Current Sexual Health Reports (2019) 11:21–28
https://doi.org/10.1007/s11930-019-00187-x

CLINICAL THERAPEUTICS (B MCCARTHY AND R SEGRAVES, SECTION EDITORS)

New Treatments for Female Sexual Dysfunction: Are they Safe and Effective for Older Post-Menopausal Women?

Janelle Sobecki-Rausch[1] · Stacy Tessler Lindau[2]

Published online: 16 January 2019

Abstract

Purpose of Review Several new modalities for treatment of female sexual function problems have been approved by the US Food and Drug Administration (FDA). This review summarizes current evidence about recently approved medications to inform treatment of sexual function problems in women older than 65 years.

Recent Findings Published studies leading to FDA approval of treatment modalities were efficacy trials not widely applicable to the general population. The clinical effectiveness of these modalities remains unknown. Although some studies have included post-menopausal women, few have included women older than 65 years.

Summary Health care providers need current information about safety and effectiveness of these new treatments for all women, including the fast-growing population of older post-menopausal women. Exclusion of older women from studies of treatments for female sexual function problems presents a barrier to treatment.

Keywords Sexual dysfunction · Post-menopausal · Women

Introduction

More than 43 million people in the United States (US) are over the age of 65, a number expected to almost double by 2050 [1]. Sexual function is an important aspect of health for older adults in the US [2]. More than half of all community-residing people ages 57–85 and up to 85% of partnered people over the age of 65 are sexually active. Among women 65 and older, as many as half report one or more problems with sexual function including lack of interest, lack of pleasure, difficulty with lubrication, pain with sexual activity, and inability to achieve orgasm. Among women 65 and older, as many as one third report avoiding sex because of sexual problems [2, 3].

Since the unprecedented financial success of sildenafil and similar drugs for treatment of male erectile dysfunction 20 years ago, there has been growing investment in research and development of treatments for female sexual dysfunctions. Several treatments have received US Food and Drug Administration (FDA) approval in recent years. Drug development studies that have included post-menopausal women have focused primarily on middle-aged women in early post-menopause (mean study age ranges 58–59 years). On average, a woman aging in the US will live three decades past natural menopause. Given the unprecedented growth of the aging population in the US, and the high prevalence of sexual function problems, health care providers need current information about safety and effectiveness of treatments for older post-menopausal women. This review aims to examine recent literature regarding new US FDA-approved treatments for sexual dysfunction among women over the age of 65 and to discuss what is and is not known about safety and effectiveness in this population.

A systematic review of the literature was conducted to identify recently approved modalities for treatment of female sexual dysfunction in post-menopausal women. Studies were identified by systematic review of electronic databases (Ovid MEDLINE, Embase, Web of Science, Cochrane Database of Controlled Trials, and PsychINFO) from January 2012 to

Topical Collection on *Clinical Therapeutics*

✉ Janelle Sobecki-Rausch
jsobecki-rausch@uwhealth.org; janellesobecki@gmail.com

[1] Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, University of Wisconsin-Madison, 600 Highland Ave, H4/676, Madison, WI, USA

[2] Departments of Obstetrics and Gynecology and Medicine-Geriatrics, The University of Chicago, Chicago, IL, USA

December 2017. Identified modalities were cross-referenced with the FDA's Drugs@FDA database to determine which of these modalities were FDA-approved since 2013 [4]. Randomized controlled trials and meta-analyses of recently FDA-approved modalities for treatment of female sexual dysfunction in post-menopausal women were included. Hand-reviewed searches of references of included studies were performed to identify older randomized controlled trials of identified modalities. Because several included studies were completed prior to the publication of the Diagnostic and Statistical Manual of Mental Disorders 5th Edition (DSM-V), this review reflects the diagnostic terminology used by authors of the included studies [5]. Modalities are discussed chronologically by year of FDA approval.

Ospemifene

Ospemifene (US trade name Osphena®) is an orally administered selective estrogen receptor modulator (SERM) approved by the FDA in 2013 for the treatment of moderate to severe dyspareunia due to vulvovaginal atrophy (VVA) in menopause. VVA has long been considered a component of physiologic genitourinary changes of menopause and has been associated with sexual dysfunction in women [6, 7]. Ospemifene is thought to improve dyspareunia by acting as an estrogen agonist to the vaginal epithelium [8, 9].

Six randomized, placebo-controlled trials of ospemifene were conducted in post-menopausal women with VVA and dyspareunia [10–15]. Five studies included women ages 40–80 years old [10, 11, 13–15], and one included women ages 45 to 65 years [12]. All studies compared the use of oral ospemifene (30 mg or 60 mg) versus placebo for two duration periods, 12 weeks [10–12] and 1 year [13–15].

