

Review

Venlafaxine and desvenlafaxine in the management of menopausal hot flashes

Emily D. JOHNSON, Dana G. CARROLL.

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ABSTRACT*

Vasomotor flushes are common complaints of women during and after menopause, affecting about 75 percent of this population. Estrogen therapy is the most effective treatment for hot flashes.

However, there are a significant number of women who have contraindications or choose not to use estrogen due to potential risks such as breast cancer and thromboembolic disorders. These women need alternative options. The selective norepinephrine reuptake inhibitors, venlafaxine and desvenlafaxine, have shown efficacy in alleviating hot flashes.

Objective: The purpose of this review is to assess the efficacy and tolerability of these two agents for treatment of hot flashes in healthy postmenopausal women.

Methods: A literature search of the MEDLINE and Ovid databases from inception to June 2011 was conducted. Randomized controlled trials, published in English, with human participants were included. Studies included postmenopausal women, and trials with breast cancer only populations were excluded.

Results: Venlafaxine reduced hot flashes by 37 to 61 percent and desvenlafaxine by 55 to 69 percent. Both agents were well tolerated. The most common adverse effects were headache, dry mouth, nausea, insomnia, somnolence, and dizziness.

Conclusion: Based on the evidence, venlafaxine and desvenlafaxine are both viable options for reducing the frequency and severity of hot flashes.

Keywords: Hot Flashes. Venlafaxine. Desvenlafaxine. Menopause.

VENLAFAXINA Y DESVENLAFAXINA EN EL MANEJO DE SOFOCOS POSTMENOPAUSICOS

RESUMEN

Los sofocos vasomotores son quejas frecuentes en mujeres durante y después de la menopausia, afectando a cerca del 75% de esta población. La terapia estrogénica es el tratamiento más efectivo para los sofocos. Sin embargo, hay un número significativo de mujeres que presentan contraindicaciones o no eligen la terapia estrogénica por los posibles riesgos como el cáncer de mama o las alteraciones tromboembólicas. Estas mujeres necesitan opciones alternativas. Los inhibidores selectivos de la recaptación de noradrenalina, venlafaxina y dexvenlafaxina, han demostrado eficacia en el alivio de los sofocos.

Objetivo: El objetivo de esta revisión es evaluar la eficacia y tolerabilidad de estos dos agentes para el tratamiento de los sofocos en mujeres postmenopáusicas sanas.

Métodos: Se realizó una búsqueda de la literatura en las bases de datos MEDLINE y Ovid desde su inicio a junio de 2011. Se incluyeron ensayos controlados aleatorizados, publicados en inglés, con participantes humanos. Los estudios que incluían sólo mujeres postmenopáusicas y ensayos únicamente con poblaciones de cáncer de mama fueron excluidos.

Resultados: La venlafaxina redujo los sofocos en un 37 a 61% y la desvenlafaxina del 55 al 69%. Ambos agentes fueron bien tolerados. Los efectos adversos más comunes fueron dolor de cabeza, boca seca, náuseas, insomnio, somnolencia y mareos.

Conclusión: Basándose en la evidencia, la venlafaxina y la desvenlafaxina son opciones viables para reducir la frecuencia y gravedad de los sofocos.

Palabras clave: Sofocos. Venlafaxina. Desvenlafaxina. Menopausia.

INTRODUCTION

Vasomotor flushes are among the most common complaints of women during and after the menopausal transition, affecting about 75 percent of this population.¹⁻³ Episodes are characterized by a sudden sensation of intense heat, joined by skin flushing, profuse sweating, and possibly palpitations or anxiety.^{1,2} Hot flashes can significantly impair

* Emily D. JOHNSON. PharmD. Auburn University, Harrison School of Pharmacy. Auburn AL (United States). Dana G. CARROLL. PharmD. Clinical Associate Professor. Department of Pharmacy Practice, Auburn University, Harrison School of Pharmacy. Auburn, AL (United States).

