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**Is Desvenlafaxine effective for reducing hot flashes in
postmenopausal females?**

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

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In

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ABSTRACT

OBJECTIVE: The objective of this selective Evidence Based Medicine (EBM) review is to determine whether or not Desvenlafaxine is effective in reducing daily hot flashes in postmenopausal females.

STUDY DESIGN: Review of three primary randomized controlled trials (RCTs) published after the year 2000 in the English language.

DATA SOURCES: Three double-blind, randomized controlled trials were found using PubMed and EBSCOhost Web. All trials selected compared treatment with Desvenlafaxine to a visually matched placebo.

OUTCOMES MEASURED: Patients completed daily diary cards on which they recorded the number and severity of daily hot flashes from the screening period through the 12 weeks of therapy. Patients completed self-administered questionnaires at baseline and after 12 weeks of treatment: Profile of Mood States, Work Limitations, Menopause Symptoms Treatment Satisfaction, Sexual Functioning, EuroQuality of Life Visual Analog Scale, Greene Climacteric Scale (GCS).

RESULTS: All three RCTs demonstrated a statistically significant reduction in the number of moderate to severe daily hot flashes in postmenopausal women receiving treatment with Desvenlafaxine compared to those receiving the placebo.

CONCLUSION: The results of the RCTs evaluated suggest Desvenlafaxine is effective in reducing the daily number of moderate-severe hot flashes in postmenopausal women.

KEY WORDS: Desvenlafaxine, hot flashes, vasomotor symptoms, menopause, serotonin-norepinephrine reuptake inhibitor

INTRODUCTION

Vasomotor symptoms, more commonly known as hot flashes, are transient periods of extreme warmth, flushing and sweating, most commonly affecting the trunk and face.¹

Subsequent chills, anxiety and heart palpitations often occur concomitantly with hot flashes.¹ Hot flashes ordinarily begin during the transition to menopause, and according to several trajectory studies, are most bothersome during late perimenopause and early postmenopause.¹

Hot flashes are the most commonly reported menopausal symptom and affect as many as 79% of postmenopausal females in the United States.¹ Vasomotor symptoms are such a prevalent problem for women, and result in increased direct and indirect costs as well as increased healthcare utilization.² In a study of more than 500,000 women, it was calculated that women with hot flashes incurred an additional \$339,559,598 in direct health care costs per year and \$27,668,410 in indirect costs.² Women affected by hot flashes in the study population had 1.5 million office visits over the one year period, representing an 82% increase in general outpatient visits, and a 121% increase in visits specifically for hot flashes as compared to control counterparts.²

The mechanism of hot flashes is multifaceted and not entirely understood, but it is likely related to declining estrogen production from the ovaries during menopause.³ More noticeable oscillations in core body temperature result from a restricted thermoneutral zone in females undergoing the menopausal transition.³ Vasodilation and increased blood flow to the trunk and face are responsible for the initial flushing feeling that is often followed by profuse sweating.³ Palpitations, anxiety, night sweats and consequent insomnia frequently accompany hot flashes.³

There are several therapies currently available to treat vasomotor symptoms associated with menopause. For quite some time, the mainstay of treatment was hormone replacement

therapy, consisting of estrogen, progestogen or a combination of the two.³ Nonhormonal pharmacological therapies include selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), Clonidine, and Gabapentin.³ An emphasis is also placed on nonpharmacologic therapies including behavioral changes, such as dressing in layers, setting a low room temperature and avoiding spicy foods and alcohol.³ Complementary and alternative treatments such as Black Cohosh, acupuncture and hypnosis are additionally being studied for the reduction of vasomotor symptoms.³

While hormone therapy remains the most effective method for treating hot flashes, the use of hormone therapy has significantly declined after results were released from the 2002 Women's Health Initiative (WHI).⁴ The WHI highlighted several major risks associated with hormone therapy including breast cancer, pulmonary embolism, stroke and coronary heart disease, causing many to question whether the benefits outweighed the risks.⁴ Treatment with Desvenlafaxine, a serotonin norepinephrine reuptake inhibitor (SNRI), is being proposed because Desvenlafaxine has been shown to be an effective nonhormonal treatment alternative for hot flashes.⁵

This review evaluates three double-blind, randomized, placebo-controlled trials comparing the efficacy of Desvenlafaxine, a SNRI, as an oral nonhormonal medication for reducing hot flashes in postmenopausal females.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not Desvenlafaxine is effective in reducing daily hot flashes in postmenopausal females.

