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Selective serotonin reuptake inhibitors and serotonin norepinephrine reuptake inhibitors for menopausal vasomotor symptoms

Kathryn M. Holt, PharmD[1]
Amy N. Thompson, PharmD, BCACP, CDE[2]

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Abstract

Introduction: Some of the most bothersome symptoms associated with menopause are the vasomotor symptoms (VMS), characterized by transient elevations in body temperature associated with a narrowing of the thermoneutral zone and an abnormal firing rate of thermosensitive neurons in the hypothalamus. These VMS have traditionally been treated with hormone replacement therapy (HRT); however, after a trial suggesting an association between HRT and a number of serious adverse events, alternative therapies for VMS are being studied. The purpose of this review is to evaluate the available literature regarding the use of selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) for the alleviation of VMS associated with menopause.

Methods: PubMed and Ovid/MEDLINE keyword searches were conducted. Literature was reviewed for inclusion if it included any SSRI or SNRI for menopausal symptoms published prior to August 31, 2014.

Results: Seven studies were included in this review article. No articles were found directly comparing HRT to either SSRIs or SNRIs. Multiple agents within these two classes have been studied for VMS in menopausal and postmenopausal women.

Discussion: Vasomotor symptoms related to the perimenopausal and postmenopausal period can lead to significant physical distress, often requiring medical intervention. Traditional therapies for VMS of menopause have been dominated by the use of HRT. There are conflicting data regarding the use of SSRIs and SNRIs for patients with vasomotor symptoms related to menopause, and these agents may not be ideal for all patients. These agents may be considered as an alternative in patients who have a contraindication or are concerned about using hormonal therapies.

Keywords: vasomotor symptoms, SSRIs, SNRIs, menopause

[1] (Corresponding author) PGY2 Ambulatory Care Resident, Adjunct Instructor, South Carolina College of Pharmacy, Medical University of South Carolina, Charleston, South Carolina, holtk@musc.edu; [2] Associate Professor of Ambulatory Care, Department of Clinical Pharmacy and Outcomes Sciences, South Carolina College of Pharmacy-MUSC Campus; Residency Program Director-Ambulatory Care, Medical University of South Carolina, Charleston, South Carolina

Introduction

Menopause is defined as a loss of ovarian function leading to a state of permanent amenorrhea. With the increase in life expectancy, the number of postmenopausal women in the United States is growing. The most bothersome menopause-related disorder is the vasomotor symptoms (VMS), or hot flashes, associated with menopause. Physiologically, VMS is thought to result from reductions in estrogen levels, which prevents the estrogen-driven modulation of the firing rate of thermosensitive neurons in the hypothalamus.[1,2] As such, estrogen-containing hormone therapy has long been the first-line treatment for VMS.[1-4] This treatment strategy has been questioned by many after the Women's Health Initiative. A random-

ized trial of 16 808 postmenopausal women receiving hormone replacement therapy (HRT) versus placebo demonstrated that HRT-treated patients experienced an increase in major adverse events, such as breast cancer, venous thromboembolism, and cardiovascular events.[4]

Estrogens are neuromodulators of serotonergic and noradrenergic systems and play an important role in the maintenance of temperature regulation. The hypothalamus is particularly hormone responsive, and the unpredictable hormones associated with menopause require flexibility in neuronal responsiveness.[2] Increased brain norepinephrine has been shown to narrow the width of the thermoneutral zone, the space in which the thermoregulatory responses of sweating and shivering are balanced and do not result in VMS.[2] Small elevations in body temperature within an already narrowed thermoneutral zone lead to the VMS commonly associated with menopause.[2,3,5] Because of the balance between norepinephrine and serotonin in the brain, it has been suggested that increasing the availability of serotonin may help in relieving VMS.[2,5,6] Selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) have been studied as an alternative therapy to HRT for the alleviation of VMS associated with menopause.[6] The purpose of this review is to evaluate the existing literature regarding the use of SSRIs and SNRIs for treatment of VMS in perimenopausal, menopausal, and postmenopausal women.