quality of life by affecting ability to work, social life, sleep patterns, and other daily activities, resulting in fatigue, loss of concentration, or depression.^{1,2,4}

Estrogen therapy, with or without progesterone, is currently the most effective treatment for vasomotor symptoms.⁵⁻⁷ However the Women's Health Initiative (WHI)⁵ gave rise to concerns regarding estrogen and progesterone replacement, such as increased risk of breast cancer, heart disease, and thromboembolic disorders. There are a significant number of women who have contraindications or who choose not to use estrogen due to the potential risks. Currently estrogen products are the mainstay of therapy, for that reason there is a need for safe and effective therapies to aid this population.

The pathophysiology of hot flashes is not completely understood, but the proposed mechanism is dysfunction of the thermoregulatory process caused by alterations in hypothalamic neurotransmitters.^{1-3,8} It is known that hot flashes are related to low estrogen levels, as proven by the facts that hot flashes commonly occur after natural or surgical menopause and that estrogen therapy significantly improves them.⁹ Catecholesterogen, an estrogen metabolite, is responsible for the production of endorphins, which inhibit norepinephrine synthesis. Therefore, diminished estrogen and progesterone levels lead to an increase in systemic norepinephrine.¹⁻³ Norepinephrine causes an elevation in core body temperature prior to the onset of the hot flash. Women who experience hot flashes have a narrow temperature neutral zone, meaning the core body temperature required to reach the upper threshold is greatly reduced. Once this threshold is crossed the body's heat loss mechanisms, such as sweating and peripheral vasodilation, are activated causing a hot flash.^{1,3} Furthermore, diminished estrogen levels are associated with low blood levels of serotonin, which leads to an upregulation of serotonin receptors in the hypothalamus.¹ The upregulation of serotonin receptors is responsible for resetting the natural thermostat, mentioned previously. In addition the activation of the 5-HT_{2A} receptor precipitates further heat loss.^{1,8}

Although their mechanism of action for relieving hot flashes cannot be explained fully, antidepressants affecting serotonin and norepinephrine have proven effective in breast cancer populations.¹⁰⁻¹³ Venlafaxine and its major active metabolite, desvenlafaxine, inhibit the reuptake of both norepinephrine and serotonin.^{14,15} The purpose of this review is to assess specifically the efficacy and tolerability of these two agents for treatment of hot flashes in healthy postmenopausal women.

METHODS

A literature search of the MEDLINE and Ovid databases was performed using the search term "hot flash" combined with each "venlafaxine" and "desvenlafaxine". The time frame for the search was inception through June 2011. Randomized controlled trials, published in English, with human participants were included. Studies also included

only postmenopausal women, and trials with a breast cancer only population were excluded.

LITERATURE REVIEW

Venlafaxine

One of the first trials to assess the efficacy of venlafaxine for treatment hot flashes is the extension of a pilot study that showed promising results. A randomized, double-blind, placebo-controlled trial included 221 women with a history of breast cancer or fear of developing breast cancer as a result of taking estrogen.¹⁶ To be included, women needed to have at least 14 troublesome hot flashes per week, occurring for at least one month. Participants were randomly assigned to receive venlafaxine 37.5 mg, 75 mg, 150 mg, or placebo daily for 4 weeks. Participants kept hot flash diaries every day for 1 week at baseline and during the treatment period. Diaries were used to calculate the hot flash scores, which combine the number and severity of hot flash episodes. After 4 weeks of therapy, all three venlafaxine groups had significantly greater reductions compared to placebo. The median score reductions were 37 percent, 61 percent, and 61 percent for the venlafaxine 37.5 mg, 75 mg, and 150 mg groups compared to only 27 percent for placebo (all $p < 0.001$). As the venlafaxine dose increased, hot flash activity significantly decreased, with the exception of the 150 mg group. In terms of toxicity, significantly more nausea, dry mouth, appetite loss, and constipation were reported in the 75 mg and 150 mg groups, with the most occurring in the latter. Based on the results of this trial, it seems 75 mg is the preeminent dose, being that it is more effective than 37.5 mg and less toxic than the 150 mg dose. The strengths of this trial were the study design, large sample size, and doses were titrated to improve toleration. The short duration (4 weeks) and lack of reporting baseline characteristics were limitations.

