

# Progress in Vulvovaginal Atrophy Treatments

Janet A. Chollet, MD

**While menopausal hormone therapy was once accepted as the ideal approach for optimizing changes associated with menopause, prospective randomized clinical trials have challenged that view. The result has led to a marked decrease in the use of such therapy and an intense search for alternatives. This commentary will highlight the progress in vulvovaginal atrophy treatments and what's new on the horizon.**

**V**ulvovaginal atrophy (VVA) is a thinning of the epithelium secondary to decreased levels of circulating estrogen. The affected tissue becomes more friable, and petechiae, ulcerations, and bleeding may occur after minimal trauma. Blood flow to the vagina is also reduced, leading to a decrease in the transudation, which normally lubricates the vagina during sexual intimacy, resulting in dryness and dyspareunia.

The symptoms of VVA are not limited to the menopausal population; symptoms can start before perimenopause, increase during the early perimenopausal period, and further increase in the 2 to 3 years after menopause. VVA is progressive and does

not spontaneously resolve. Thus, long-term therapy may be necessary to maintain urogenital health.

Currently, women spend more than one-third of their lives in the estrogen-deficient menopausal state. In 2008, there were 50 million American women 50 or older, and this segment of the population is expected to grow to about 85 million by 2014.<sup>1</sup> According to the North American Menopause Society (NAMS), an estimated 10% to 40% of menopausal women will experience symptoms related to VVA.<sup>2</sup> That translates into approximately 16 million women, including 500,000 new patients per year presenting with symptoms of VVA.

The 600,000 US women currently taking aromatase inhibitors report symptoms of VVA at about twice the rate of the general population. Overall, only 20% to 25% of symptomatic women seek medical help, despite the availability of FDA-approved treatment.

Data presented at the NAMS 19th Annual Meeting reported the results of a survey that evaluated the prevalence and impact of VVA symptoms and perceptions about safety of hormone therapy (HT) among women. Of the 2,290 respondents, 45% of women said they experience or had experienced symptoms of VVA.<sup>3</sup> The most common symptoms were vaginal dryness, pain, irritation, and itching. HT-related safety concerns were the main reason for discontinuance or never use among the respondents. For those women using HT, a third expressed concerns about its long-term safety and would prefer estrogen-free products to treat their condition. Of the women who had never used HT, 26% assumed their symptoms would go away over time.

Safety appears to be of paramount importance to this patient population—as impor-

## FOCUSPOINT

**VVA is progressive and does not spontaneously resolve. Thus, therapy may be necessary to maintain urogenital health.**

**Janet A. Chollet, MD**, is ObGyn, Beth Israel Deaconess Medical Center, Boston; and Director, Pear Tree Pharmaceuticals, Cambridge, MA.

**TABLE 1. Current FDA-Approved Therapies for Vulvovaginal Atrophy**

Drug Name	Drug Category	Pharmaceutical Co
Vagifem®	Estrogen derivative	Novo Nordisk
Premarin®	Estrogen derivative	Wyeth
Estring®	Estrogen derivative	Pfizer
Estrace®	Estrogen derivative	Warner Chilcott

tant as or more important than efficacy. The majority of women simply will not use HT. Also, the VVA market is substantially underserved. Less than a third of the potential patients are being treated, and a large number of those being treated could likely be convinced to use a product that has been demonstrated to be safer than HT. Even though the market is underserved, almost \$2 billion of HT is still sold annually in the United States alone.<sup>4</sup> Vaginal HT, used exclusively for VVA, sold about \$500 million products in 2008.

**PRESCRIPTION TREATMENTS**

Notwithstanding the foregoing, there seems to be a growing satisfaction among both patients and clinicians with the use of HT to effectively treat VVA. There is currently only one approved method for the treatment of VVA, and that is the administration of exogenous estrogens. Current prescription treatments approved for this condition are administered either systemically or locally in the vagina. The FDA recommends that vaginal formulations are the first choice for the initial management of VVA symptoms.

**TABLE 2. Therapies for Vulvovaginal Atrophy in Clinical Development**

Drug Name	Drug Category	Pharmaceutical Co	Clinical Phase
Ospemifene	SERM	QuatRx	NDA
BZA/CE	STEAR	Wyeth	Phase III
Seala®	SERM	Bionovo	Phase I-II
Prasterone	Androgen derivative	EndoCeutics	Phase III

Abbreviation: BZA/CE, bazedoxifene and conjugated estrogens; NDA, new drug application; SERM, selective estrogen receptor modulator; STEAR, selective tissue estrogenic activity regulator.

Today, local treatments available to clinicians for VVA are in the form of creams, tablets, and a vaginal ring. Leading estrogens Vagifem (Novo Nordisk), Premarin cream (Wyeth), Estring (Pfizer), and Estrace (Warner Chilcott) are examples (Table 1). These products generally work well and are believed to be safe, even though vaginal formulations have not been tested in long-term trials to support an assumed more favorable risk-benefit ratio.

