A Closer Look at the Women's Health PRN

Overview of the PRN

The Women's Health PRN has multiple opportunities for residents, fellows, and students to get involved, such as serving on PRN committees, writing articles for the biannual PRN newsletters, and participating in other initiatives. The PRN offers committees in advocacy and scholarship, communications, programming, and more. Learners are also encouraged to participate in the student, resident, and fellow PRN committee dedicated specifically to their needs. Many exciting initiatives are planned for 2019–2020, so there is no wait if you would like to get involved! The Women's Health PRN also offers travel awards for student, resident, and fellow members to assist learners in attending the ACCP Annual Meeting, including the PRN business meeting, which provides leadership opportunities directly affecting the PRN membership.

Current Officers:

Chair: Nicole Lodise, Pharm.D., TTS
Chair-Elect: Kylie Barnes, Pharm.D., BCPS
Secretary/Treasurer: Lauren D. Leader, Pharm.D., BCPS
Public Policy Liaison: Ashley Meredith, Pharm.D., FCCP, BCACP, BCPS, CDE
Student Liaison: Zaneera Hassan
Board Liaison: Judith Smith, Pharm.D., FCCP, BCOP

Membership:

Total Members: 138
Student Members: 75
Resident Members: 6

Current Clinical Issue:

Intrarosa (Prasterone): Trial Review for Treatment of Moderate to Severe Dyspareunia caused by Vaginal Atrophy in Postmenopausal Women*

Sarah Lowry, Pharm.D., PGY2 Ambulatory Care Pharmacy Resident

*Adapted from the September 2018 Women's Health PRN Newsletter, a semiannual publication provided to members of the Women's Health PRN.

Vulvovaginal atrophy, more recently termed *genitourinary syndrome of menopause* (*GSM*), remains largely underdiagnosed and undertreated, leading to bothersome, distressing symptoms that reduce quality of life. It is projected by 2020, more than 889 million women worldwide will be 50–80 years of age, almost one-half of whom will experience GSM symptoms at some point.[1,2] The most commonly reported menopause-related symptoms are vaginal dryness, vaginal itching or irritation, and dyspareunia.[3] In November 2016, the FDA approved the steroid prasterone (Intrarosa) for the intravaginal treatment of moderate to severe dyspareunia caused by GSM in postmenopausal women.[4]

Table 1. Current Treatment Options for Postmenopausal GSM[1,5-8]

Treatment Options	Recommendations
Vaginal moisturizers or lubricants (K-Y®, Replens®, Vagisil®)	Trial of moisturizer used at least twice weekly for GSM symptoms; lubricants if insufficient vaginal secretions for sexual activity

Vaginal estrogens (low dose)	In those without a history of hormone-dependent cancer seeking relief of GSM symptoms that persist despite moisturizer and lubricant trials
Oral selective estrogen receptor modulator (ospemifene)	Moderate to severe dyspareunia associated with vaginal atrophy in postmenopausal women without contraindications
Intravaginal inactive synthetic steroid (prasterone)	Moderate to severe dyspareunia in postmenopausal women without contraindications

Although vaginal moisturizers and lubricants are readily available OTC with minimal adverse effects, they do not treat the underlying physical causes of dyspareunia (Table 1). Conversely, estrogen therapies reduce GSM symptoms by replacing the principal intracellular human estrogen, yet these carry boxed warnings surrounding breast and endometrial cancers and thromboembolic diseases[5,9-11] (though the increased risks of breast and endometrial cancers and cardiovascular outcomes associated with systemic estrogen therapy may differ from low-dose vaginal estrogen therapy). Ospemifene carries risks and warnings similar to estrogen therapy and is a major CYP 2C9 and 3A4 substrate, which requires additional necessary drug monitoring because of medication interactions.[9] Therefore, continued development of new pharmacologic agents of varying dosage forms is needed.

Prasterone, also called dehydroepiandrosterone (DHEA), is produced in the body's adrenal glands, gonads, and brain and converted intracellularly into active androgens and estrogens.[6,12] Intravaginal prasterone produces a topical and localized effect on the genitourinary tissues, compared with the OTC oral DHEA supplement claimed to aid in several ailments, including depression, cognitive function, physical performance, aging skin, coronary heart disease, and sexual dysfunction.[13] Intravaginal prasterone increases serum sex steroid concentrations compared with baseline and placebo, but concentrations remain within the normal postmenopausal steroid concentration ranges.[12,14] Currently, there are no known drug interactions with topical prasterone.[6] Contraindications to intravaginal therapy include women with undiagnosed, persistent, or recurring genital bleeding and a known or suspected history of breast cancer. However, prasterone was not studied in women with a history of breast cancer.

The effectiveness of prasterone on moderate to severe dyspareunia caused by menopause was examined in two primary placebo-controlled efficacy trials, one open-label safety and efficacy study, and one comparison review article.