Methods

Literature searches were conducted through PubMed and Ovid/MEDLINE. Keyword terms searched were *hot flashes*, *menopausal vasomotor symptoms*, *alternative therapy*, *selective serotonin reuptake inhibitors*, serotonin norepinephrine reuptake inhibitors, *menopause*, *SSRIs*, and *SNRIs*. All searches were limited to adults, humans, and only articles written in the English language. Additionally, searches were limited to data published prior to August 2014. Most of the literature available involved desvenlafaxine, venlafaxine, and paroxetine and was included in this review.

Results

Selective Serotonin Reuptake Inhibitors

Paroxetine 7.5 mg is currently Food and Drug Administration (FDA) approved as nonhormonal therapy for moderate to severe VMS associated with menopause. Two double-blind, placebo-controlled studies were conducted to evaluate the efficacy of paroxetine in controlling menopausal vasomotor symptoms.[7] The primary outcomes included mean changes in the frequency and severity of moderate to severe VMS at weeks 4 and 12, with an additional end point of persistence of benefit at week 24. The studies were 12 and 24 weeks in length and randomized a total of 591 patients to paroxetine and 593 patients to placebo.[7] The median age of patients in each study was 54 years; the mean daily frequency in hot flashes was 11.3 at baseline. The mean weekly frequency of hot flashes at baseline was 82.55 in the paroxetine group and 81.54 in the placebo group.[7] At weeks 4 and 12, frequency in hot flashes improved significantly more in the paroxetine groups compared with placebo (at 4 weeks, −33.0 versus −23.5, respectively [$P < .0001$]; at 12 weeks, −43.5 versus −37.3, respectively [$P = .0090$]).[7] All end points were significantly improved in the 24-week study. In the 12-week study, a benefit in severity of symptoms was significant at 4 weeks ($P = .0048$) but not at 12 weeks ($P = .2893$); however, persistence of treatment benefit was seen with paroxetine treatment.[7] Compared with placebo, patients treated with paroxetine were more likely to experience nausea (3.8% versus 1.4%), fatigue (3.4% versus 1.5%), and dizziness (2.0% versus 0.8%). The results of this study showed that paroxetine 7.5 mg is well tolerated and may be an effective option in reducing the frequency and severity of menopausal VMS.[7]

A double-blind, placebo-controlled trial, 8 weeks in duration, compared the effects of escitalopram 10 to 20 mg/d on menopause-specific quality of life and pain. A total of 205 women were randomized to escitalopram ($n = 104$) or placebo ($n = 101$).[8] The primary outcome was improvement in frequency and severity of VMS as assessed by daily diaries at 4 and 8 weeks. Of note, all patients randomized to the treatment arm received escitalopram 10 mg daily for the first 4 weeks. If after 4 weeks there was not at least a 50% reduction in frequency or there was no decrease in severity of symptoms, the dosage was increased to 20 mg daily.[8] Most of the women were white or African American (>90%), and the mean age was 54 years. The mean number of VMS episodes per day at baseline was 9.78. The mean difference in patient-reported hot flash frequency was 1.41 at week 8 in women in the treatment arm ($P < .001$). Additionally, more women in the treatment arm (55%) reported a greater than 50% reduction in hot flash frequency compared with placebo (36%) at the end of the study period.[8] A total of 71 women in the placebo arm (70%) and 53 women in the treatment arm (51%) had their dosage increased to 20 mg daily at week 4 because of a lack of improvement in symptoms.[8] Regarding adverse events, there was no significant difference between the treatment group (53%) versus placebo (63%).[8] The study showed that compared with placebo, escitalopram significantly reduced hot flash frequency.[8]

The effects of citalopram and fluoxetine have also been compared with placebo therapy in a double-blind trial that