A 12-week, randomized, controlled trial looked at the efficacy of extended-release venlafaxine in 80 women with natural or surgical menopause.⁴ The women were required to experience at least 14 hot flashes per week and were excluded for taking any hormone, antidepressant, or chemotherapy agents. Participants were randomized to receive either venlafaxine 37.5 mg daily for 1 week, then 75 mg daily for 11 weeks or placebo. Daily hot flash severity scores were reported by participants, along with the completion of monthly questionnaires. The study was completed by 61 participants, 29 in the treatment group and 32 in the control group. At week 4, the patient-perceived hot flash score had declined in both the venlafaxine and placebo groups, but there was no significant difference between the two. At week 12, the mean score for the venlafaxine group further declined, while the control group rebounded. These correspond to a 51 percent reduction in patient-perceived hot flash score for the venlafaxine group, compared to a 15 percent reduction with placebo ($p < 0.001$). Although dry mouth, loss of appetite, and sleeplessness were commonly observed side effects, 93 percent of

participants in the venlafaxine group chose to continue treatment at the conclusion of the trial. This illustrates that most women felt the benefits of venlafaxine therapy outweighed the risk of adverse effects. This trial had several limitations including a small sample size, lack of a run-in period, short duration (11 weeks) and hot flush severity scores were not obtained at baseline. Strengths were the study design and the focus on a general menopausal population, as opposed to including women with breast cancer as did the previous trial.

Currently, there is only one trial¹⁷ comparing venlafaxine to active treatment in women with or without breast cancer. This double-blind randomized, controlled trial compares a single intramuscular injection of depomedroxyprogesterone acetate (MPA) 400 mg to oral venlafaxine 37.5 mg daily for 1 week, followed by 75 mg daily. Thirty-nine percent of the trial population had no history of breast cancer. The 220 subjects reported bothersome hot flashes, occurring at least 14 times per week for at least one month. Participants completed a daily hot flash diary questionnaire for 1 week at baseline and throughout the 6-week treatment period. MPA significantly reduced hot flash scores by 79 percent, compared to 55 percent reduction with venlafaxine ($p < 0.001$). In the group assigned to MPA, 86 percent reported a greater than 50 percent reduction in hot flash score, while this was reported for 53 percent in the venlafaxine group ($p < 0.0001$). Although venlafaxine was not as effective as MPA, 68 patients chose to continue therapy after 6 weeks. Of these, 33 percent reported a greater than 90 percent reduction in hot flash scores at 6 months. During the first week of the trial, venlafaxine had significantly more nausea, appetite loss, constipation, dizziness, mouth dryness, and sleepiness. However, when comparing side effects at week 6 to baseline, there was no difference. Strengths of this trial included study design, larger sample size, a longer follow up period (6 months), and doses being titrated up to improve toleration. The high dose of MPA may have been a limitation; however there is no well-established maximum dose for this agent and higher doses have been well tolerated. Long-term safety issues of MPA, particularly relating to breast cancer, should also be considered. One last limitation to consider is approximately 60% of the population in this trial had a history of breast cancer, which limits application to a general menopausal population.

Desvenlafaxine

A multi-centered, double-blind, placebo-controlled trial observed the efficacy and tolerability of desvenlafaxine in 707 healthy, postmenopausal women.¹⁸ Eligible participants experienced 50 or more moderate to severe hot flashes per week, which is significantly more episodes than the venlafaxine trials required for inclusion. In this dose-escalation trial, patients received desvenlafaxine 50, 100, 150, or 200 mg or placebo daily for 52 weeks. Participants maintained daily hot flash diaries throughout the trial to track the frequency and severity of episodes. Reductions in the average