Two clinical trials evaluated prasterone 6.5 mg (equivalent to DHEA 0.5%) in postmenopausal women with moderate to severe GSM over 12 weeks – one with an active comparator vaginal insert (DHEA 0.25%) and placebo and the other compared solely with placebo. Because DHEA 0.25% was tested as a potential version of prasterone that is unavailable, its results will not be discussed. The results of the four co-primary outcomes are listed in Table 2.

Limitations of these studies include the applicability of their findings to the general population because of the lack of participant diversity, given that 92% of patients were Caucasian, and given the study exclusion criteria, including uncontrolled diabetes, thromboembolic disease, cardiac failure, hypertension (blood pressure 140/90 mm Hg or greater), and coagulation disorders. These studies show the benefit of the prasterone 6.5-mg (0.5%) dose in alleviating dyspareunia and improving objective vaginal atrophy parameters compared with placebo and the DHEA 0.25% dose, with few adverse effects (Table 3).

Table 2. Trial 1 and 2 Co-primary Outcomes[15,16]

Outcome	Archer et al.[15]			Labrie et al.[16]		
Population	Prasterone (n=87) Placebo (n=81)			Prasterone (n=376) Placebo (n=182)		
Dyspareunia[a] (severity score units)		Baseline	12 wk		Baseline	12 wk
	Placebo	2.58	1.71	Placebo	2.56	1.50
	Prasterone	2.63	1.36	Prasterone	2.54	1.13
	At 12 wk, prasterone significantly improved over placebo (p=0.013)			At 12 wk, prasterone significantly improved over placebo (p=0.0002)		
Vaginal pH (units)		Baseline	12 wk		Baseline	12 wk
	Placebo	6.51	6.31	Placebo	6.32	5.39
	Prasterone	6.47	5.43	Prasterone	6.34	5.39
	At 12 wk, prasterone significantly improved over placebo (p<0.0001)			At 12 wk, prasterone significantly improved over placebo (p<0.0001)		
Superficial cells (% of)		Baseline	12 wk		Baseline	12 wk
	Placebo	0.73%	1.64%	Placebo	1.04%	2.78%
	Prasterone	0.68%	6.30%	Prasterone	1.02%	11.2%
	At 12 wk, prasterone significantly improved over placebo (p<0.0001)			At 12 wk, prasterone significantly improved over placebo (p<0.0001)		
Parabasal cells (% of)		Baseline	12 wk		Baseline	12 wk
	Placebo	68.48%	66.86%	Placebo	51.7%	39.7%
	Prasterone	65.05%	17.65%	Prasterone	54.3%	12.7%
	At 12 wk, prasterone significantly improved over placebo (p<0.0001)			At 12 wk, prasterone significantly improved over placebo (p<0.0001)		

[a]GSM symptoms were evaluated with a questionnaire at screening, baseline, week 6, and week 12, with a scale of none (score 0), mild (score 1), moderate (score 2), or severe (score 3).

In another study assessing dyspareunia, the efficacy and safety of daily intravaginal prasterone administration on moderate to severe symptoms and signs of GSM were observed over 52 weeks.[14] The trial found the therapeutic effect was sustainable over 12 months and significant beneficial effects occurred at gynecologic examination on vaginal secretions, color, and epithelial integrity and thickness (p<0.0001 vs. baseline for all).

Table 3. Treatment of Dyspareunia with Prasterone: Withdrawal Rates and Reasons[15]

Treatment Withdrawn	DHEA 0.5% (n=11)	DHEA 0.25% (n=13)	Placebo (n=9)
Adverse event	2 1 = arthralgia 1 = suicidal ideation	4 1 = palpitations/HF 1 = vaginal intraepithelial lesion 1 = boating accident	1 1 = vaginal burning/tingling
Nonadherence	0	0	1
Withdrew consent	2	0	4
Investigator's decision	0	1	0
Other[a]	7	8	3

[a]Inclusion criteria not met, sponsor decision, or lack of efficacy per subject.
HF = hot flashes.

To compare prasterone with two local estrogen therapies, a review of independent prospective, randomized, double-blind and placebo-controlled phase III 12-week clinical trials was performed.[17] The total severity score of dyspareunia decreased from baseline by 1.27 to 1.63 units with prasterone treatment, 1.4 with conjugated equine estrogens (CEE), and 1.23 with estradiol. The total decreases in vaginal dryness severity were 1.44–1.58 units for prasterone, 1.1 units for CEE, and 1.23 units for estradiol. In this review, the authors concluded that once-daily prasterone was at least as effective in treating dyspareunia and vaginal dryness as 0.3 mg of CEE cream or 10-mcg estradiol vaginal tablets, without the systemic adverse effects. Some limitations to this review are that GSM symptoms were assessed through questionnaires and relatively short trials, with different patient demographics, were compared.

