22:1197–1203.
- Rahn D, Ward RM, Sanses TV, et al. Society of gynecologic surgeons systematic review group. Vaginal estrogen use in postmenopausal women with pelvic floor disorders: systematic review and practice guidelines. *Int Urogynecol J*. 2015;26:3–13.
- Anonymous. To combat the annoying symptoms of the menopause. *N Y Med J*. 1910;91:756.
- Bachmann G, Bancroft J, Braunstein G, et al. Female androgen insufficiency: the Princeton consensus statement on definition, classification, and assessment. *Fertil Steril*. 2002;77(4):660–665.
- Borell M. Organotherapy and the emergence of reproductive endocrinology. *J Hist Biol*. 1985;18:1–30.
- Labrie F, Martel C, Belanger A, et al. Androgens in women are essentially made from DHEA in each peripheral tissue. *J Steroid Biochem Mol Biol*. 2017;168:9–18.
- Bienenfeld A, Azarchi S, Lo Sicco K, et al. Androgens in Women: androgen mediated skin disease and patient evaluation (Part I). *J Am Acad Dermatol*. 2018. DOI:10.1016/j.jaad.2018.08.062.
- Beato M, Sanchez-Pacheco A. Interaction of steroid hormone receptors with transcription initiation complex. *Endocr Rev*. 1996;17(6):587–609.
- Nallasamy S, Yoshida K, Atkins M, et al. Steroid hormones are key modulators of tissue mechanical function via regulation of collagen and elastic fibers. *Endocrinology*. 2017;158(4):950–962.
- Labrie F, Belanger A, Luu-The V, et al. DHEA and the intracrine formation of androgens and estrogen's in peripheral target tissues: its role during aging. *Steroids*. 1998;63(5–6):322–328.
- Webb SJ, Geoghegan TE, Prough RA, et al. The biological actions of dehydroepiandrosterone involves multiple receptors. *Drug Metab Rev*. 2006;38(12):89–116.
- Labrie F, Bélanger A, Cusan L, et al. Marked decline in serum concentrations of adrenal C19 sex steroid precursors and conjugated androgen metabolites during aging. *J Clin Endocrinol Metab*. 1997;82:2396–2402.
- Orentreich N, Brind JL, Rizer RL, et al. Age changes and sex differences in serum dehydroepiandrosterone sulfate concentrations throughout adulthood. *J Clin Endocrinol Metab*. 1984;59:551–555.
- Labrie F, Bélanger A, Bélanger P, et al. Androgen glucuronides instead of testosterone, as the new markers of androgenic activity in women. *J Steroid Biochem Mol Biol*. 2006;99:182–188.
- Simuniae V. Local estrogen treatment in patients with urogenital complaints. *Int J Gynaecol Obstet*. 2003;82:187–197.
- European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP) Assessment Report Intrarosa. 2017. [cited 2019 Dec 17]. Retrieved from https://www.ema.europa.eu/en/documents/assessment-report/intrarosa-epar-public-assessment-report_en.pdf
- Intrarosa, DHEA intravaginal (prasterone, intravaginal) dosing, indications, interactions, adverse effects, and more. Published March 12, 2018. [cited May 25, 2019]. <https://reference.medscape.com/drug/intrarosa-dhea-intravaginal-prasterone-intravaginal-1000137#5>
- Archer DF, Labrie F, Bouchard C, et al. Treatment of pain at sexual activity (dyspareunia) with intravaginal dehydroepiandrosterone (prasterone). *Menopause*. 2015;22(9):950–963.
- This reference contains the published data of ERC-231, which is a first pivotal phase III study investigating the efficacy of DHEA, a primary focus of this paper**
- Labrie F, Archer DF, Koltun W, et al. Efficacy of intravaginal dehydroepiandrosterone (DHEA) on moderate to severe dyspareunia and vaginal dryness, symptoms of vulvovaginal atrophy, and of the genitourinary syndrome of menopause. *Menopause*. 2016;23(3):243–256.
- This article contains the published data of ERC-238, which is a pivotal phase III study investigating the efficacy of intravaginal DHEA, a primary focus of this paper**
- Labrie F, Archer DF, Bouchard C, et al. Prasterone has parallel beneficial effects on the main symptoms of vulvovaginal atrophy: 52-week open-label study. *Maturitas*. 2015;81(1):46–56.
