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Ospemifene versus Conjugated Estrogens in the Treatment of Postmenopausal Sexual Dysfunction

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Abstract & Relevance

57% of postmenopausal women suffer from female sexual dysfunction (FSD). Vulvovaginal atrophy (VVA) is a condition that impacts up to 60% of the growing postmenopausal female population, and the most common symptom is dyspareunia. Women with FSD are 3.84 times as likely to also have VVA. Vaginal estrogen is the most common treatment for VVA, but it only marginally improves overall sexual function, and many women and clinicians avoid using it because of the risks of exogenous estrogen use during menopause. Ospemifene is a SERM that is FDA-approved for dyspareunia related to VVA, and has shown superb improvements in overall sexual health. This oral medication, taken daily, improves vaginal health, and has demonstrated protective activity in the breast and bone tissues. It also has not demonstrated any carcinogenic activity in the endometrium or liver. This study hopes to determine if ospemifene is superior to conjugated estrogens in improving sexual function and vaginal atrophy symptoms. 104 women will be randomized to receive 12 weeks of 60mg oral ospemifene, taken daily, or 12 weeks of 0.5mg vaginal conjugated estrogens, which is placed vaginally twice per week. The improvements in sexual health and VVA symptom severity will be compared in each group. This study will help determine if ospemifene is a better treatment medication than conjugated estrogens. The implications of this study may provide an attractive alternative to the many women who continue to suffer from sexual dysfunction and VVA because of concerns surrounding the use of exogenous hormones.

Introduction

In May 2013, the Board of Directors of the International Society for the Study of Women's Sexual Health (ISSWSH) and the Board of Trustees of The North American Menopause Society (NAMS) endorsed the term genitourinary syndrome of menopause (GSM). This term encompasses the numerous changes that occur as a result of the decrease in estrogen and other sex steroids, including vaginal atrophy and sexual dysfunction [1]. In a cross-sectional study of US postmenopausal women, those with sexual dysfunction were 4 times more likely to have vulvovaginal atrophy [2]. With the rising elderly population, the impact of VVA and sexual dysfunction on quality of life and health care costs is a growing issue. In 2000, there were 26.25 million women over the age of 60 years old, and this number is expected to almost double by the year 2030 [3]. Currently VVA affects up to 60% of postmenopausal women, and its most common

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symptom is dyspareunia [4,5]. Further, if left untreated, it can increase rates of infection, and negatively impact a woman's sexual health and quality of life [6]. While only 25% of women with VVA seek medical advice, only 3% of women reveal problems with sexual health without being prompted [7,8].

There are several established methods of treatment for VVA. Vaginal estrogen is considered the treatment of choice. While several studies have shown that vaginal estrogen does not increase serum estrogen levels above postmenopausal values, there is still significant controversy surrounding the use of estrogen and the risk of breast cancer and uterine cancer [9,10]. This study is important because we hope to prove a non-estrogen medication to be an effective non-hormonal alternative therapy for vulvovaginal atrophy.

In 2013, Ospemifene was approved by the Food and Drug Administration for the treatment of moderate to severe dyspareunia that is due to menopause [10]. Ospemifene is a non-estrogen selective estrogen receptor modulator (SERM). SERMs are estrogen receptor (ER) agonist/antagonists that typically induce the desirable effects of estrogen while avoiding estrogen-related adverse effects. Unlike other drugs in this class, Ospemifene has been shown to have significant estrogenic agonist effects on the vagina and bone, but antagonist effects on breast tissue [6]. Furthermore, it significantly improves overall sexual function [12]. Despite this promising medical profile, it remains a second or third line of therapy to treat VVA. More research is needed to determine if ospemifene is an acceptable, and possibly a favorable, alternative to vaginal estrogen for the treatment of vulvovaginal atrophy, especially if there is any concern for sexual function. In this research study, we aspire to determine the efficacy of ospemifene compared to a vaginal estrogen. The primary aim of this research is to compare female sexual function as measured by a validated instrument in women randomized to receive ospemifene and vaginal estrogen. Secondary aims include comparing markers of vaginal health and safety in both treatment groups.