randomized 150 Finnish women to receive placebo (n = 50), fluoxetine (n = 50), or citalopram (n = 50) therapy.[9] Primary outcomes were hot flashes and the Kupperman index. The Kupperman index is a numeric conversion index that ranks 11 menopausal symptoms: hot flashes, paresthesia, insomnia, nervousness, melancholia, vertigo, weakness, arthralgia or myalgia, headache, palpitations, and formication. Each symptom is ranked from 0 to 3, corresponding to no, slight, moderate, and severe complaints, respectively. This study had a follow-up period of 9 months. Both citalopram and fluoxetine were initiated at 10 mg daily, and then increased to 20 mg daily at 1 month and 30 mg daily at 6 months.[9] Dosages could be decreased if patients were unable to tolerate side effects. Mean age at the time of the study was 54 years (range, 45-66 years), with a mean age of onset of menopausal symptoms of 50 years. The number of hot flashes decreased significantly in all groups ($P < .001$), and there were no significant differences in baseline characteristics between the 3 arms of the study.[9] At 6 months, hot flashes had been reduced by more than 50% in all 3 arms (58% reduction in placebo group, 62% in fluoxetine group, and 65% in citalopram group.[9] Specific baseline numbers of hot flashes were not provided in the study, and end points were listed in percentages. Additionally, there was no difference seen in the reduction in the Kupperman index between the 3 arms. From a safety and tolerability standpoint, the dosages of citalopram and fluoxetine were well tolerated in this study, with the most common side effects reported being nausea and dry mouth. There were no differences in discontinuation rates between the 3 arms. From this study, the use of citalopram or fluoxetine was not shown to be superior to placebo in treating patients with menopausal symptoms; however, the maximum allowed dosage of fluoxetine in the study was below the FDA-approved dosages often used in clinical practice, which may have confounded the results.[9]

Serotonin Norepinephrine Reuptake Inhibitors

In an open-label, 8-week study, duloxetine was administered to perimenopausal and postmenopausal women. Study participants received duloxetine 30 mg for 1 week, followed by duloxetine 60 mg for the remaining 7 weeks of the study.[10] The primary end point of this study was to assess the efficacy of duloxetine for Major Depressive Disorder during menopause. Secondary outcomes were severity of daytime and nighttime hot flashes associated with the menopausal transition. Of the 19 patients who received the study medication, 16 patients were evaluated in the final analysis. Daytime frequency and severity of hot flashes decreased significantly ($P = .04$ and $P = .007$), although baseline numbers of hot flashes were not provided in the study.[10] The change in nighttime frequency and severity of vasomotor symptoms was not significant. Results were largely based on tracking symptoms through a hot flash diary.[10] The small sample size of this study and the fact that the primary outcome studied was not specific for VMS suggests that more information is needed before recommending duloxetine for this purpose.[10] Additionally, hot flashes are commonly listed as a side effect for duloxetine, which might confound results of any studies specifically for VMS.

One double-blind 12-week study compared venlafaxine 75 mg to placebo in postmenopausal women who experienced more than 14 hot flashes per week, to evaluate the effect of hot flashes on daily activities. Most participants were age 52 years (±6.1), white (68% in control group and 85% in treatment group), and about 4 years (4 ± 3.5 years in control group and 4.9 ± 4.4 years in treatment group) after menopause.[11] Of the 80 women enrolled in the study, 61 participants (n = 29 in venlafaxine group and n = 32 in placebo group) completed the treatment. Hot flashes declined in both groups at the 1-month follow-up. In the venlafaxine group, hot flash scores continued to decline until the end of the study, but in the placebo group scores rebounded (a 51% decrease in venlafaxine compared with a 15% decrease in placebo). Adverse events of dry mouth, sleeplessness, and decreased appetite were observed more in the venlafaxine group than in the placebo group. Dizziness, tremors, anxiety, diarrhea, and rash were more frequent in the placebo group than in the venlafaxine group. Adverse effects of constipation, nausea, headache, and decreased libido were similar in both groups. Upon completion of the study, 93% of women in the venlafaxine group continued treatment despite the adverse effects.[11] The authors concluded that venlafaxine can decrease the patient-perceived effects of hot flashes on daily activities.[11]

An 8-week trial compared low-dose estradiol and venlafaxine to placebo for the alleviation of vasomotor symptoms in perimenopausal and postmenopausal women. The dosing strategy compared 0.5 mg/d of 17β-estradiol, 75 mg/d of venlafaxine, and placebo.[12] Women were ages 40 to 62 years, postmenopausal, and had at least 14 VMS per week. A total of 339 patients were randomized in a 2:2:3 fashion between those receiving estradiol (n = 97), venlafaxine (n = 96), and placebo (n = 146).[12] The primary objective of this study was to determine the efficacy and tolerability of estrogen therapy and venlafaxine compared with placebo in reducing VMS. The secondary outcomes were VMS severity, VMS bother, and perceived VMS interference. Mean VMS frequency at baseline among all groups was 8.1 episodes per day.[12] Compared with baseline, VMS decreased to 3.9 VMS per day in the estradiol group, 4.4 VMS per day in the venlafaxine group, and 5.5 VMS per day in the placebo group.[12] Estradiol was slightly more