Two of these trials reported dyspareunia outcomes [10, 11]. The first, published in 2010, randomized post-menopausal women ($N = 826$, mean age 58.4–58.9 years, range 40 to 80 years, mean BMI 26 kg/m^2, 90% white race, sexual orientation not reported) with VVA to ospemifene 30 mg, 60 mg, or placebo taken orally daily for 12 weeks [10]. Neither age distribution nor age-stratified efficacy or safety analyses were reported. VVA was defined as 5% or less superficial cells on vaginal smear, vaginal pH greater than 5.0, and one symptom of self-assessed moderate or severe VVA (vaginal dryness, vaginal, and/or vulvar irritation/itching, dysuria, vaginal pain with sexual activity, or vaginal bleeding associated with sexual activity). Exclusion criteria were extensive, including, but not limited to, thickened endometrial stripe (4 mm on transvaginal ultrasound), abnormal pathologic findings on endometrial biopsy or Papanicolaou smear, BMI of ≥ 37 kg/m^2, abnormal breast exam or mammogram, history of malignancy within the past 10 years, current or past severe renal or hepatic dysfunction, current or past history of thromboembolic disease, heavy alcohol use (more than 14 drinks per week), or use of certain anti-fungal medications or digitalis alkaloids. Prior use of hormone therapy required a washout period before study enrollment (14 days for vaginal products, 60 days for systemic products). Outcomes included four primary co-endpoints measured between baseline and 12 weeks: percentage of superficial and parabasal cells on vaginal smear, vaginal pH, and self-assessment most bothersome symptom (MBS) of moderate to severe vaginal dryness or dyspareunia. A secondary outcome was defined as change between baseline and 4 weeks for the same primary co-endpoints. Symptoms related to VVA were measured as self-reported severity scale (0, none; 1, mild; 2, moderate; 3, severe) at baseline and 4- and 12-week intervals. Safety was measured by a combination of patient self-reported adverse events as well as physical, gynecologic and breast exams, lab assessments, and electrocardiograms. Baseline and 12-week endometrial biopsies and Papanicolaou smears were performed.

Of the 826 randomized participants, 689 completed 12 weeks of treatment. Analyses were performed as intention-to-treat for primary outcomes and safety analysis. Forty-six percent of participants reported dyspareunia as their MBS. Among those reporting dyspareunia as their MBS, women treated with ospemifene 60 mg daily had a statistically significant decrease in dyspareunia symptoms from baseline to 12 weeks as compared to placebo (mean symptom scores: 1.19 vs. 0.89, $p = 0.02$). A significant difference was not found with the use of ospemifene 30 mg daily as compared to placebo. The rest of the primary and secondary endpoints were significantly improved with both 30 mg and 60 mg of ospemifene as compared to placebo. Reported adverse events included hot flashes (9.6%, 60 mg; 8.3%, 30 mg; 3.4%, placebo), urinary tract infections (7.2%, 60 mg; 4.6%, 30 mg; 2.2%, placebo), and headaches (2.5%, 60 mg; 6.0%, 30 mg; 5.2%, placebo). No cases of endometrial hyperplasia or carcinoma were found in women with an intact uterus (approximately 45% of participants) between baseline and 12 weeks.

The second study, published in 2013, randomized post-menopausal women ($N = 605$, mean age 58 years, range 40 to 80 years, mean BMI 26 kg/m^2, 90% white, no sexual orientation reported) with VVA and MBS of moderate to severe dyspareunia to ospemifene 60 mg or placebo taken orally daily for 12 weeks [11]. Eighty-four women (14%) included in the study were 65 years of age or older. No age-related efficacy or safety analyses were performed. Inclusion and exclusion criteria, safety assessment, outcomes, and analysis were nearly identical to the previously discussed trial. Symptoms related to VVA were again measured as self-reported severity scale (0, none; 1, mild; 2, moderate; 3, severe) at baseline and 4- and 12-week intervals. Nearly 90% of participants completed the trial. Intention-to-treat analysis was performed. Ospemifene 60 mg daily was found to significantly improve all four primary co-

endpoints as compared to placebo from baseline to 12 weeks. With regard to dyspareunia, participants randomized to ospemifene 60 mg had a statistically significant mean decrease in MBS severity score as compared to placebo (1.5, ospemifene; 1.0, placebo, $p = 0.0001$). Additionally, more women in the ospemifene group reported no vaginal pain with sexual activity at 12 weeks as compared to placebo (38%, ospemifene; 28%, placebo). Reported adverse events were similar to the previously discussed trial. No cases of endometrial hyperplasia or carcinoma were found as measured at baseline to 12 weeks.

A systematic review and meta-analysis of six randomized controlled trials of ospemifene conducted between 2003 and 2013 was published in 2014 [16]. Pooled analysis of the previously mentioned two trials investigating dyspareunia (N = 1149 total randomized participants) showed a significant decrease in dyspareunia compared to baseline among women treated with 12 weeks of ospemifene versus placebo (standardized mean difference (SMD) = − 0.37, 95% CI = − 0.43 to − 0.30, $p = 0.00001$). No age distributions were reported, and no age-related efficacy or safety analyses were performed. The authors concluded, based on their safety analysis, ospemifene was generally safe with regard to endometrial thickness and adverse events. The most common side effects included hot flashes (8–9%, ospemifene; 3%, placebo), urinary tract infections (4–7%, ospemifene; 2%, placebo), and headaches (2–6%, ospemifene; 5%, placebo). No thromboembolic events, endometrial hyperplasia, or endometrial carcinoma were reported.