- This article contains the published data of a 52-week open-label study investigating the efficacy and safety of intravaginal DHEA, a primary focus of this paper**
- Archer DF, Labrie F, Montesino M, et al. Comparison of intravaginal 6.5Mg (0.50%) prasterone, 0.3Mg conjugated oestrogens and 10 mcg estradiol on symptoms of vulvovaginal atrophy. *J Steroid Biochem Mol Biol*. 2017;174:1–8.
- Sauer U, Talalikalikar V, Davies MC. Efficacy of intravaginal dehydroepiandrosterone (DHEA) for symptomatic women in the peri- or postmenopausal phase. *Maturitas*. 2018;116:79–82.
- Labrie F, Archer DF, Bouchard C, et al. Intravaginal dehydroepiandrosterone (prasterone), a highly effective treatment of dyspareunia. *Climacteric*. 2011;14:282–288.

37. Labrie F, Archer DF, Martel C, et al. Combined data of intravaginal prasterone against vulvovaginal atrophy of menopause. *Menopause*. 2017;24(11):1246–1256.
38. Bouchard C, Labrie F, Derogatis L, et al. Effect of intravaginal dehydroepiandrosterone (DHEA) on the female sexual function in postmenopausal women: ERC-230 open-label study. *Horm Mol Biol Clin Investig*. 2016;25(3):181–190.
39. Labrie F, Archer DF, Bouchard C, et al. Lack of influence of dyspareunia on the beneficial effect of intravaginal prasterone (dehydroepiandrosterone, DHEA) on sexual dysfunction in postmenopausal women. *J Sex Med*. 2014;11:1766–1785.
40. Portman DJ, Labrie F, Archer DF, et al. Lack of effect of intravaginal dehydroepiandrosterone (DHEA, prasterone) on the endometrium in postmenopausal women. *Menopause*. 2015;22:1289–1295.
 - **This article contains evidence showing that intravaginal DHEA has no significant effect on endometrial proliferation of postmenopausal women, lending to the safety of intravaginal DHEA in comparison to other treatment modalities that have systemic estrogenic effects**
41. Chin SN, Trinkaus M, Simmons C, et al. Prevalence and severity of urogenital symptoms in postmenopausal women receiving endocrine therapy for breast cancer. *Clin Breast Cancer*. 2009;9(2):108–117. Epub 05/13/2009.
42. Baumgart J, Nilsson K, Evers AS, et al. Sexual dysfunction in women on adjuvant endocrine therapy after breast cancer. *Menopause*. 2013;20(2):162–168.
43. Alliance for Clinical Trials in Oncology, National Cancer Institute, Mayo Clinic. Prasterone (Dehydroepiandrosterone) in treating postmenopausal cancer survivors with vaginal symptoms. *ClinicalTrials.gov*. <https://clinicaltrials.gov/ct2/show/results/NCT01376349>
44. EndoCeutics, Inc., AMAG Pharmaceuticals, Inc. Effect of intravaginal prasterone on symptoms of VVA in women under treatment with an aromatase inhibitor for breast cancer. <https://clinicaltrials.gov/ct2/show/NCT03740945>
45. Naumova I, Castelo-Branco C. Current treatment options for postmenopausal vaginal atrophy. *Int J Women's Health*. 2018;10:387–395.
46. Constantine G, Graham S, Portman DJ. Female sexual function improved with ospemifene in post-menopausal women with vulvar and vaginal atrophy: results of a randomized, placebo-controlled trial. *Climacteric*. 2015;18:226–232. [Osphena]
47. Goldstein AT, Pukall C, Brown C, et al. Vulvodynia: assessment and Treatment. *J Sex Med*. 2016;13(4):572–590.
48. Simon J, Altomare C, Sort S, et al. Overall safety of ospemifene in postmenopausal women from placebo-controlled phase 2 and 3 trials. *J Women's Health*. 2018;24(1):14–23.
49. Fought BM, Soulbán G, Year J, et al. Ospemifene versus local estrogen: adherence and costs in postmenopausal dyspareunia. *J Comp Off Res*. 2019;8:1111–1123. Epub 2019 Aug 21.
50. Barton DL, Shuster LT, Dockter T, et al. Systemic and local effects of vaginal dehydroepiandrosterone (DHEA): NCTG N10C1 (Alliance). *Support Care Cancer*. 2018;26(4):1335–1343.