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ORIGINAL ARTICLE

The effect of serotonin reuptake inhibitors on the vaginal epithelium in postmenopausal women

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ABSTRACT

Purpose: Selective serotonin reuptake inhibitors (SSRIs) and serotonin–norepinephrine reuptake inhibitors (SNRIs) are used as alternative treatments for the vasomotor symptoms of menopause in women who are unwilling or unable to receive hormone therapy. These agents have been associated with sexual dysfunction and xerostomia (dry mouth), but the effect on the vagina has not been studied. The objective of this study was to determine the effect of SSRIs and SNRIs on the vaginal epithelium and sexual function in postmenopausal women, using both subjective and objective measures.

Materials and methods: A cross-sectional study of postmenopausal women not using any local or systemic estrogen therapy was conducted. The main outcomes included the Female Sexual Function Index (FSFI), vaginal epithelial maturation index (MI), and pH.

Results: Sixty-six women were recruited, 30 using SSRIs/SNRIs and 36 who were not (control). Both the proportion of superficial vaginal epithelial cells and the total MI were higher in the SSRI/SNRI group ($p = 0.006$ and $p = 0.047$, respectively). There were no significant differences in FSFI scores, vaginal pH, or total MI values.

Conclusion: The use of serotonin reuptake inhibiting drugs does not appear to have a negative influence on the vaginal epithelium and associated vaginal atrophy.

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Introduction

Vasomotor symptoms of menopause (VMS), including hot flashes and night sweats experienced by women during perimenopause and postmenopause, significantly affect the quality of life for many women. VMS are the most frequently reported symptoms of menopause, with up to 75% of women experiencing VMS and/or sleep disturbances for a median of 7 years[1]. The associated palpitations, perspiration, and feelings of anxiety lead to physical discomfort and functional impairment[2].

Systemic hormone therapy with combined estrogen and progesterone is the first-line and most effective treatment for VMS[3]. However, alternative non-hormonal treatments are required for patients who have contraindications to hormones (history of estrogen-dependent cancers, history of venous thromboembolism/stroke) or who are unwilling to use hormones due to personal preference. Non-hormonal treatments that have shown efficacy for the treatment of VMS include clonidine, gabapentin, as well as serotonergic reuptake inhibiting agents[4].

Selective serotonin reuptake inhibitors (SSRIs) and serotonin–norepinephrine reuptake inhibitors (SNRIs) are two of the most commonly used treatments that have demonstrated superiority to placebo for treatment of VMS in several studies[5]. Among these agents, only paroxetine mesylate, an SSRI, has been officially approved by the US Food and Drug Administration as a treatment for VMS in menopausal women. However, other serotonergic agents, such as the SNRIs venlafaxine and desvenlafaxine, are commonly prescribed off-label for the treatment of VMS[4]. Prescription of these medications for the treatment of VMS has demonstrated an inverse relationship with prescription of hormone therapy, with hormone prescription declining and SSRI/SNRI prescription rising annually in Canada since 2002[6]. These medications were initially developed to treat major depression and anxiety disorders, and are therefore commonly prescribed to mature women by family physicians and psychiatrists.

Despite the efficacy of serotonergic agents for the treatment of VMS, some women are intolerant to their adverse effects, the most common of which are drowsiness, sexual dysfunction, and dry mouth[7]. The associated sexual dysfunction, which has been reported in up to 70% of users, can negatively affect all three phases of the normal sexual response cycle: desire, arousal, and orgasm[8]. These potential adverse effects may be concerning for a population at risk

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Table 1. Demographic characteristics.

Characteristic	*SSRI/SNRI (n = 25)*	*Control (n = 29)*
Age (years)	57.7 (8.0)	56.9 (5.4)
Age at FMP (years)	50.2 (5.2)	51.4 (5.2)
BMI (kg/m^2)	26.4 (6.2)	27.6 (4.2)
Comorbidities, *n* (%)		
Hypertension	2 (8.0%)	4 (13.3%)
Thyroid disease	5 (20.0%)	7 (23.3%)
Diabetes	1 (4.0%)	0

Data presented as mean (standard deviation) unless stated otherwise. BMI, body mass index; FMP, final menstrual period; SNRI, serotonin–norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

Table 2. Medications used by the SSRI/SNRI group.

Drug	*Type*	*Number*
Citalopram	SSRI	7
Escitalopram	SSRI	4
Fluoxetine	SSRI	3
Paroxetine	SSRI	4
Sertraline	SSRI	1
Desvenlafaxine	SNRI	1
Venlafaxine	SNRI	5

SNRI, serotonin–norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

for lower desire, lubrication, and atrophy of vaginal tissues. The genitourinary symptoms of menopause affect up to 70% of mature women and include vaginal pain, dryness, and dyspareunia[9,10]. Limited studies exist that evaluate the effect of serotonergic agents on sexual function in non-depressed, menopausal women, and those that do exist have mixed results[11–13].