Hypothesis

Ospemifene is a nonhormonal alternative that has proven to significantly improve sexual health and vulvovaginal atrophy, yet vaginal estrogen is still considered the first-line therapy. Our null hypothesis is that ospemifene has a similar efficacy as vaginal conjugated estrogens for improving sexual function in postmenopausal women who have vulvovaginal atrophy.

Specific Aims

Specific Aim 1: *To compare the efficacy of ospemifene and vaginal conjugated estrogens on female sexual function.* Ospemifene is the only non-estrogen that is FDA-approved to treat dyspareunia in postmenopausal women. Further, studies report a significant improvement in sexual health in patients that are treated with ospemifene [12]. However, vaginal estrogen therapy (with conjugated equine estrogen or estradiol) remains the most commonly prescribed treatment for dyspareunia. To our knowledge, a direct comparison of ospemifene and local vaginal estrogen therapy on postmenopausal female sexual function has not been performed. We hypothesize that ospemifene provides a greater improvement in sexual function in postmenopausal women with dyspareunia and VVA.

Specific Aim 2: *To compare the effects of ospemifene and vaginal conjugated estrogens on symptoms of VVA.* We hypothesize that treatment with either ospemifene or vaginal conjugated

estrogens will demonstrate comparable improvements in VVA symptoms. In the population randomly treated with vaginal conjugated estrogens or ospemifene in specific aim 1, we will compare the change from baseline and between groups.

Significance

Female Sexual Dysfunction

Traditionally, female sexual dysfunction (FSD) is defined as the disorder of desire, arousal, pain and/or muted orgasm in women [28]. While many people may consider this disorder to be pertinent only during reproductive years, it is very common in the menopausal women population, affecting 57% of women in menopause [5]. In 2014, Nappi et al published a review of data that shows the importance of discussing sexual function and vaginal atrophy with postmenopausal women. 1 in 5 women over the age of 70 still engage in intercourse. Moreover, 71% of women agree that, "it was important to them to maintain an active sex life." The article also adds that only 3% of women will seek advice about sexual function if not prompted. Many who do bring this problem to their provider's attention feel as though it is dismissed. Meanwhile, providers tended not to proactively address sexual health for middle and later life-aged women, because of time constraints, inadequate training, personal attitudes and beliefs that sex is not a priority for older patients [29].

What is Vulvovaginal Atrophy?

There is significant overlap between FSD and VVA. Women with FSD are almost 4 times as likely to have VVA [29]. Once a woman reaches menopause, her ovarian production of estrogen decreases dramatically. The vagina and vulva are two organs that are affected by the lack of estradiol in the body. Without estrogen, the vagina epithelial cells decline in maturation, and there is also an increase in the vaginal pH. These changes lead to the common symptoms of painful intercourse, vaginal dryness, pain, and itching. They also put the vaginal epithelium at risk for infection and inflammation. Further, the increase in pH is associated with an increased rate of recurrent urinary tract infections in postmenopausal women [13]. In the US, approximately 60% of women report symptoms related to vulvovaginal atrophy [4].

There are a few effective treatment options for VVA. The most commonly used treatment is vaginal estrogen. This is prescribed in various forms, including a vaginal cream (Estrace, Premarin, compounded), a vaginal tablet (Vagifem), and a vaginal ring (Estring). Aside from the ring, the medication dosing typically involves nightly dosing for two weeks, followed by dosing twice per week. Estrogen functions by improving the percentage of vaginal superficial cells, while decreasing the pH, and improving symptom scores in participants [14,5]. Studies have also shown that the serum estradiol levels remained below 20mcg/mL, which is the typical maximum optimum estradiol level in PMP women [15]. Other related estrogens, particularly estrone and estrone sulfate, also remained within postmenopausal levels [14]. With these findings, many clinicians feel comfortable recommending vaginal estrogen to patients who suffer from symptomatic vaginal atrophy. However, estrogen's causal relationship with breast cancer and endometrial cancer causes many women to avoid using vaginal estrogen [16]. Hence, treatment options that do not involve the introduction of estrogen into the bloodstream are likely to be well sought after.