According to the current literature and efficacy trials, prasterone is available as a 6.5-mg vaginal insert with 28 vaginal inserts and applicators per box.[4,6] The recommended dosing is one 6.5-mg prasterone vaginal insert once daily at bedtime. Vaginal discharge was the most common adverse reaction in studies, with an incidence of 5.7%–6.1%.[15,16] In the 52-week open-label clinical trial, the most common adverse reactions were vaginal discharge (14.2%) and abnormal Pap smear (Papanicolaou test) (2.1%).[14] Table 3 includes additional information about withdrawal from clinical trials. The current average wholesale price (AWP) per unit of prasterone is $7.95.[18] In comparison, the AWPs per unit of other dyspareunia treatments are $8.15 for ospemifene, $7.29–$8.44 for estradiol vaginal cream, $14.23 for conjugated estrogens vaginal cream, $24.24 for estradiol vaginal tablet, and $517.61 for estradiol vaginal ring.[18]

Overall, prasterone once-daily vaginal inserts can improve moderate to severe dyspareunia in postmenopausal women. Despite this, current guidelines do not make a strong recommendation for its place in therapy for GSM.[1,5,7] However, expert consensus currently deems vaginal estrogen and intravaginal prasterone as available contemporary vaginal treatments of GSM.[1] According to the current literature, intravaginal prasterone may be a more cost-effective dyspareunia therapy after trialing vaginal lubricant and moisturizer because of its safety profile and efficacy with respect to symptom reduction and objective physiologic improvement. To date, no published studies have compared prasterone with ospemifene or other vaginal products of varying doses. Additional research comparing prasterone with other vaginal estrogen products and ospemifene for the treatment of dyspareunia in head-to-head trials is needed to evaluate the efficacy, cost, and place in therapy of prasterone while considering its risks and adverse effects.

References

1. 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;25:837-47.
2. PopulationPyramid.net. Population Pyramids of the World from 1950 to 2100. Available at https://www.populationpyramid.net/world/2020/. 2017. Accessed July 22, 2018.
3. Krychman M, Graham S, Bernick B, et al. The women's EMPOWER survey: women's knowledge and awareness of treatment options for vulvar and vaginal atrophy remains inadequate. J Sex Med 2017;14:425-33.
4. Prasterone. In: Lexi-Comp Online [Internet database]. Hudson, OH: Lexi-Comp. Accessed July 15, 2018.
5. North American Menopause Society (NAMS). The NAMS 2017 Hormone Therapy Position Statement Advisory Panel. The 2017 hormone therapy position statement of the North American Menopause Society. Menopause 2017;24:728-53.
6. Intrarosa (prasterone) [prescribing information]. Quebec City, Quebec, Canada: Endoceutics, February 2018.

7. Stuenkel CA, Davis SR, Gompel A, et al. Treatment of symptoms of the menopause: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2015;100:3975-4011.
8. Imvexxy (estradiol topical) [prescribing information]. Boca Raton, FL: Therapeutics MD, May 2018.
9. American College of Obstetricians and Gynecologists' Committee on Gynecologic Practice, Farrell R. ACOG Committee Opinion No. 659: The use of vaginal estrogen in women with a history of estrogen-dependent breast cancer. Obstet Gynecol 2016;127:e93-e96.
10. Crandall CJ, Hovey KM, Andrews CA, et al. Breast cancer, endometrial cancer, and cardiovascular events in participants who used vaginal estrogen in the Women's Health Initiative Observational Study. Menopause 2018;25:11-20.
11. Osphena (ospemifene) [prescribing information]. Florham Park, NJ: Shionogi, August 2015.
12. Intrarosa: Assessment Report. London: European Medicines Agency, November 2017. Available at www.ema.europa.eu/docs/en_GB/document_library/EPAR_Public_assessment_report/human/004138/WC500243737.pdf. Accessed July 31, 2018.
13. Therapeutic Research Center (TRC). DHEA Professional Monograph. Natural Medicines. Therapeutic Research Center. Summerville, MA: TRC. Available at https://naturalmedicines.therapeuticresearch.com. Accessed July 22, 2018.
14. 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;81:46-56.
15. Archer DR, Labrie F, Bouchard C, et al. Treatment of pain at sexual activity (dyspareunia) with intravaginal dehydroepiandrosterone (prasterone). Menopause 2015;22:950-63.
16. Labrie F, Archer DF, Kolton 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;23:243-56.
17. Archer DF, Labrie F, Montesino M, et al. Comparison of intravaginal 6.5mg (0.5%) prasterone, 0.3mg conjugated estrogens, and 10 mcg estradiol on symptoms of vulvovaginal atrophy. J Steroid Biochem Mol Biol 2017;174:1-8.
18. REDBOOK® (electronic version). Greenwood Village, CO: Truven Health Analytics. Available at www.micromedexsolutions.com. Accessed July 31, 2018.