The effects of the SSRIs and SNRIs on the vaginal epithelium and other symptoms of genitourinary symptoms of menopause are currently unknown. Given the commonly experienced adverse effect of xerosis (dry mouth), these medications may adversely affect the vagina, as they share a similar histological composition[14]. No studies reporting objective measures of SSRI/SNRI effects on the vagina could be located to date. The objective of this study was to assess the effect of SSRIs and SNRIs on the vaginal epithelium and associated sexual function in postmenopausal women, using both subjective and objective measures.

Methods

This was a cross-sectional investigation, approved by the Research Ethics Board at Mount Sinai Hospital, Toronto, Canada (REB #16-0156E). All patients provided written, informed consent. Menopausal women were recruited through the Menopause and General Gynecology Clinics at Mount Sinai Hospital. Potential subjects were identified if their final menstrual period was $\geq$12 months ago. Exclusion criteria included: use of systemic or local estrogen therapy, or vaginal moisturizers within 3 months; current use of aromatase inhibitors; and unexplained vaginal bleeding. Women who were taking an SSRI/SNRI on presentation to the clinic were recruited into the SSRI/SNRI group. Patients recruited into the control group were not taking these medications and did not meet the exclusion criteria.

Study participants completed the Female Sexual Function Index (FSFI)[15]. This self-rated questionnaire scores the domains of sexual functioning (arousal, orgasm, satisfaction, pain). All women underwent a physical examination as part of routine clinical care. The vaginal tissues were assessed using nitrazine paper (pH) and the ThinPrep cytobrush. The epithelial cells collected using the cytobrush were quantified using the standardized maturation index (MI) at the Mount Sinai Hospital Laboratory. The MI details the proportions of parabasal, intermediate, and superficial cells. These objective measures have been used in similar populations; a more alkaline pH (6.0–7.5) and a lower MI suggest atrophic changes of the vagina[16].

In addition, the following information was collected from each of the patient's charts: age; BMI; age at final menstrual period; current medical diagnoses; current medications, vitamins and supplements; history of any hormonal treatments; smoking status (yes/no); and alcohol use (yes/no). Patients with missing information were contacted via telephone call to abstract remaining data.

The primary outcome of this study was the MI. Secondary outcomes included: the proportion of parabasal, intermediate, and superficial cells; and vaginal pH and FSFI scores. It was hypothesized that women exposed to SSRI/SNRIs would have a lower MI and higher rated scores of sexual dysfunction, as measured using the FSFI.

Data analysis

All women taking SSRI/SNRIs for a minimum of 3 months were grouped together and compared to the control group for statistical analyses. Univariate analyses of variance were completed to compare the proportion of parabasal, intermediate, and superficial cells, as well as the total MI values between the groups, controlling for patient age. Student's *t*-tests were conducted to compare the pH values, as well as the scores from the FSFI. Age was used as a covariate as it can influence MI values. Regression analyses were done to examine any relationship between the percentage of superficial cells and the FSFI total scores and the various subscales, controlling for patient age. The sample size of the trial was predetermined using the primary outcome (MI). The MI values of postmenopausal women not exposed to directed pharmacotherapy range from 30 to 65 in the literature. Assuming an ~25% difference in the MI values between the groups, a sample size of 25 subjects per group is required to perform a Student's *t*-test with $\alpha = 0.05$ and power = 0.8.

Results

We recruited 66 postmenopausal women, 30 who were taking an SSRI or SNRI and 36 who were not (control). Of these women, 12 were excluded because their cytological smear could not be processed by the laboratory (five with insufficient sample; five with bacterial vaginosis; one with endometrial cells present; one with low-grade squamous intraepithelial lesion seen). For the remaining 54 women, the demographics are presented in Table 1. Women included in the study were fairly healthy; 21.7% of patients had thyroid disease, 10.0% of patients had hypertension, and 1.7% of

Table 3. Mean (standard deviation) FSFI scores in patients taking SNRI/SNRIs vs. control.

FSFI	*SSRI/SNRI group*	*Control group*	p-*Value*
Desire	2.4 (1.4)	2.5 (1.2)	0.83
Arousal	2.5 (1.7)	2.1 (1.9)	0.38
Lubrication	2.7 (2.0)	1.9 (2.1)	0.19
Orgasm	2.9 (1.8)	2.1(2.3)	0.18
Satisfaction	2.6 (1.9)	2.6 (1.9)	0.96
Pain	2.4 (2.5)	1.9 (2.3)	0.46
Total	15.4 (9.0)	13.1 (10.7)	0.41

FSFI, Female Sexual Function Index; SNRI, serotonin–norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