A study published in 2015 investigated the effect of ospemifene with regard to female sexual dysfunction (FSD) in post-menopausal women with VVA and MBS of dyspareunia or vaginal dryness ($N = 919$) [17]. Using previously reported primary data from phase 3 randomized placebo-controlled trials of daily ospemifene 60 mg versus placebo, this study reported secondary endpoint analyses of female sexual dysfunction (FSD) as measured by the Female Sexual Function Index (FSFI) total and domain scores from baseline to 4 and 12 weeks. The FSFI is a validated index that includes 6 domains of female sexual function: desire, arousal, lubrication, orgasm, satisfaction, and pain as measured out of a total possible score of 36 (less than 26.55 indicates dysfunction) [18]. Study participants completed the survey at baseline, week 4, and week 12. The group taking ospemifene 60 mg daily was found to have statistically significant improvement in total FSFI score as compared to placebo between baseline (total FSFI score: 19.84, ospemifene; 19.55, placebo) and week 4 (mean improvement change in total FSFI score: 5.29, ospemifene; 3.70, placebo; $p < 0.001$) as well as week 12 (mean improvement change in total FSFI score: 6.69, ospemifene; 4.14, placebo; $p < 0.001$). Additionally, all individual domains of the FSFI were significantly improved in the ospemifene 60 mg daily group as compared to placebo at week 12. The authors concluded that ospemifene 60 mg daily improved female sexual function across all FSFI domains as compared to placebo.

Ospemifene has been shown to be generally safe and efficacious in improving dyspareunia in post-menopausal women with VVA as measured by self-reported differences in severity of dyspareunia as compared to placebo. Analysis of female sexual dysfunction, as measured by FSFI, was investigated as a secondary outcome in one study by Constantine et al. and demonstrated a significant improvement in overall sexual dysfunction and in individual FSFI domains in women taking ospemifene. There was, however, considerable placebo effect of up to 3 to 4 point improvements in total FSFI score for women in the placebo group compared to 5 to 6 point improvements for women taking ospemifene.

The effectiveness of ospemifene in an inclusive population of post-menopausal women is unknown. These ospemifene trials were efficacy studies of predominately non-obese White women (> 90% in trials investigating dyspareunia) with few or no co-morbidities. The average age of participants in trials of ospemifene was approximately 58 years old. Only one of two trials investigating the effect of ospemifene on dyspareunia reported age subgroups. No efficacy or safety analyses in these studies were stratified by age. Although ospemifene can be considered for treatment of dyspareunia related to VVA in older women, with close monitoring for clinically relevant improvement and side effects, we have not yet identified a patient for whom this modality was optimal or preferred.

Flibanserin

Flibanserin (US trade name Addyi®) was FDA-approved in 2015 for the treatment of hypoactive sexual desire disorder (HSDD) in pre-menopausal women. It is not currently approved for the treatment of HSDD in post-menopausal women. The mechanism of action of flibanserin is not fully understood. A post-synaptic serotonin $5HT_{1A}$ agonist and serotonin $5HT_{2A}$ antagonist, one theory is that it may improve sexual desire by modulating a transient decrease in serotonin and increase in dopamine and epinephrine in certain areas of the brain [19].

Two published, randomized, placebo-controlled trials of flibanserin were conducted in post-menopausal women [20, 21]. The first of these trials (the SNOWDROP trial), published in 2013, randomized post-menopausal women with HSDD ($N = 949$, mean age 55.4 years, age range not published, mean BMI 27 kg/m^2, 86% white, heterosexual orientation) to flibanserin 100 mg tablets or matching oral placebo [21]. Fewer than 5% of the women in this study were over the age of 65, and no age-stratified efficacy or safety analyses were performed. Participants had to be naturally post-

menopausal, diagnosed with HSDD, have a score of 15 or more on the Female Sexual Distress Score – Revised (FSDS-R) [22] indicating distress associated with sexual problems, and have a score of 0 or 1 on the Sexual Interest and Desire Inventory – Female Receptivity [23] item indicating little or no receptivity to partner's sexual advances. Inclusion criteria additionally required that participants were engaged in a monogamous heterosexual relationship for at least 1 year with a sexually functional male partner readily available for sexual activity during a 24-h period at least 50% of the time. Exclusion criteria were extensive, including but not limited to common mental health disorders (depression, suicidal ideation), gynecologic problems (pelvic pain, urinary tract infection, interstitial cystitis, vulvodynia, symptomatic vaginal atrophy, thickened endometrial stripe), prior surgeries (hysterectomy, oophorectomy), and medications (CYP3A inducers, antidepressants, mood stabilizers, chronic narcotics).

Two primary co-endpoints were measured: change in number of sexually satisfying events (SSEs) per month and Female Sexual Function Index desire domain (FSFI-d) score between baseline and week 24 [21]. An eDiary was used to record SSEs. Participants would enter any sexual events and whether or not they were satisfying into the diary daily. This study found that women taking flibanserin had a statistically significant increase in the mean number of SSEs from baseline to 24 weeks as compared to placebo (flibanserin, 1.0; placebo, 0.6; $p = 0.004$) and increased sexual desire as measured by FSFI desire domain score (flibanserin, 0.7; placebo, 0.4; $p < 0.001$). Reported adverse events included dizziness (flibanserin, 9%; placebo, 3%), somnolence (flibanserin, 8.7%; placebo, 1.4%), and nausea (flibanserin, 7.4%; placebo, 3.5). With regard to primary endpoints, the authors concluded flibanserin improved sexual desire and number of SSEs in post-menopausal women with HSDD as compared to placebo.

