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New Treatments for Women's Sexual and Genital Health

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Introduction

IN THIS CLINICAL UPDATE, we selected recent publications relevant to the care of women with sexual and genital health concerns. Sexual health concerns in women, including difficulty with low sexual desire, sexual arousal, orgasm, and sexual pain, are common and often go unrecognized as providers may not ask and women are unlikely to initiate the discussion. Medical treatments for women with sexual dysfunction are few, and until recently only included local vaginal estrogen therapy. We have chosen to highlight articles on new (flibanserin) and experimental (DHEA, lidocaine, lasers) treatments for low sexual desire, vaginal dryness, and sexual pain.

FDA-Approval of Flibanserin

Joffe HV, et al. FDA approval of flibanserin—Treating hypoactive sexual desire disorder. *N Engl J Med* 2016;374:101–104.

What we know

Low sexual desire in women is common, underrecognized, and undertreated. Before August 2015, there were no medications approved by the Food and Drug Administration (FDA) for low sexual desire in women. Flibanserin was recently approved for treatment of hypoactive sexual desire disorder (HSDD), defined as persistent deficient sexual fantasies and desire for sexual activity associated with marked distress or interpersonal difficulty,¹ in premenopausal women.

Study results

Joffe *et al.* reviewed the approval process for flibanserin, which involved two rejections by the FDA before approval in 2015. Three-phase 3 trials provide evidence for the efficacy of flibanserin and deserve review. The Violet trial,² the Daisy trial,³ and the Begonia trial⁴ collectively revealed small, although significant treatment benefits as follows: sexually satisfying events increased (by 0.5–1.0 per month over a baseline of 2–3 per month); sexual desire scores as measured by the Female Sexual Function Index (FSFI) increased significantly (by 0.3–0.4 over a mean baseline of 1.8–1.9, where a higher number indicates greater sexual desire); and distress about sexual function as measured by the Female Sexual Distress Scale-Revised (FSDS-R) decreased significantly (by 0.3–0.4 over a mean baseline of 3.2–3.4, where a higher number indicates greater distress).

Before approval of the drug, an alcohol-interaction study was requested by the FDA, and included 25 participants, 23 of whom were men. Some study participants required intervention for hypotension or syncope when the drug was taken in the morning and alcohol was consumed quickly. However, the use of alcohol was not restricted or monitored in the phase 3 trials, and the incidence of syncope with flibanserin taken at bedtime was 0.4% versus 0.2% with placebo. Central nervous system depression (*e.g.*, somnolence) was a concern in addition to hypotension and syncope, and the concomitant use of a moderate or strong inhibitor of cytochrome P-450 3A4 (CYP3A4), such as antiretroviral drugs, antifungal drugs (*e.g.*, fluconazole, itraconazole, and ketoconazole), certain antibiotics (*e.g.*, ciprofloxacin and erythromycin), and antihypertensives (*e.g.*, diltiazem and verapamil), increases these risks.

In addition, the FDA required a risk evaluation and mitigation strategy to ensure safe use of flibanserin. This program requires that only certified prescribers and pharmacies that have enrolled and completed the training program may prescribe or dispense the drug (www.addyirems.com). Patients must be counseled to completely abstain from alcohol, and both patient and provider sign an agreement form; dispensing pharmacies are also required to counsel the patient on the need to abstain from alcohol. Flibanserin 100 mg is taken daily at bedtime. Assessment of the treatment response is suggested after 8 weeks, and discontinuation of the drug is recommended for nonresponders.

What this changes or adds

Flibanserin is the only FDA-approved treatment option currently available for HSDD in women. Flibanserin has modest efficacy for low sexual desire in premenopausal women in whom other biopsychosocial factors (*e.g.*, relationship discord, mood disorder, or fatigue) are not the primary cause. It has the potential for concerning side effects, the risk for which will be managed with labeling that includes a boxed warning and a medication guide. It is expensive (~\$800 per month), requires complete abstinence from alcohol and a certified prescriber and dispensing pharmacy.