Ospemifene

Ospemifene is a selective estrogen receptor modulator (SERM), and it is the only SERM approved in the United States to treat moderate to severe dyspareunia associated with VVA [6,17].

It is an oral medication that is taken as a 60mg tablet once daily. Food intake increases its absorption by 2 to 3-fold, and this is not impacted by the fat or calorie content of the food. It is metabolized primarily in the liver, and is excreted in feces [4]. SERMs are estrogen receptor (ER) agonist/antagonists that typically induce the desirable effects of estrogen while avoiding estrogen-related adverse effects. Ospemifene is unique within this class because in addition to its protective activity in bone and breast tissue, it has a significant beneficial influence in the vagina without a carcinogenic effect on the endometrium. Initially, the drug was developed because of its bone-sparing reduction of bone resorption in OVX rats. However, its performance in other hormone-sensitive tissue led to further investigation [17].

In its clinical development, ospemifene was singled out because unlike tamoxifen and raloxifene, ospemifene significantly improves vaginal maturation. As a non-estrogen substance, its mechanism involves activation of estrogen receptors in the vagina, which leads to an increased thickness, mucification, and vacuolization of vaginal epithelium [18]. Several RCTs have shown an improvement in VVA with the use of ospemifene compared to placebo [6]. Importantly, the serum estradiol levels have been documented as unchanged in patients that use the medication for 12 weeks [19].

Equally important is the activity of ospemifene in mammary tissue. In ER+ human breast cancer cells, ospemifene has either had no impact, or has had a dose-dependent growth inhibitory effect [20,21]. This implies its dependence on ER-alpha expression in this tissue. Two studies examined ospemifene's ability to prevent dimethylbenzanthracene (DMBA)-induced breast cancer in mice. For up to 52 weeks of drug exposure, ospemifene prevented breast tumor formation similarly to tamoxifen [22]. Moreover, in normal human breast tissue, ospemifene also has similar antiestrogenic inhibitory effects as tamoxifen [23].

An additional pilot study involving ospemifene administration to rhesus macaques suggest that it has a lower carcinogenic potential than tamoxifen, which is another SERM that is used in breast cancer treatment and prevention. In this study, there was no evidence of DNA adduct production in the liver or the endometrium from daily ospemifene, while tamoxifen, the positive control, showed production of several DNA adducts in each organ [24]. Furthermore, clinical trials mirrored animal studies in that there was an increase in uterine weight and proliferative tissue, but there has never been any evidence of endometrial hyperplasia or bleeding with use of ospemifene [25,26]. These findings have been strengthened by six RCTs, where no cases of endometrial hyperplasia or cancer has been identified [6].

Sexual Health

As may be expected, VVA is four times more likely in patients who suffer from sexual dysfunction [14]. Ospemifene is FDA-approved specifically for dyspareunia in postmenopausal women with VVA. Studies show that it also improves the overall sexual health for women [12]. While estrogen has been shown to improve dyspareunia and lubrication, its impact on overall sexual health is not well-identified [27].

In essence, Ospemifene seems to be a possible wonder drug for menopausal women. While it's primary use is for VVA-associated dyspareunia, there is consistent evidence of protective activity in bone and breast tissue, while showing no evidence of carcinogenic potential in the endometrium, breast, or liver. Similar to vaginal estrogen, ospemifene has not been studied longer than 12 months to determine long term risks of the medication [6]. Appendix 1 shows a summary of adverse events in various safety studies for vaginal estrogen and ospemifene. Research is

promising that Ospemifene may prove to be a safer and more beneficial choice for all postmenopausal women, regardless of their history of breast or endometrial cancer.

Innovation

Several studies have published data regarding the unique behavior of ospemifene in postmenopausal women. Nonetheless, vaginal estrogen is still seen as the gold standard for the treatment of VVA, regardless of the woman's most bothersome symptom. To our knowledge, for the first time, this study will directly compare the efficacy of vaginal conjugated estrogens and ospemifene in improving sexual function in postmenopausal women who have vulvovaginal atrophy. By also directly comparing symptom improvement with VVA treatment, this study hopes to answer the question of whether or not clinicians should shift towards ospemifene as a first line treatment for sexual dysfunction in postmenopausal women with VVA.