The second trial (PLUMERIA), published in 2017, also randomized post-menopausal women with HSDD ($N = 745$, mean age 56.1 years, age range not published, mean weight 71 kg, 85% White, heterosexual orientation) to flibanserin 100 mg tablets or matching oral placebo [24]. Seven percent of participants were over the age of 65. No age-related efficacy or safety analyses were performed. Participants were screened using similar inclusion and exclusion criteria as the previously mentioned trial including patients in heterosexual monogamous relationships for at least 1 year with readily available, sexually functional partners. Primary co-endpoints included number of SSEs and FSFI-d score measured at baseline and 24 weeks. The study was prematurely terminated early in 2011 due to temporary discontinuation of flibanserin production, at which time approximately 45% of randomized participants had completed 16 weeks of therapy. The study analyzed outcomes between baseline and 16 weeks of therapy. Authors reported a significant improvement in sexual desire as measured by FSFI-d (flibanserin, 0.6; placebo, 0.4; $p = 0.011$) but failed to detect significance in number of SSEs (flibanserin, 1.0; placebo, 0.7; p value reported as not significant). Adverse events reported included somnolence, insomnia, and dizziness, each experienced by approximately 6–7% of participants in the flibanserin group as compared to 2–3% in the placebo group.

Jaspers et al. published a systematic review of the literature and meta-analysis in 2016 analyzing the safety and efficacy of flibanserin in women with HSDD studied in randomized clinical trials from inception through June 2015. They reported pooled mean difference for number of SSEs (increase of 0.58 events in published studies), FSFI-d score (improvement of 0.27), and eDiary desire score (scale 0–84, pooled mean difference 1.63, only measured in pre-menopausal women). They also reported that flibanserin significantly increased the risk of side effects including dizziness, hypotension, and somnolence. No age-related efficacy or safety analyses were performed. They concluded the quality of evidence supporting flibanserin use was low, and further studies, particularly for women with medical co-morbidities, were warranted [25].

The FDA also expressed concern regarding the efficacy and safety of flibanserin. Concomitant use of flibanserin with cytochrome P-450 3A4 inhibitors (including antibiotics commonly used by sexually active women to treat fungal and bacterial infections) and alcohol were shown to increase central nervous system (CNS) and cardiovascular side effects, including CNS disturbances, hypotension, and syncope [26]. The FDA reviewed flibanserin three times prior to its approval in 2015 for treatment of HSDD in pre-menopausal women and stipulated it include box warnings regarding its use with other medications as well as alcohol. It also required physicians and dispensing pharmacists to be certified and to enroll in the FDA's Risk Evaluation Mitigation Strategy (REMS) program. Patients are also required to sign a written consent regarding abstaining from alcohol while using flibanserin [26]. As a result of relatively low efficacy, cost, required duration of use to determine therapeutic effect, side effect profile, contraindications with alcohol and common medications, the REMS strategy, and lack of approval for use in post-menopausal women, flibanserin uptake has been very low.

The trials of flibanserin provide insufficient evidence for safety and effectiveness in older post-menopausal women. Flibanserin has been studied predominantly in healthy, non-obese, White, monogamous heterosexual women with long-term sexually active partner. Its effectiveness for a general population of women, including older post-menopausal women, remains unknown. Although rates of low libido are high among the general population of women 65 and older, clinical trials of flibanserin included too few women over the age of 65 to establish safety and efficacy in this population. Additionally, reported adverse events of flibanserin (hypotension, dizziness,

somnolence) raise concerns about safety, especially in older post-menopausal women given changes in balance and cognition that can occur with aging.

Many post-menopausal women with low libido are interested in a safe and effective therapy. Use of flibanserin to treat low sexual desire in post-menopausal women is currently an off-label use. To date, we have had no post-menopausal patients choose flibanserin as a treatment for low libido.

Vaginal Prasterone

Vaginal prasterone (dehydroepiandrosterone, DHEA, US trade name Intrarosa®) is a vaginal suppository approved by the FDA in 2016 for the treatment of dyspareunia related to VVA in menopausal women. It is thought to improve symptoms of VVA by aromatizing testosterone and androstenedione to estrone and estradiol in vaginal tissue. The approval of vaginal prasterone was based on two primary 12-week randomized, placebo-controlled phase 3 clinical efficacy trials [27, 28].

The first of these trials, published in 2015, randomized post-menopausal women ($N = 255$, mean age 58.5 years, range 40–75 years, mean BMI 26 kg/m^2, 92% white, no sexual orientation reported) with VVA (as defined as 5% or fewer superficial cells on vaginal smear, vaginal pH ≥ 5) and self-reported moderate to severe pain with sexual activity to daily insertion of an intravaginal ovule (suppository) containing DHEA. Participants were randomized to 0.25% DHEA, 0.50% DHEA, or placebo for a total of 12 weeks [27]. Neither age distribution nor age-stratified efficacy or safety analyses were reported. Exclusion criteria included a wide range of common co-morbid health conditions including but not limited to hypertension (≥ 140/90 mmHg), malignancy (except non-melanoma skin cancer), thromboembolic disease, uncontrolled diabetes, palpable uterine fibroids, and stage 2 uterine prolapse. BMI and smoking status were not exclusion factors. Primary co-endpoints included measures of VVA (vaginal superficial cells, vaginal parabasal cells, vaginal pH) and self-reported moderate to severe dyspareunia (range 0–3, 0: none, 1: mild, 2: moderate, 3: severe). The study demonstrated statistically significant improvements in all four primary co-endpoints in patients receiving DHEA as compared to placebo. The authors reported a significant decrease in mean severity score for dyspareunia as compared to baseline for women receiving 0.50% DHEA as compared to placebo (decrease in mean severity score 2.63 to 1.36, $p = 0.013$ vs. placebo). A total of 52.9% of participants treated with 0.50% DHEA ($n = 87$) reported at least one adverse event including vaginal discharge (5.7%), urinary tract infection (5.7%), headache (5.7%), and nausea (4.6%). These rates were comparable in the 0.25% DHEA-treated group and placebo group. No changes in serum steroid measurements or endometrial histology were considered clinically relevant. The authors concluded prasterone was effective for post-menopausal women in the treatment of VVA, including dyspareunia.