effective at reducing VMS; however, the clinical significance of 3.9 VMS per day compared with 4.4 VMS is not as relevant, and the study was not powered to directly compare the 2 active treatment arms.[12] Insomnia was the most frequently reported adverse effect associated with estrogen therapy, whereas fatigue was the most common with venlafaxine. Increases in systolic and diastolic blood pressure occurred more commonly in the venlafaxine group but were not clinically significant. Of note, treatment satisfaction in this study was highest in the estrogen therapy group and lowest in the placebo group, although authors did not directly note how satisfaction was measured.[12]

Desvenlafaxine was compared to placebo in a controlled trial of postmenopausal women (n = 707) who experienced 50 or more moderate to severe hot flashes per week.[13] The duration of this trial was 52 weeks, significantly longer than most trials for this purpose. The primary outcomes were change in average daily number of hot flashes and change in daily hot flash severity score. Of the 707 women enrolled, 620 women completed therapy through at least 1 evaluation (4 weeks), with 368 completing the entire study.[13] Participants received 50, 100, 150, or 250 mg of desvenlafaxine or placebo. Primary efficacy end points were completed at 4 and 12 weeks. Women treated with desvenlafaxine 100 mg had a significantly greater decrease in average daily number of hot flashes compared with placebo at weeks 4 and 12 (−6.62 hot flashes in desvenlafaxine group versus −5.22 in placebo [$P = .013$] at 4 weeks; −7.23 in desvenlafaxine vs. −5.50 in placebo [$P = .005$] at 12 weeks).[13] For other desvenlafaxine doses, the reduction in daily number of hot flashes was less than that of the 100-mg dose. Almost 90% of patients treated with either desvenlafaxine or placebo experienced adverse effects, which accounts for the high dropout rate in the study. Women treated with higher doses of desvenlafaxine (150 or 200 mg) experienced significantly more side effects and were more likely to discontinue the study medication than those treated with either lower doses of desvenlafaxine or placebo. The most common adverse effects reported were constipation, dry mouth, hypertension, nausea, vomiting, decreased libido, and abnormal thinking. The authors concluded that desvenlafaxine 100 mg/d significantly reduced number of hot flashes compared with placebo.[13]

Discussion

VMS related to the perimenopausal and postmenopausal period can lead to significant physical distress, often requiring medical intervention. Traditional therapies for VMS of menopause have been dominated by the use of HRT. This treatment strategy has fallen out of favor after a randomized trial of postmenopausal women receiving HRT versus placebo demonstrated a clinically significant increase in adverse events, such as coronary heart disease and breast cancer. Given these risks, practitioners have turned to other treatment options to help alleviate VMS.

The data are conflicting regarding the use of SSRIs and SNRIs for patients with VMS related to menopause, and these agents may not be ideal for all patients. For women treated with tamoxifen, a selective estrogen receptor modulator that precludes use of HRT in these patients, SSRIs and SNRIs that inhibit cytochrome P450 2D6 (paroxetine, fluoxetine, and duloxetine) would not be appropriate because of the potential for serious drug-drug interactions. For women with uncontrolled blood pressure, SNRIs would not be the most appropriate choice for the treatment of VMS, because these medications have been shown to increase blood pressure. However, most adverse events associated with SSRIs and SNRIs in the trials were mild and tolerated relatively well by study patients.

SSRIs and SNRIs may be considered as an alternative in patients who have a contraindication or are concerned about using hormonal therapies. FDA approval for treatment of VMS has been sought for agents such as desvenlafaxine and duloxetine, but approval for these agents was denied. To date, only paroxetine in its mesylate salt formulation is approved for VMS. In postmenopausal patients with a history of venous thromboembolism, coronary heart disease, estrogen-driven cancers, underlying/concomitant depression, or those unwilling to be treated with hormone therapy, SSRIs and SNRIs may be an acceptable alternative to HRT, given their frequent use in a range of disease states and favorable tolerability profile. Future research with head-to-head trials of these agents for menopausal symptoms is warranted to determine the ideal agent.

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