Approach

Overview

This study will be a prospective, randomized study that will compare efficacy and safety of ospemifene and vaginal estrogen. Because of the route of administration for each drug, it is not possible to blind the participants or clinicians to the treatment. However, we will be collecting objective data that cannot be misinterpreted by those collecting and analyzing the data. We hope to effectively inform clinicians who treat postmenopausal women that suffer from VVA about the efficacy of ospemifene as it compares to vaginal conjugated estrogens cream. As a specialty with a high population of patients who complain of VVA, we are very familiar with this patient population, as well as the use of vaginal estrogen in their treatment. This puts this research team in an ideal position to properly execute the study and interpret the findings.

Patient Groups

All research activities will be performed after obtaining Institutional Review Board Approval from Emory University. A consecutive sample of women will be recruited from the FPMRS and Menopause patients within The Emory clinics. Subjects are identified after their management plan has been established to include treatment of vulvar and/or vaginal atrophy. Patients will be approached by the principal and/or co-investigators. For women that agree to participate, written informed consent will be obtained. All women who agree to participate in this study must meet inclusion criteria listed in Table 1. Once the exclusion criteria have been applied (Table 2), the qualifying subjects will be enrolled in the study. Once enrolled, each subject will complete the Female Sexual Function Index (FSFI) questionnaire and a symptom severity Likert scale. Finally, they will receive instructions on medication compliance, as well as potential adverse events for the designated medication. If we assume 50% of women offered enrollment in this study will agree and be eligible to participate, we expect to reach our target enrollment in seven to eight months.

Table 1. Inclusion Criteria
Interested in resuming or continuing sexual activity

Table 1. Inclusion Criteria

Greater than 12 months since last menstrual cycle or prior bilateral oophorectomy
40yo or older
Dyspareunia as a vulvovaginal atrophy symptom
Normal mammogram within 12 months prior to entry into the study

Table 2. Exclusion Criteria

History or suspicion of breast carcinoma
History of hormone-dependent tumor
Genital bleeding of unknown cause
Ongoing vaginal infection
History of CVA, MI or heart disease, uncontrolled HTN over 160/100
Serious disease or chronic condition that may prevent completion of study, BMI over 40
Hypercoagulable state, or currently on anticoagulant therapy
Use of any exogenous sex hormone within three months from study entry, or during the study
Pelvic surgery within the last 12 months

Randomization and Allocation Concealment

Once a qualifying subject is identified, she will be randomized into a treatment group. The participant will be randomized to receive either a vaginal conjugated estrogens prescription or an ospemifene prescription. A computerized randomization program will be used to perform block randomization in random blocks of 4 and 10. Allocations envelopes containing the assignment will be used for the study. They will be sealed opaque envelopes with aluminum foil inside. They will also contain carbon-copy paper. The treatment number will be printed on the envelope. Once the participant has signed the informed consent form, her name will be printed on the envelope, which will transfer over to the carbon-copy paper, and the envelope will be opened.

Study Plan

The patient will be informed of her assigned medication, and she will receive a medication coupon to help offset the cost of the medication. Each medication is FDA-approved for long-term use of at least 52 weeks. For this study, a 12-week prescription for the medication will be sent electron-