The second trial, published in 2016, randomized post-menopausal women ($N = 558$, median age 59.0 years, range 40–80 years, mean BMI 26 kg/m^2, 90% White, no sexual orientation reported) with moderate to severe dyspareunia to daily insertion of an intravaginal ovule containing 0.50% DHEA versus placebo suppository for 12 weeks [28]. Neither age distribution nor age-stratified efficacy or safety analyses were reported. Primary co-endpoints again included measures of VVA (vaginal superficial cells, vaginal parabasal cells, vaginal pH) and self-reported moderate to severe dyspareunia (range 0–3, 0: none, 1: mild, 2: moderate, 3: severe). Inclusion and exclusion criteria were similar to the previously discussed trial. This study reported women treated with 0.50% DHEA daily for 12 weeks had a significant improvement in all primary co-endpoints. They reported a significant decrease in self-reported dyspareunia as compared to placebo (2.54 to 1.13 in 0.50% DHEA group, 2.56 to 1.50 in placebo group, $p < 0.0002$). Reported adverse events were similar to the previous discussed study of DHEA. The authors concluded 0.50% DHEA was safe and efficacious in the treatment of VVA of menopause, including dyspareunia, with a high benefit to risk ratio in this population.

A study published in 2015 sought to further investigate the use of DHEA in the treatment of overall sexual function by analyzing Female Sexual Function Index (FSFI) data collected from previous placebo-controlled trials of DHEA [29]. The FSFI individual domain scores range from 0 to 5 or 1–5 with a total score range of 1.2 to 36. A score less than approximately 26 is typically considered diagnostic of female sexual dysfunction.

Post-menopausal women with moderate to severe dyspareunia (mean age 59.5 years, range 40 to 80 years) randomized to either placebo ($n = 157$) or 0.5% DHEA ($n = 325$) daily for 12 weeks completed the FSFI at baseline and 12 weeks. Participants randomized to DHEA were found to have significant improvement in all domain scores of the FSFI from baseline to 12 weeks as compared to placebo: desire (DHEA 2.58 to 3.22; placebo 2.64 to 3.11, $p = 0.01$), arousal (DHEA 2.57 to 3.74; placebo 2.59 to 3.33 $p = 0.002$), lubrication (DHEA 2.00 to 4.13; placebo 1.91 to 3.53, $p = 0.0005$), orgasm (DHEA 2.53 to 3.80; placebo 2.41 to 3.42, $p = 0.047$), satisfaction (DHEA 2.84 to 4.21; placebo 2.92 to 3.80, $p = 0.001$), pain (DHEA 1.61 to 3.82; placebo 1.68 to 3.24, $p = 0.001$). The total FSFI score for those randomized to DHEA was also significantly improved between baseline to 12 weeks as compared to placebo (DHEA 14.29 to 23.14; placebo 14.25 to 20.53, $p = 0.0006$). The main side effect reported was vaginal discharge, similar to previous studies.

Studies of prasterone yield no major safety concerns, and the therapy is well tolerated. Similar to studies of ospemifene, the efficacy of prasterone was measured by self-reported

severity scale of dyspareunia (range 0–3, 0: none, 1: mild, 2: moderate, 3: severe). There was, however, considerable placebo effect of up to 6 point improvements in total FSFI score for placebo groups compared to 9 point improvements for women taking prasterone. Trials of prasterone were efficacy studies, conducted in primarily healthy, non-obese, White post-menopausal women; evidence for effectiveness in the general population is limited. Post-menopausal women between the ages of 40 and 80 years old were included in the trials, and the mean reported ages for the two trials was less than 60 years old. No safety or efficacy analyses by age were performed. Prasterone may be a reasonable option for older and healthier post-menopausal women without contraindications, but patients should be counseled that this modality is new and evidence for safety in the general population of older women is limited. Women may find the suppository modality less messy than estradiol cream, but an advantage of the cream is that it can also be applied externally to address vulvar atrophy.

Estradiol Vaginal Insert

In May 2018, the FDA approved an estradiol vaginal insert (US trade name IMVEXXY®) for the treatment of moderate to severe dyspareunia due to menopause. Vaginal estrogen has long been used to treat dyspareunia due to vulvovaginal atrophy (VVA) in post-menopausal women and is available in several formulations including vaginal cream applied with an applicator, vaginal tablet, and vaginal rings [30]. Less is known regarding effectiveness of vaginal estrogen products on sexual function.