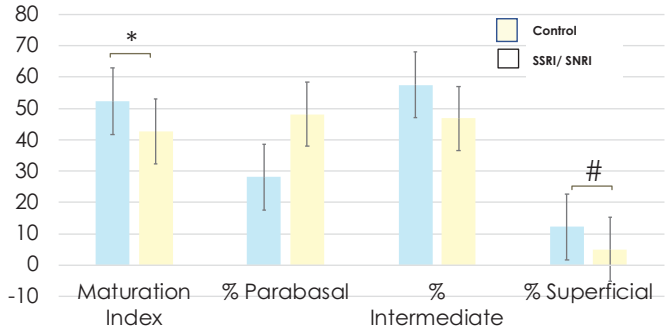

Figure 1. Vaginal maturation indices (total and proportions) for post-menopausal women exposed to SSRI/ SNRI and control women. *$p = 0.047$; #$p = 0.006$. SNRI, serotonin–norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

patients had a diagnosis of diabetes mellitus. Of the women in the SSRI/SNRI group, 63.3% were prescribed the SSRI/SNRI for treatment of a psychiatric disorder, 30.0% for treatment of VMS, and 3.3% for both indications. The majority of the women took an SSRI medication ($n = 19$) while a smaller proportion took an SNRI ($n = 6$). The list of medications used by participants is presented in Table 2.

Sexual function was measured by the FSFI, with a score less than 26 representing significant sexual dysfunction[15]. As per this interpretation, 85% of all included women had scores suggesting sexual dysfunction. The total FSFI and individual domain scores did not vary significantly between the groups (Table 3).

The MI was successfully generated from the vaginal swab samples of 54 patients. The MI results are presented in Figure 1. The MI was significantly higher in the SSRI/SNRI group, controlling for age ($F = 4.15$; $p = 0.047$). The proportion of superficial cells was significantly higher in the SSRI/SNRI group, controlling for age ($F = 8.26$; $p = 0.006$). The intermediate and parabasal epithelial cell types did not vary significantly between the two groups. The vaginal pH was not significantly different between the SSRI/SNRI group and the control group. Regression analyses showed that the percentage of superficial cells was significantly associated with the total FSFI score and the lubrication and pain subscales after controlling for age ($R = 0.39$; $p = 0.14$ and $R = 0.37$; $p = 0.022$, respectively).

Discussion

In our cross-sectional study, we found that women who were using serotonin reuptake inhibiting drugs had a higher proportion of superficial vaginal cells and a higher overall MI, as compared to women who were not using these medications. We also noted that women using SSRIs and SNRIs did not rate their sexual function any worse than control women using the FSFI. The proportion of superficial cells was significantly associated with improved scores on the lubrication and pain subscales of the FSFI. Our findings suggest that these medications, which are used for a variety of reasons in this population, do not have a detrimental role on the vaginal epithelium. These results were contrary to what we expected, but they do provide some reassurance for women who require these medications.

We found that SSRI and SNRI use may be beneficial for vaginal physiology among mature women. This is the first study to describe the effects of serotonergic medications on the vaginal epithelium using objective measures. Previous studies have measured sexual function and vaginal dryness using various self-report scales, such as the FSFI and visual analog scales. Of note, women who underwent an 8-week course of venlafaxine (75 mg) for VMS noted significantly less vaginal dryness and pain penetration scores, but no objective measures were obtained[12]. The potential mechanism involved in improved dryness, pain, and maturation indices may be related to the vasodilatory properties of serotonergic reuptake inhibiting medications on small arterioles, demonstrated in animal studies[17,18]. Given that both lubrication and pain were improved in our patients with a higher proportion of superficial cells, we speculate that the increased circulating serotonin concentrations may influence vaginal arteriole dilation, which may influence potential lubrication.

Although there is evidence that up to 50% of women taking SSRIs and SNRIs may suffer from sexual dysfunction, most of these studies were done in patients suffering from major depression[19–21]. Women suffering from VMS who opt to use SSRIs/SNRIs may not represent a comparable group, as lower doses are often successful in alleviating symptoms. Certainly, higher doses of SSRIs have been associated with worsening sexual dysfunction[20]. In our sample, 30% of women were using SSRIs/SNRIs for VMS and 63% for psychiatric symptoms. However, the majority of women were not on high doses. The use of low-dose paroxetine for VMS was not associated with a change in sexual function scores after 24 weeks of treatment, and neither was there any difference from the placebo-control group of women[22]. Further, two separate randomized placebo-controlled trials of SSRIs/SNRIs for VMS did not find a significant difference in FSFI scores among women using escitalopram or venlafaxine versus placebo[11,12].

While these results are promising for mature women requiring this type of pharmacotherapy, we must acknowledge some limitations. First, the study participants were drawn from only one center, introducing a potential selection bias into the study. We did not collect information about whether a participant had previously used an SSRI or SNRI, and what effect that had on vaginal or sexual function, which may impose further selection bias. Additionally, the MI values for 12 women could not be used for various reasons. However, we did recruit a higher proportion so that we

could still meet our power calculation for the primary outcome ($n = 25$ per group). Further, our data would be strengthened if we had been able to compare subjects to themselves after an 8–12-week course of treatment. Although we met our power sample size goal, larger studies are needed in order to clarify some of the associations observed. In conclusion, we found that the use of serotonin reuptake inhibiting drugs does not appear to have a negative influence on the vaginal epithelium and associated vaginal atrophy. Alternately, this information can provide some reassurance for women who require these medications.

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