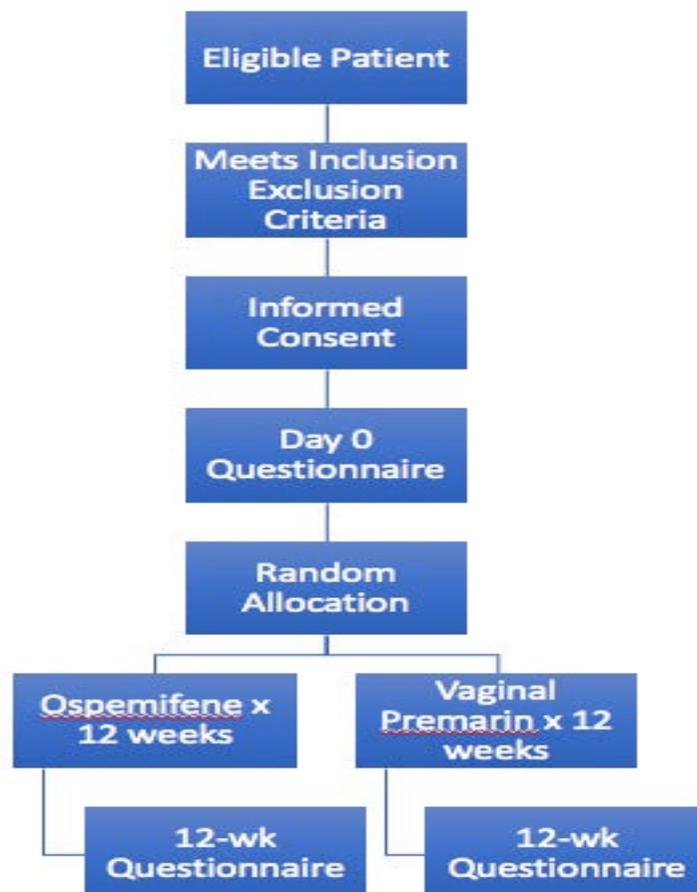
ically to the pharmacy of her choice. Treatment with estrogen will consist of 0.5 gram of conjugated estrogens placed vaginally for 12 weeks. Treatment with ospemifene will consist of a 60mg tablet that will be taken at the same time daily for 12 weeks.

The patient will receive an intake packet that includes the following information:

1. Copy of signed informed consent form
2. Important contacts and instructions for emergency/adverse events
3. Allocation card
4. Medication's FDA packet insert
5. Instructions on dosing
6. 12-week date to repeat questionnaires

She will be called the following day to confirm her start date of the medication. They will return at 12 weeks and complete the same FSFI and Likert Scale questionnaires regarding sexual function and VVA symptoms. The questionnaires may also be completed over the phone with the investigator.

Alternatively, if time during clinic is limited, the patient can be consented and allocated to a medication in person, by a co-investigator. She will be called by a co-investigator on the same day to complete the enrollment and questionnaires. Below is a summary of the study plan.



Sample Size Analysis

To our knowledge, there has been no prior study that reported the prevalence of female sexual dysfunction amongst women using vaginal conjugated estrogens, defined as having an FSFI score of 26.55 or less. With an FSD prevalence of 57%, we determine a 50% reduction in the prevalence to be clinically significant. Setting an alpha of 0.05, and a power of 0.80, and assuming a minimum of 15% dropout rate, the sample size is set to 52 in each group.

Specific Aims

Specific Aim 1: To compare the efficacy of each drug in improving sexual function.

- a. Experimental Design: In this study, participants will be asked to complete the 19-question female sexual function index (FSFI) questionnaire at the beginning of the study period and at 12 weeks. The results will be used to compare the effect of each medication on the various domains of sexual function.

The mean total score in each treatment group at baseline will be compared using Student's t-test. Additionally, the score of the components of desire, arousal, lubrication, orgasm, satisfaction and pain will be similarly compared. Later, the change in these scores between the two treatment groups at 12 weeks will be compared using a paired t-test analysis.

Anticipated Results and Interpretation: We expect to see similar results in this study, showing comparable improvements in vaginal lubrication and dyspareunia, while showing greater improvement for overall sexual health in the ospemifene group.

Potential Pitfalls, Alternative Approaches, and Future Directions: We do not anticipate any challenges with the administration and analysis of this questionnaire.

Specific Aim 2: To compare each drug's impact on VVA symptoms

- a. Experimental Design: Participants will complete a Likert scale of symptom severity at the beginning and at the end of the study. The symptoms listed will include dyspareunia, vaginal dryness, vaginal pain, and vaginal itching. The survey will ask them to rate the severity of each VVA symptom on a scale of 0 to 3, with 0 being none, 1 being mild, 2 being moderate, and 3 being severe. It will also ask them to choose their most bothersome symptom (MBS).