A phase 3 randomized, double-blinded, placebo-controlled trial (the REJOICE trial) published in 2017 investigated the use of TX-004HR, a 17β-estradiol vaginally inserted soft gel capsule for treatment of dyspareunia in post-menopausal women with VVA [31]. This trial randomized sexually active post-menopausal women ($N = 764$, mean age 59 years, range 40 to 75 years, mean BMI 26 kg/m^2, 87% White, no sexual orientation reported) with vulvovaginal atrophy (defined as ≤ 5% superficial cells on vaginal cytological smear, vaginal pH > 5.0) and moderate to severe vaginal pain associated with sexual activity to 12 weeks of treatment with 4, 10, or 25 μg of TX-004HR versus placebo daily for 2 weeks followed by biweekly for 10 weeks. No age distribution or age-related analyses were performed. Exclusion criteria included numerous medical and behavioral conditions including but not limited to liver or kidney disease, thromboembolic disorders, cerebrovascular accidents including transient ischemic attack and stroke, endocrine disease, alcohol or drug abuse, and heavy tobacco use. Primary endpoints included change in the percentage of parabasal and superficial cells, vaginal pH, and patient-reported dyspareunia using the VVA Symptom Self-Assessment Questionnaire (range 0 = none to 3 = severe) from baseline to 12 weeks. Secondary endpoints included changes over other time intervals (2, 6, and 8 weeks) as well as vulvar or vaginal itching/irritation and vaginal dryness. All four primary endpoints were significantly improved with TX-004HR versus placebo, except dyspareunia with the 4 μg formulation. A significant decrease in self-reported dyspareunia symptoms for women treated with 10 and 25 μg formulations of TX-004HR was found between baseline and 12 weeks as compared to placebo (10 μg, 1.7; 25 μg, 1.7; placebo, 1.3; $p = 0.01$). With regard to safety, all participants underwent endometrial sampling at baseline and 12 weeks. No cases of endometrial hyperplasia or malignancy were identified. Few adverse events were reported with headache being the most common side effect in treatment group (range 3.2–7.4%, not dose dependent) versus 7.8% in placebo group.

A follow-up subgroup analysis of the REJOICE trial data published in 2017 investigated differences in the effect of TX-004HR by age, weight, uterus status, pregnancy status, and vaginal birth history [32••]. Three age groups were defined: ≤ 56, 57–61, and ≥ 62 years old. Dyspareunia was measured by VVA Symptom Self-Assessment Questionnaire (range: 0, none to 3, severe). Efficacy analysis by age demonstrated all three age groups showed significant improvement in mean dyspareunia scores from week 2 to week 12 of treatment with TX-004HR as compared to placebo. Specifically, for women ≥ 62 years old, those randomized to 10 μg formulation of TX-004HR had significant improvement in mean dyspareunia score as compared to placebo (mean change decrease 1.66 versus 1.19, $p < 0.01$). There was no significant improvement in mean dyspareunia score found for women ≥ 62 years old randomized to 4 μg and 25 μg formulations of TX-004HR.

The estradiol vaginal insert is the most recent FDA-approved modality for treatment of dyspareunia in post-menopausal women. It is the only FDA-approved medication for treatment of dyspareunia for which age-related efficacy analysis was performed demonstrating efficacy in a population of women 62 years old or older. Efficacy studies demonstrate the estradiol vaginal insert is overall safe and well tolerated with no reported serious adverse events and few side effects. Limitations include its strict medical exclusion criteria. Similar to previously discussed modalities, the estradiol vaginal insert was also studied predominantly in healthy, non-obese White women.

Conclusions

Since 2012, three new modalities have been FDA-approved for use in post-menopausal women with dyspareunia (ospemifene, prasterone, estradiol vaginal insert) and one in pre-menopausal women with HSDD (flibanserin). Clinical trials of these treatment modalities have focused largely on pre-

and recently post-menopausal women without inclusion of older post-menopausal women despite known prevalence of sexual problems in this population. While development of novel therapeutics for treatment of female sexual function is needed to address female sexual dysfunction, available data raise questions regarding clinical effectiveness and safety for the general population of women, especially older post-menopausal women, with these conditions.

All trials of recently FDA-approved medications for female sexual dysfunction are efficacy-based trials conducted in homogeneous populations of healthy, White, non-obese, early post-menopausal women with strict exclusion criteria. Studies of flibanserin strictly included only women in monogamous, heterosexual relationships with a sexually available and functional male partner. Large population-based studies have demonstrated that people of all races, ages, and sexual identities value their sexual function in later life, including older post-menopausal women [2, 33]. Efficacy-based study designs limit the applicability of these trials to a general population of post-menopausal women and may over-estimate the benefit of these modalities when used in a real-world clinical setting [34].

Trials of modalities for treatment of dyspareunia (ospemifene, prasterone, vaginal estradiol insert) measure dyspareunia using a 4-point patient-reported severity scale. Efficacy in these trials is reported as significant mean severity scale changes in treatment groups as compared to placebo. Further research is needed to understand whether small severity scale changes are clinically meaningful. Trials of flibanserin for treatment of HSDD measure efficacy using patient-reported number of SSEs per month. These studies demonstrated a statistically significant improvement of approximately half an event per month as compared to placebo. Whether or not an increase of one or fewer sexually satisfying events per month is clinically meaningful to a woman or her partner remains unknown. Data of relevance to women in same-sex partnerships or who are sexually active without a partner are needed.

