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Do SSRIs and SNRIs reduce the frequency and/or severity of hot flashes in menopausal women

Chris Stubbs, MD (PGY-2), **Lisa Mattingly, MD (PGY-3)**, **Steven A. Crawford, MD**, **Elizabeth A. Wickersham, MD**, **Jessica L. Brockhaus, BA**, and **Laine H. McCarthy, MLIS**

University of Oklahoma Health Sciences Center Family Medicine Residency Program, Oklahoma City, OK

Abstract

Clinical Question—In menopausal women who experience regular hot flashes, does treatment with selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs) reduce the frequency and/or severity of hot flashes?

Answer—Yes. Review of the literature suggests that treatment with SSRIs or SNRIs reduces the frequency and severity of hot flashes in menopausal and post-menopausal women. Studies demonstrated that paroxetine (Paxil), citalopram (Celexa) and escitolapram (Lexapro) were the most effective SSRIs, and venlafaxine (Effexor) was the most effective first line SNRI, with desvenlafaxine as a second option. The most common side effects reported for both SSRIs and SNRIs are nausea and constipation, with most resolving within the first week of treatment. SNRIs have been associated with increased blood pressure in some patients and should be used with caution in women with hypertension. Women with a history of breast cancer and taking tamoxifen should avoid SSRIs, which have been shown to interfere with tamoxifen metabolism. SNRIs are the safest drugs for this population. Treatment choice should be patient-specific and begin with the lowest dose available.

Level of Evidence for the Answer—A

Search Terms—SSRI, SNRI, hot flashes, vasomotor symptoms, menopause

Search Conducted—August 2014, February 2016 and August 2016

Inclusion Criteria—menopausal, perimenopausal or postmenopausal women 18 years of age or older with frequent and/or severe vasomotor symptoms, meta-analyses, systematic reviews, randomized controlled trials, cohort studies.

Exclusion Criteria—pre-menopause, anxiety, depression, panic disorder, bipolar disorder, co-morbid conditions.

Corresponding Author: Elizabeth Wickersham, MD, Assistant Professor, Research Division, Department of Family & Preventive Medicine, University of Oklahoma Health Sciences Center, 900 NE 10th St., Oklahoma City, OK 73104. (405) 271-2370. elizabeth-wickersham@ouhsc.edu.

Summary of the Issues

Between 80% and 90% of perimenopausal and menopausal women will experience vasomotor symptoms (VMS), commonly called hot flashes. Depending on severity and frequency, hot flashes may adversely affect a woman's quality of life from 5 to 7 years or more.[1-4] Hot flashes are the result of decreased estrogen levels associated with menopause.[1,2] Hormone replacement therapy (HRT) is considered the gold standard treatment for hot flashes.[1,3] However, HRT is linked to increased risk of estrogen-dependent pathologies, including breast cancer, endometrial cancer, cardiovascular disease and thromboembolism.[2] Women experiencing hot flashes who either cannot take HRT or who would prefer other options are looking to nonhormonal therapies to control the frequency and severity of menopausal vasomotor symptoms.[1-3]

Research into nonhormonal options has focused on two major categories of nonestrogen therapy: nonpharmaceutical and pharmaceutical. Nonpharmaceutical therapies include lifestyle changes, such as exercise weight loss; yoga and other mindfulness or relaxation techniques; cognitive behavioral therapy; a variety of vitamins and supplements; and over-the-counter herbal remedies, such as black cohosh, ginseng and combination botanical remedies. Although some of these therapies have demonstrated some degree of efficacy – weight loss and mindfulness stress reduction techniques, for example – in general, these options “may not be the best for women with severe VMS or those seeking immediate relief.”[3]

Several nonestrogen pharmaceutical, or prescription, therapies have also been evaluated for hot flashes. These include clonidine, an alpha-adrenergic agonist, the anticonvulsant gabapentin, selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs). Clonidine and gabapentin have both demonstrated some effectiveness. However, each have significant adverse side effects that may make them impractical options for many women. Gabapentin is associated with dizziness, drowsiness, peripheral edema, loss of balance and suicidal thoughts. Side effects from clonidine are similar and include dizziness, sedation, headache and a significant elevation in blood with abrupt cessation.[1-4]

SSRIs and/or SNRIs have demonstrated promise for reducing both the frequency and severity of hot flashes without the risks of HRT or the more severe side effects of the other prescription drugs studied.[1-4] This brief review examines the current evidence to determine if SSRIs and/or SNRIs may be effective and safe alternatives to HRT for reducing the frequency and/or severity of hot flashes in menopausal women.

Summary of the Evidence

In 2013, Shams et al. published a systematic review and meta-analysis evaluating the effectiveness of five SSRIs – escitalopram, paroxetine, sertraline, citalopram and fluoxetine – for reducing vasomotor symptoms (hot flashes) in healthy perimenopausal women.[5] The review analyzed 11 randomized controlled trials (RCTs) with rigorous methodology published between 2003 and 2012. The studies included 2,069 women between 36 and 76

years of age who were followed for a period of 1 to 9 months, depending on the study. Meta-analyses showed that treatment with an SSRI resulted in a significant decrease in the average number of daily hot flashes at 4 to 8 weeks, down from 10 per day to 9 (95% CI -1.49 to -0.37) compared to placebo. In this study, escitolapram (Lexapro) was the most effective SSRI for reducing the daily frequency of hot flashes. Participants in the SSRI group also reported a reduction in severity of residual hot flashes compared to placebo. The most common side effects reported included nausea, fatigue and drowsiness but were not significantly different from placebo. The investigators concluded that SSRIs are a reasonable substitute for HRT.[5]