The mean score of the MBS in each treatment group at baseline will be compared using Student's t-test. Later, the change in score of the MBS between the two treatment groups at four weeks and again at 12 weeks will be compared using a paired t-test analysis.

Anticipated Results and Interpretation: Similar to objective findings, prior studies have shown significant improvement in VVA symptoms in patients using ospemifene or vaginal estrogen. We anticipate that the improvements seen with ospemifene will be comparable to those seen with vaginal estrogen.

Potential Pitfalls, Alternative Approaches, and Future Directions: The Likert scale is commonly used to assess symptom improvement in VVA treatment studies. We do not anticipate any pitfalls in this specific aim.

Safety Monitoring

Participants in the study will be provided with contact information to be used in the case of an adverse event related to the medication. For emergencies, they will be instructed to dial 911 and/or seek immediate medical attention. They will be instructed to contact the study team at (404) 686-1000, to inform the team about any adverse event that may be related to the medication.

All reports of injury will be logged in one password-protected electronic file, by members of the study team. Patient data, including adverse events will be reviewed every two weeks by the Dr. Gina Northington and Dr. Chidimma Eto. Appendix 1 shows adverse events that have been documented during prior clinical trials of the two medications. This data will be used to determine whether the study will be discontinued due to occurrence or frequency of any given adverse event.

Individual Stopping Rules

Any event that involves new onset of vaginal bleeding, cardiovascular event, venous thromboembolism, or new diagnosis of cancer, will require the individual to discontinue the medication and withdraw from the study.

Timeline

Item	Start	Complete/Submit
IRB application	Started	November 1, 2016
Grant/Funding applications	Started	February 2017
Subject recruitment	November 1, 2016	August 1, 2017
Data Analysis	March 1, 2017	August 30, 2017
Thesis/Report	November 15, 2017	December 1, 2017

Required Resources & Budget

Resource	Estimated Cost
Personnel	
Consent forms, severity scale, questionnaire, other paper documents	
Counseling office	

\$10 gift cards for return visit, 104 subjects	\$1040.00
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Appendix 1. TEAEs in Vaginal Conjugated Estrogens Cream and Ospemifene Trials				
	Ospemifene 60mg x 12 weeks [17]	Ospemifene 60mg x 52wks [7]	Vaginal CE 0.3mg x 12 weeks [30]	Vaginal CE 0.3mg x 52 weeks [30]
% w/ 1 or more TEAE	Not stated, 1892 exposed patients total, 1000 patient years of exposure	63.8%	71.4%	61.4%
Headache	2.4%		18.6%	14.4
Muscle spasm	3.2%			
Arthralgia				9.1
Vaginal discharge	3.8%			
Vaginal candidiasis or mycotic infection		4.3%		
Vaginitis				6.1%
Hot flashes	7.5%	7.2% (1.6% discontinuation rate)		
UTI	Similar to placebo	8.7% (8.2% for placebo)		
Vaginal bleeding			*1.4% of all groups	*1% of all groups
Proliferative endometrium				0.08%
Hyperplasia or cancer	0%	0%		0%
Cardiovascular events/VTE	0.3%	0%		
URI/Nasopharyngitis/Sinusitis		5% or more		
Pharyngolaryngeal pain		5% or more		
Hypercholesterolemia		5% or more		
Serious/Severe TEAEs <5%	0.13 per patient year (0.21 in placebo group)	5 participants with 7 TESAEs: breast prosthesis implantation, encephalitis herpes, non-cardiac chest pain, candida meningitis, gastritis, chronic obstructive pulmonary disease, and dehydration	5 participants from all groups, considered unrelated to study	6 participants from all groups, considered unrelated to study
<i>TEAE: treatment-emergent adverse event; CE: conjugated estrogens; VTE: venous thromboembolism; *: study does not distinguish between placebo and the two treatment arms.</i>				