More than 43 million older adults rely on Medicare Part D for prescription drug coverage [35]. Medicare Part D drug plans exclude coverage for therapies for sexual dysfunction, including flibanserin and medications for treatment of male erectile dysfunction [36]. According to the Centers for Medicare and Medicaid Services Formulary Guidance for 2019 document, ospemifene, vaginal prasterone, and estradiol vaginal insert are covered under Medicare Part D plans [37].

Exclusion of older women from studies of treatments for female sexual dysfunction presents a barrier to treatment and raises a justice-based ethical concern. Given the rapid aging of the population, it is crucial to investigate the safety and effectiveness of treatment modalities for female sexual dysfunction in older and more demographically heterogenous populations of post-menopausal women. The prevalence of both bothersome sexual dysfunction and co-morbid conditions is highest in this age group, but evidence is limited for safety and effectiveness of available treatments. Future studies of existing and emerging therapies for female sexual dysfunction should aim to assess real-world safety and effectiveness including for use by older post-menopausal women.

Acknowledgements Stacy Tessler Lindau reports a grant from the Ellie Fund at Jewish Women's Foundation of Metropolitan Chicago to the University of Chicago; reports being a member of the board of the Scientific Network on Female Sexual Health and Cancer; reports being a founder, co-owner, and investor in NowPow, LLC; reports investments in Glenbervie Health; reports stocks and mutual funds, including some with healthcare relevance, that are managed by third parties; and reports being contracted to be a peer reviewer for UpToDate, which will pay small fees to the University of Chicago for this activity.

Compliance with Ethical Standards

Conflict of Interest Janelle Sobecki-Rausch declares no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

Papers of particular interest, published recently, have been highlighted as:
•• Of major importance

1. Ortman JM, Velkoff VA, Hogan H. An aging nation: the older population in the United States. Suitland: United States Census Bureau, Economics and Statistics Administration, US Department of Commerce; 2014.
2. Lindau ST, Schumm LP, Laumann EO, Levinson W, O'muircheartaigh CA, Waite LJ. A study of sexuality and health among older adults in the United States. N Engl J Med. 2007;357(8):762–74.
3. Laumann EO, Waite LJ. Sexual dysfunction among older adults: prevalence and risk factors from a nationally representative US probability sample of men and women 57–85 years of age. J Sex Med. 2008;5(10):2300–11.
4. US Food and Drug Administration Drugs@FDA: FDA Approved Drug Products. www.accessdata.fda.gov/scripts/cder/daf. Accessed October 18, 2018.
5. Association AP. Diagnostic and statistical manual of mental disorders (DSM-5®). Philadelphia: American Psychiatric Pub; 2013.
6. Kingsberg SA, Wysocki S, Magnus L, Krychman ML. Vulvar and vaginal atrophy in postmenopausal women: findings from the REVIVE (REal Women's VIews of Treatment Options for Menopausal Vaginal ChangEs) survey. J Sex Med. 2013;10(7):1790–9.
7. Simon JA, Nappi RE, Kingsberg SA, Maamari R, Brown V. Clarifying Vaginal Atrophy's Impact on Sex and Relationships (CLOSER) survey: emotional and physical impact of vaginal discomfort on north American postmenopausal women and their partners. Menopause. 2014;21(2):137–42.