DHEA for Dyspareunia and Vaginal Dryness

Labrie F, et al. Efficacy of intravaginal dehydroepiandrosterone (DHEA) on moderate to severe dyspareunia and vaginal dryness, symptoms of vulvovaginal atrophy and of

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the genitourinary syndrome of menopause. *Menopause* 2015 [Epub ahead of print].

What we know

Vaginal dryness and dyspareunia are symptoms of genitourinary syndrome of menopause (GSM), which is caused by estrogen depletion around the time of menopause. As systemic hormone therapy does not reliably treat urogenital symptoms, local vaginal estrogen therapy is the preferred treatment for symptoms related to GSM.⁵ Although symptoms of GSM occur in more than half of postmenopausal women and have a significant negative impact on sexual intimacy, few receive prescription therapy.⁶ Many women struggling with GSM are concerned about estrogen-based treatments and achieve sub-optimal relief with over-the-counter products.⁶

Study results

Labrie *et al.* conducted a prospective, randomized, double-blind placebo-controlled phase 3 clinical trial evaluating the effect of 0.5% intravaginal DHEA (6.5 mg) given daily for 12 weeks on four coprimary objectives, including percentage of parabasal cells, percentage of superficial cells, vaginal pH, and moderate to severe pain with sexual activity (dyspareunia) as the most bothersome symptom related to vaginal atrophy. All four endpoints improved compared to baseline in the treatment group, including a statistically significant decrease in the percentage of parabasal cells, increase in the percentage of superficial cells, decrease in vaginal pH, and decrease in sexual pain. In addition, moderate to severe vaginal dryness improved over placebo compared to baseline. Serum steroid levels (DHEA and its main metabolites, including DHEA-S, testosterone, and estradiol) remained within normal postmenopausal levels, although no data were reported on changes in serum steroid levels within the postmenopausal range.

What this changes or adds

Intravaginal DHEA is associated with improvement in both subjective and objective measures of the changes related to GSM. It was not found to increase serum steroid levels above the postmenopausal range and is a promising treatment for women with GSM who are concerned about the use of estrogen-based therapies.

A previous 52-week study of intravaginal DHEA 6.5 mg daily showed no stimulation of the endometrium, consistent with the lack of aromatase in the endometrium that could convert androgens (from DHEA) to estrogens.⁷ However, it is still unclear if there are clinical implications to *any* increase in serum steroid levels, particularly in breast cancer survivors, even if they remain well within the postmenopausal range. Additional study of clinical outcomes is needed, especially in women with a history of hormone-responsive cancers.

DHEA is not currently approved by the FDA and requires a compounding pharmacy to dispense.

Topical Lidocaine for Dyspareunia

Goetsch ME, *et al.* A practical solution for dyspareunia in breast cancer survivors: A randomized controlled trial. *J Clin Oncol* 2015;33(30):3394–3400.

What we know

The recommended treatment for insertional dyspareunia due to a low estrogen state is low-dose vaginal estrogen therapy.⁵ However, hormone therapy may be contraindicated for some breast cancer patients, leaving limited and less effective alternative treatment options (lubricants and moisturizers).

Study results

The authors performed a randomized, controlled double-blind trial of 43 estrogen-deficient breast cancer survivors with severe dyspareunia. Participants were randomized to self-apply saline plus silicone lubricant (saline) or 4% aqueous lidocaine plus silicone lubricant (lidocaine) to the vulvar vestibule, 3 minutes before either tampon insertion or penile-vaginal penetration. Penetrative pain was self-reported twice weekly on a pain scale for 1 month. Saline reduced penetrative pain by 38%, whereas lidocaine reduced pain by 87.5%. This study extended for a 2-month open-label lidocaine phase, for which 41 women continued their participation. At completion of the 2-month open-label extension, sexual function improved in nearly all domains, sexual distress significantly decreased, and 90% of patients reported engaging in comfortable penile-vaginal penetration. Two participants with pelvic floor myalgia reported no reduction in dyspareunia due to deeper penetration. One participant declined to engage in penile-vaginal penetration with her partner, despite complete resolution of pain. At a 6-month phone follow-up, results were essentially maintained. Furthermore, all participants reported that without the use of lidocaine, they continued to experience “introital tenderness.”