A 2015 systematic review by Handley and Williams examined 18 RCTs published between 2000 to 2012 that compared SSRIs/SNRIs to placebo for reducing peri- and postmenopausal hot flashes.[6] Participants were healthy women between the ages of 27 and 78 years who reported experiencing an average of 46 to 76 hot flashes per week, depending on the study. All studies assessed hot flash frequency and severity using a self-reported daily hot flash diary. The severity rating and frequency were multiplied to yield a composite score, with higher scores representing more severe symptoms. SSRIs/SNRIs reduced hot flash symptoms by as much as 65% compared to placebo. Potential first line SSRIs were paroxetine (Paxil), paroxetine ER (Paxil CR), citalopram (Celexa) and escitalopram (Lexapro). Venlafaxine (Effexor XR) was identified as a potential first line SNRI. Paroxetine ER demonstrated the greatest statistically significant reduction in hot flash frequency at both 12.5mg/day (62%, p=0.007) and 25mg/day (64%, p=0.03). Venlafaxine provided more immediate symptom relief than the SSRIs, but had a higher incidence of side effects, most notably nausea and constipation. SNRIs may increase blood pressure and should be used with caution in hypertensive patients.[6]

In 2015, The North American Menopause Society (NAMS) released a position statement regarding nonhormonal management of menopause-associated vasomotor symptoms.[3] Panel members searched five databases for high-level evidence articles (RCTs or systematic reviews) focused on nonhormonal therapies for hot flashes. The search identified 340 original research articles and 105 systematic reviews appropriate for further evaluation. NAMS panel members reviewed all articles and assigned levels of evidence. A limited number of head-to-head RCTs comparing HRT to other pharmacological agents were identified. One such study reported that the SNRI venlafaxine (Effexor) demonstrated similar effectiveness for reducing VMS symptoms compared to a low-dose estradiol. A limitation of that RCT was that the protocol did not include a comparison of the two therapies with up-dosing.

After evaluation of the evidence, the NAMS panel concluded that multiple nonhormonal therapies are appropriate considerations for menopausal and post-menopausal hot flashes. Recommendations include the following SSRIs and SNRIs:paroxetine salt 7.5mg/day (Brisdelle®); paroxetine or paroxetine ER 10–25mg/day; escitalopram 10–20mg/day; citalopram 10–20mg/day; desvenlafaxine 50–150mg/day; and venlafaxine XR 37.5–150mg/day. Patients should be started at the lowest available dose and titrated up as needed. Brisdelle® is only available in 7.5mg and is currently the only drug FDA-approved for hot

flashes. [3] The Table summarizes the efficacy, safety and costs associated with SSRI/SNRI treatment.

Conclusion

HRT is still considered the most effective treatment for reducing hot flashes in menopausal and post-menopausal women. However, concerns that HRT can increase the risks of estrogen-dependent pathologies have led to studies investigating other treatments for vasomotor symptoms. Based on the evidence reviewed, SSRIs and SNRIs reduce the frequency and severity of menopause-associated vasomotor symptoms by 10% to 64%, depending on the study. Side effects from SSRIs and SNRIs, which included nausea, constipation, and dry mouth, were generally not severe and often subsided within the first week.[3,4] SSRIs escitalopram and paroxetine ER and SNRI venlafaxine XR were shown to be the most effective.[3-5] Although less effective than HRT, SSRIs/SNRIs are demonstrated to reduce hot flashes and may be recommended for women who wish to avoid the risks of HRT. Additional placebo-controlled studies are needed to evaluate risks, benefits and dosing. Women with a history of breast cancer who are taking tamoxifen should avoid SSRIs. Studies have demonstrated that some SSRIs inhibit the activity of the enzyme CYP2D6, which can result in lower therapeutic levels of tamoxifen. The SNRIs venlafaxine and desvenlafaxine appear to have little or no impact on tamoxifen activity and should be considered as the first line therapy for these patients.[5,6]

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Table

SSRI/SNRI Safety, Efficacy and Cost for Treatment of Hot Flashes[5,6]

To avoid side effects, patients should be started on the lowest dose available and gradually increased as needed to control hot flashes. Drugs are listed by class in the order of demonstrated safety and effectiveness. Costs are for generic drugs where available and are for reference purposes only. Actual costs will vary dependent on pharmacy and insurance coverage.

Generic (Brand Name) Recommended First Line Medications for Hot Flashes	**Daily Doses**	**Appropriate for Tamoxifen users**	**Approximate cost of 30 day supply**
Selective Serotonin Reuptake Inhibitors (SSRIs)			
1. Paroxetine (Paxil)			
Paroxetine salt (Brisdelle®) (FDA approved for hot flashes)	7.5mg	No	$150-$200+
Paroxetine (Paxil)	10mg 20mg	No No	$5.00+ $5.00+
Paroxetine ER (Paxil CR)	12.5mg 25mg	No No	$40-$250 $40-$250
2. Citalopram (Celexa)	20mg	No	$4.00-$12.00
3. Escitalopram (Lexapro)	10mg	No	$8.00-$10.00
Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)			
1. Venlafaxine (Effexor XR)	37.5mg	**Yes**	$6.00-$12.00+
2. Desvenlafaxine ER (Pristiq)	50mg	**Yes**	$140-$240+

CR, controlled release; ER, extended release; XR, extended release.