daily number of moderate to severe hot flashes from baseline to 12 weeks were 55 percent, 64 percent, 60 percent, and 60 percent for the desvenlafaxine 50, 100, 150, and 200 mg groups and 51 percent for the placebo group. Desvenlafaxine 100 mg daily was the only dose that generated a significantly greater decrease in frequency from baseline compared to placebo at both 4 weeks (-6.62 compared to -5.22, $P = 0.013$) and 12 weeks (-7.23 compared to -5.50, $P = 0.013$). Although statistically significant, the clinical significance of these reductions could be questioned. The 150 mg group had a significant decrease from baseline at week 12, but not week 4. The desvenlafaxine 50 and 200 mg doses were not significantly different from placebo at 4 or 12 weeks. The 100 and 200 mg groups had significant reductions in hot flash severity score from baseline compared to placebo at week 12 only, while the severity scores in the 50 and 150 mg groups did not differ from placebo at any time point. Desvenlafaxine seemed to be well-tolerated in all groups, however more adverse events and discontinuations due to adverse events were reported in the 150 and 200 mg treatment groups compared to placebo during the first week. There were no differences in adverse effects between any groups after week 1. The most common adverse reactions were nausea, dizziness, and insomnia, which were dose-related and probably due to the fact that no dose titration method was used in this trial. Other weaknesses were the possible lack of ability to generalize results (greater than 80 percent of the study population was Caucasian) and that efficacy endpoints were measured and reported for a short duration of time (12 weeks). There were strengths in study design, large sample size, and inclusion of exclusive general menopausal population. One additional strength was safety and tolerability data were collected and reported for 52 weeks.

Two other randomized, placebo-controlled trials demonstrate the efficacy of desvenlafaxine in a design similar to the previous trials. Both of these included generally healthy, menopausal women experiencing at least 7 hot flashes a day for a minimum of one week. Again this required number of episodes at baseline is much higher compared to studies using venlafaxine. In the first multicenter, double-blind study, 458 participants were randomly assigned to receive a daily dose of desvenlafaxine 100 mg, 150 mg, or placebo.¹⁹ As in the previous study, change from baseline in daily number of moderate to severe hot flashes and average daily severity scores were compared at 4 and 12 weeks. Subjects kept daily hot flash diaries for 2 weeks at baseline and throughout the 12 week treatment phase. The results showed significant improvement in all efficacy endpoints for both desvenlafaxine doses compared to placebo. The desvenlafaxine 100 mg and 150 mg groups achieved 65.4 percent and 66.6 percent reductions from baseline in the daily number of hot flashes compared to 50.8 percent reduction with placebo at 12 weeks ($p = 0.005$, $p = 0.012$ respectively). The average daily severity scores were also reduced significantly in both treatment groups compared to placebo at 4 and 12 weeks. This trial utilized a specific dose

titration and tapering protocol. There were no significant differences between any groups in the number of discontinuations due to adverse events; proving that dose titration upon initiation improved tolerability. Only during the first week, did desvenlafaxine groups report significantly more adverse events compared to placebo (52.8 percent compared to 31.1 percent, $p < 0.001$); the majority of these events were reported during the first 3 days of the trial. Desvenlafaxine 100 mg daily proved to be the most favorable dose, with the 150 mg dose having no improvement in efficacy and slightly higher incidence of adverse events. Additional strengths include the trial design and large patient population. The short duration of the taper period, which led to a high number of discontinuation symptoms in the first 3 days, and the short duration of the study (12 weeks) were limitations of this trial.