8. Soe LH, Wurz GT, Kao CJ, DeGregorio MW. Ospemifene for the treatment of dyspareunia associated with vulvar and vaginal atrophy: potential benefits in bone and breast. Int J Health. 2013;5(1):605–11.
9. Archer DF, Carr BR, Pinkerton JV, Taylor HS, Constantine GD. Effects of ospemifene on the female reproductive and urinary tracts: translation from preclinical models into clinical evidence. Menopause (New York, NY). 2015;22(7):786.
10. Bachmann GA, Komi JO, Group OS. Ospemifene effectively treats vulvovaginal atrophy in postmenopausal women: results from a pivotal phase 3 study. Menopause. 2010;17(3):480–6.
11. Portman DJ, Bachmann GA, Simon JA, Group OS. Ospemifene, a novel selective estrogen receptor modulator for treating dyspareunia associated with postmenopausal vulvar and vaginal atrophy. Menopause. 2013;20(6):623–30.
12. Rutanen E-M, Heikkinen J, Halonen K, Komi J, Lammintausta R, Ylikorkala O. Effects of ospemifene, a novel SERM, on hormones, genital tract, climacteric symptoms, and quality of life in postmenopausal women: a double-blind, randomized trial. Menopause. 2003;10(5):433–9.
13. Simon J. Efficacy and safety of daily ospemifene 60 mg for up to 1 year when used in the treatment of vulvar and vaginal atrophy in postmenopausal women. Menopause. 2012;19(12):1397–8.
14. Simon J, Bachmann G, Goldstein S, Lin V, Portman D, Phelps M. Evaluation of the safety of daily ospemifene 60 mg for up to 1 year when used in the treatment of vulvar and vaginal atrophy in postmenopausal women. Climacteric. 2011;14(suppl 1):87.
15. Simon JA, Lin VH, Radovich C, Bachmann GA, Group OS. One-year long-term safety extension study of ospemifene for the treatment of vulvar and vaginal atrophy in postmenopausal women with a uterus. Menopause. 2013;20(4):418–27.
16. Cui Y, Zong H, Yan H, Li N, Zhang Y. The efficacy and safety of ospemifene in treating dyspareunia associated with postmenopausal vulvar and vaginal atrophy: a systematic review and meta-analysis. J Sex Med. 2014;11(2):487–97.
17. Constantine G, Graham S, Portman DJ, Rosen RC, Kingsberg SA. Female sexual function improved with ospemifene in postmenopausal women with vulvar and vaginal atrophy: results of a randomized, placebo-controlled trial. Climacteric. 2015;18(2):226–32.
18. Wiegel M, Meston C, Rosen R. The female sexual function index (FSFI): cross-validation and development of clinical cutoff scores. J Sex Marital Ther. 2005;31(1):1–20.
19. Stahl SM, Sommer B, Allers KA. Multifunctional pharmacology of flibanserin: possible mechanism of therapeutic action in hypoactive sexual desire disorder. J Sex Med. 2011;8(1):15–27.
20. Portman DJ, Brown L, Yuan J, Kissling R, Kingsberg SA. Flibanserin in postmenopausal women with hypoactive sexual desire disorder: results of the PLUMERIA study. J Sex Med. 2017;14(6):834–42.
21. Simon JA, Kingsberg SA, Shumel B, Hanes V, Garcia M Jr, Sand M. Efficacy and safety of flibanserin in postmenopausal women with hypoactive sexual desire disorder: results of the SNOWDROP trial. Menopause. 2014;21(6):633–40.
22. DeRogatis L, Clayton A, Lewis-D'Agostino D, Wunderlich G, Fu Y. Validation of the female sexual distress scale-revised for assessing distress in women with hypoactive sexual desire disorder. J Sex Med. 2008;5(2):357–64.
23. Clayton AH, Segraves RT, Leiblum S, Basson R, Pyke R, Cotton D, et al. Reliability and validity of the Sexual Interest and Desire Inventory–Female (SIDI-F), a scale designed to measure severity of female hypoactive sexual desire disorder. J Sex Marital Ther. 2006;32(2):115–35.
24. Portman DJ, Johnson D, Yuan J, Barbour K, Kissling R. Flibanserin in postmenopausal women with hypoactive sexual desire disorder: results of the PLUMERIA study. Menopause. 2016;23(12):1393.
25. Jaspers L, Feys F, Bramer WM, Franco OH, Leusink P, Laan ET. Efficacy and safety of flibanserin for the treatment of hypoactive sexual desire disorder in women: a systematic review and meta-analysis. JAMA Intern Med. 2016;176(4):453–62.
26. Joffe HV, Chang C, Sewell C, Easley O, Nguyen C, Dunn S, et al. FDA approval of flibanserin—treating hypoactive sexual desire disorder. N Engl J Med. 2016;374(2):101–4.
27. Archer DF, Labrie F, Bouchard C, Portman DJ, Koltun W, Cusan L, et al. Treatment of pain at sexual activity (dyspareunia) with intravaginal dehydroepiandrosterone (prasterone). Menopause. 2015;22(9):950–63.
28. Labrie F, Archer DF, Koltun W, Vachon A, Young D, Frenette L, 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):243–56.
29. Labrie F, Derogatis L, Archer DF, Koltun W, Vachon A, Young D, et al. Effect of intravaginal prasterone on sexual dysfunction in postmenopausal women with vulvovaginal atrophy. J Sex Med. 2015;12(12):2401–12.
30. Society NAM. The role of local vaginal estrogen for treatment of vaginal atrophy in postmenopausal women: 2007 position statement of The North American Menopause Society. Menopause (New York, NY). 2007;14(3 Pt 1):355.
31. Constantine GD, Simon JA, Pickar JH, Archer DF, Kushner H, Bernick B, et al. The REJOICE trial: a phase 3 randomized, controlled trial evaluating the safety and efficacy of a novel vaginal estradiol soft-gel capsule for symptomatic vulvar and vaginal atrophy. Menopause. 2017;24(4):409–16.
32.•• Constantine GD, Bouchard C, Pickar JH, Archer DF, Graham S, Bernick B, et al. Consistency of effect with a low-dose, estradiol vaginal capsule (TX-004HR): evaluating improvement in vaginal physiology and moderate-to-severe dyspareunia in subgroups of postmenopausal women. J Women's Health. 2017;26(6):616–23 **Age-related efficacy analysis performed in a population of women 62 years or older.**
33. Sobecki-Rausch JN, Brown O, Gaupp CL, editors. Sexual dysfunction in lesbian women: a systematic review of the literature. Seminars in reproductive medicine. Stuttgart: Thieme Medical Publishers; 2017.
34. Singal AG, Higgins PD, Waljee AK. A primer on effectiveness and efficacy trials. Clin Transl Gastroenterol. 2014;5(1):e45.
35. Centers for Medicare and Medicaid Services CMS Fast Facts. https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/CMS-Fast-Facts/index.html. Accessed October 18, 2018.
36. Centers for Medicare and Medicaid Services Prescription Drug Benefit Manual Chapter 6. https://www.cms.gov/Medicare/Prescription-Drug-Coverage/PrescriptionDrugCovContra/Downloads/Part-D-Benefits-Manual-Chapter-6.pdf.
37. Centers for Medicare and Medicaid Services Formulary Guidance CY19 Formulary Reference FIle https://www.cms.gov/Medicare/Prescription-Drug-Coverage/PrescriptionDrugCovContra/RxContracting_FormularyGuidance.html. Accessed October 28, 2018.