In recent years, there has been an effort to use ultra-low-dose vaginal formulations to meet therapeutic goals, as an alternative to traditional regimens. The FDA recently approved an ultra-low-dose (10 mcg) formulation of the estradiol vaginal tablet (Vagifem) for the treatment of VVA. The approval was given based on clinical data from a 52-week study (N = 309) demonstrating that the ultra-low-dose tablet was significantly more effective than placebo for reducing the severity of VVA symptoms ( $P = .002$ ).<sup>5</sup> The study found improvement in markers for VVA: significant improvement in vaginal maturation ( $P < .001$ ), improvement in the grade of vaginal health ( $P < .001$ ), and improvement of the most bothersome symptom score ( $P = .003$ ). The higher 25-mcg formulation had also ranked high in patient acceptance and adherence to therapy.

**ALTERNATE TREATMENTS**

Generally, due to concerns about adverse effects of exogenous estrogens, there is a growing interest in alternative treatments for VVA (Table 2). To date, alternative therapies have included the selective estrogen receptor modulators (SERMs) and the selective tissue estrogenic activity regulators (STEARs). There are several products currently in clinical development.

The most advanced SERM product candidate is ospemifene (Ophena), a novel orally delivered SERM being developed by QuatRx to treat VVA. Ospemifene, a potential “estrogen-free” treatment for VVA, recently completed the second pivotal phase III clinical trial and, according to QuatRx, achieved all endpoints. The results (N = 826) showed that ospemifene was statistically significantly superior ( $P \leq .0001$ ) to placebo in maturation index, vaginal pH, and most bothersome symptom (vaginal dryness or dyspareunia) with the 60-mg

dose (and at the 30-mg dose, except for dyspareunia).<sup>6</sup>

Women with an intact uterus were enrolled into an extension safety study where the treatment blind was maintained for 12 months. In this study, 83% of those taking a 60-mg dose completed the study, compared with 69% on placebo. No trends were apparent in severe treatment-emergent adverse events, and there were no cases of venous thromboembolism, endometrial hyperplasia, or carcinoma.<sup>7</sup> QuatRx expects to submit its new drug application for ospemifene in 2010.

The most advanced STEAR product in clinical development includes a combination of oral bazedoxifene (BZA) and conjugated estrogens (CE) by Wyeth. Results of the 12-week (N = 652) SMART-3 (Selective estrogen Menopause And Response to Therapy 3) trial demonstrated improvement in the percent of superficial cells ( $P < .01$ ) and vaginal pH ( $P < .05$ ) at the 2 BZA/CE doses (20 mg/0.45 mg, 20 mg/0.625 mg), compared with placebo and BZA monotherapy.<sup>8</sup> The authors concluded that the favorable efficacy and safety profiles of BZA/CE support the use of a STEAR product containing BZA/CE as a new HT for VVA in menopausal women.

Other product candidates in clinical development include Seala (Bionovo) and intravaginal Prasterone (Endoceutics). Seala appears to be a Chinese herbal extract selective to estrogen receptor  $\beta$  and is in early development. A phase II clinical trial (N = 217) using an oral formulation of the herbal extract decreased the frequency of hot flashes compared to placebo after 12 weeks of treatment ( $P = .05$ ).<sup>9</sup> A phase I-II clinical trial of a vaginal formulation is expected to start soon (N = 40), though its regulatory pathway is unclear.

Prasterone, an intravaginal formulation containing dehydroepiandrosterone, has completed a phase III trial (N = 216). After 12 weeks, a significant increase in superficial cells ( $P < .0001$ ) and a decrease in vaginal pH ( $P < .0001$ ) were found. Comparable effects were observed at the 0.25% and 1.0% doses.<sup>10</sup> Of concern, Prasterone is a precursor to estrogen and therefore must be converted to estrogen to be effective. Further studies will need to be done to determine if this is just another way of delivering exogenous estrogens.

## CONCLUSION

According to the latest evidence-based position statement of NAMS, there is a growing body of evidence that HT, regardless of route of administration and timing of delivery, has certain benefits and risks. When HT is considered solely for VVA, then local therapy is recommended. The safety of HT use in breast cancer survivors has not been fully established, and there remains concern that it may be associated with an increased risk for breast cancer recurrence. Further research is essential.<sup>11</sup>

Overall, the ideal treatment must have benefits, minimize risks, and enhance compliance in the patient while optimizing cost-effectiveness. Therein sits the challenge in searching for the ideal treatment for VVA for the years to come.

*The author reports that she is Director and Founder of Pear Tree Pharmaceuticals.*

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## FOCUSPOINT

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