The other trial was 26 weeks in duration and also compared daily desvenlafaxine 100 mg, 150 mg, and placebo for treatment of moderate to severe hot flashes.²⁰ This multicenter, double-blind trial included 567 participants. As before, patients kept daily hot flash diaries to record the number and severity of episodes; these were used for the primary efficacy evaluations at 4 and 12 weeks, and also for the secondary analysis at 26 weeks of treatment. Both desvenlafaxine groups had a significantly greater reduction from baseline in number of hot flashes occurring at 4 and 12 weeks of therapy compared to placebo. Desvenlafaxine 100 mg, 150 mg, and placebo reduced the number of moderate to severe hot flashes by 60 percent, 66 percent, and 47 percent respectively at week 12. At week 26, only the desvenlafaxine 150 mg had a significant reduction compared to placebo (69 percent versus 51 percent, $p = 0.001$). The 100 mg group maintained similar reductions at week 26 (61 percent), while the placebo group continued to trend down, resulting in no significant difference between the two. There were a high number of discontinuations due to lack of response in the placebo group. The average hot flash severity score was significantly reduced for the desvenlafaxine 100 mg and 150 mg groups at 12 weeks. The reductions were 24 percent and 29 percent, compared with only 13 percent for placebo (all $p < 0.002$). There were significantly more discontinuations due to adverse effects for patients taking desvenlafaxine, regardless of dose, compared to placebo (28.5 percent and 8.9 percent, $p < 0.001$). Limitations of the trial include no dose titration or tapering period and a primarily Caucasian study population (87.2 percent). Strengths are the trial design, longer duration (26 weeks), large sample size, and as with previous trials, enrollment of generally healthy postmenopausal women.

DISCUSSION

Based on the evidence, venlafaxine and desvenlafaxine are both viable options for reducing the frequency and severity of hot flashes. Venlafaxine has been shown to reduce hot flashes by 37 to 61 percent^{4,16,17} and desvenlafaxine by 55 to 69 percent.¹⁸⁻²⁰ Similar to most other trials

assessing treatment for vasomotor symptoms, the placebo rates were elevated in these studies (15-51%). However, venlafaxine did differentiate from placebo in all of the reviewed trials. It also should be noted the primary efficacy endpoints of these trials are evaluated by subjective measures which is similar to other menopausal hot flash trials.

The onset of relieving hot flashes typically begins to occur within one week after initiation.^{16,18-20} Although the incidence of side effects was fairly high initially, these seemed to diminish over time, and both agents were well tolerated by the majority of patients.¹⁷⁻¹⁹ The most common adverse effects are headache, dry mouth, nausea, insomnia, somnolence, and dizziness. There are some behaviors that may help alleviate these effects, such as taking the medication with food to decrease nausea or taking a bedtime dose to help with dizziness and somnolence. Both of these agents should be titrated up, as needed, in an effort to reduce the onset and severity of adverse events. The doses for treating vasomotor symptoms are much lower than those utilized to treat depression. The starting dose for venlafaxine for menopausal hot flashes should be 37.5 mg, which can be increased to 75 mg after one week of therapy.^{4,16,17} Desvenlafaxine may be titrated more quickly, starting at 50 mg per day for 3 days, and then increasing to 100 mg daily.¹⁹ There is no advantage to further increasing the dose for either agent to relieve hot flashes and the potential for developing adverse effects is greater.^{16,19} Also, these medications should be tapered down over a two-week period, instead of abruptly stopping, at the time of discontinuation.^{14,15}

Currently, most trials assessing the use of nonhormonal therapy for treatment of hot flashes include only women with a history of breast cancer. These trials may have been complicated by additional health care issues and/or concomitant medications. Additional research is needed to address alternative treatment options for healthy postmenopausal women. Furthermore, the trials assessed in this review are relatively short in duration. Randomized, controlled clinical trials that are greater than 26 weeks in duration are needed to assess the long-term effectiveness of venlafaxine and desvenlafaxine and further clarify their role as treatment for hot flashes.

CONCLUSIONS

Evidence supports the use of venlafaxine and desvenlafaxine for treatment of hot flashes in healthy postmenopausal women. These options may be especially beneficial to women who have contraindications or concerns associated with using estrogen therapy. As always, the choice for treatment should be based on patient specific factors. Comorbidities, concurrent medications, and risk versus benefits of the chosen medication are all factors that should be considered.

CONFLICT OF INTEREST

We have no conflicts of interest. We received no financial support to write this manuscript.

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