What this changes or adds

Lidocaine plus silicone lubricant is a potential pain-reducing tool for a subset of estrogen deficient breast cancer survivors with insertional dyspareunia. The subset of women who would benefit from lidocaine includes those with no pelvic floor myalgia and whose pain is exclusive to the vulvar vestibule. It is important to note that lidocaine may be a palliative solution, not a *treatment* for dyspareunia. It does not relieve pelvic floor myalgia or repair discord in a sexual relationship. Thus, treatment of dyspareunia remains multifactorial; however, lidocaine plus silicone lubricant is a potential palliative option for some women.

Laser Treatment of Genitourinary Syndrome of Menopause

Gambacciani M, *et al.* Vaginal erbium laser: The second-generation thermotherapy for the genitourinary syndrome of menopause. *Climacteric* 2015;18:757–763.

What we know

Lasers have been approved by the FDA for “incision, excision, vaporization, and coagulation of body soft tissues....”^{8,9} This FDA approval is not specific for the treatment of GSM. Recently, lasers are being used in outpatient settings to treat GSM, with the proposed mechanism of action being stimulation of collagen synthesis. The typical laser treatment involves three 5–10 minute sessions costing

between \$600 and \$2500 per session.⁹ Advertisements for this procedure describe it as vaginal rejuvenation, claim that it is 100% safe, and encourage women to ask their healthcare providers about it.

Study results

Gambacciani *et al.* conducted a nonrandomized, prospective longitudinal pilot study of 43 postmenopausal women using a nonablative vaginal erbium laser (VEL) to treat symptoms of GSM. Participants had not taken hormone therapy for the previous 12 months. They were treated with three applications of VEL to the vaginal introitus, vestibule, and vaginal wall over a 3-month period. For a subset of 19 participants with stress urinary incontinence (SUI), they received additional laser treatment to the anterior vaginal wall. Treatment outcomes were compared to those of an active control group of 19 postmenopausal women treated with vaginal estrogen gel (estriol), twice weekly, for 3 months. At 12 and 24 weeks posttreatment completion, participants in the VEL treatment group reported significantly less vaginal dryness and dyspareunia and greater vaginal health compared to the control (estriol) group. Furthermore, compared to baseline, women with SUI reported a significant decrease in urinary incontinence. Acceptability of VEL was similar to that of vaginal estrogen gel.

This study is one of several to demonstrate the benefits of lasers for the treatment of GSM. The first, a seminal article, is worth noting here.¹⁰ Salvatore *et al.* conducted a prospective nonrandomized pilot study of 50 postmenopausal women using a microablative fractional carbon dioxide (CO₂) laser to treat GSM. Participants had not taken hormone therapy for the previous 6 months and had not used a moisturizer or lubricant in the past 30 days. They were treated with three applications of a CO₂ laser to the vaginal introitus and vaginal wall over a 3-month period. By follow-up at 12 weeks, vaginal dryness, burning, itching, dysuria, and dyspareunia significantly improved compared to baseline. At week 12, more than 80% of women were satisfied with the procedure and self-reported significant improvement in quality of life. There was no follow-up after 12 weeks, so duration of benefit and long-term adverse effects were not evaluated.

What this changes or adds

Laser technology may be a promising, although expensive, alternative to local estrogen therapy for the treatment of GSM. However, without large longitudinal randomized controlled trials, the long-term safety and efficacy of this treatment are unclear. Of concern are the unsubstantiated marketing claims that laser treatment is 100% safe and can treat a variety of vaginal issues (*e.g.*, urinary incontinence and vaginal loosening).

Summary

Flibanserin is a new FDA approved treatment for low sexual desire in premenopausal women. DHEA, lidocaine,

and lasers are experimental and potentially promising treatments that are available for management of vaginal dryness and dyspareunia in women. Additional long-term, randomized controlled trial data regarding long-term safety and efficacy will be welcomed for these experimental therapies.

Author Disclosure Statement

No competing financial interests exist.

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