METHODS

Three double-blind, placebo-controlled, RCTs that included healthy postmenopausal

females experiencing at least 50 moderate to severe hot flashes per week were chosen for analysis. All three trials compared the experimental group receiving 100mg of Desvenlafaxine to a control group receiving a visually matched placebo. The outcome measured in all three studies was change from baseline in the average daily number of moderate to severe hot flashes after 12 weeks.^{6,7,8}

A search using PubMed and EBSCOhost with the key words “Desvenlafaxine”, “hot flashes”, and “menopause” was used to find relevant studies published in English after the year 2000. Articles chosen were published in peer-reviewed journals and were selected based on relevance to the clinical question and an emphasis on patient oriented outcomes.

Inclusion criteria for all three trials selected for review consisted of healthy postmenopausal females experiencing at least 50 moderate to severe hot flashes per week. Menopause was defined as at least 12 months of spontaneous amenorrhea, 6 months of spontaneous amenorrhea with follicle-stimulating hormone (FSH) levels greater than 40mIU/mL, or 6 weeks postsurgical bilateral oophorectomy.^{6,7,8} Speroff et al. and Archer et al. included women with a BMI less than or equal to 40 kg/m².^{6,7} Pinkerton et al. included women at least 45 years old with a BMI less than or equal to 34 kg/m² and additionally defined menopause by a hysterectomy with FSH level greater than 40 mIU/mL.⁸

Exclusion criterion was similar for all three studies used in this review. The exclusion criteria included recent treatment for vasomotor symptoms with either hormone therapy, psychoactive medications or investigational drugs, known hypersensitivity to Venlafaxine, or certain comorbid medical conditions.^{6,7,8} **Table 1** highlights the specific exclusion criteria.

Statistics based on dichotomous data were reported using change from baseline, analysis of covariance (ANCOVA), and p-values. Control event rate (CER) and experimental event rate

(EER) were used to calculate absolute benefit increase (ABI) and absolute risk increase (ARI).

The number needed to treat (NNT) was calculated from the ABI; the ARI was used to determine number needed to harm (NNH).

Table 1: Demographics & Characteristics of Included Studies

Study	Type	# Pts	Age (years)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Speroff et al., 2008 (6)	Double Blind RCT	707	39-78	Healthy postmenopausal women with a BMI ≤ 40 , ≥ 50 moderate-severe hot flashes/week; Menopause defined as ≥ 12 months of spontaneous amenorrhea or ≥ 6 months of spontaneous amenorrhea with serum FSH levels > 40 mIU/mL or ≥ 6 wks. postsurgical bilateral oophorectomy	Hypersensitivity to Venlafaxine, use of hormone therapy within 4 wks- 6mo. of screening, psychoactive drug use within 4 weeks of screening, investigational drug use within 30 days of screening, history of seizure disorder, MI (within 6 months), malignancy or treatment for malignancy (within 2 years), narrow-angle glaucoma or current raised intraocular	97 (29= placebo, 68= 100mg Desvenlafaxine)	Desvenlafaxine 100 mg orally once daily
Archer et al., 2009 (7)	Double Blind RCT	567	53.5 \pm 5.20 years	Same as above inclusion criteria. Plus: Age ≥ 45 y/o, BMI ≤ 34.0 ; GCS total score of ≥ 12 & a GCS hot flash Score of ≥ 2 ; Menopause defined as a hysterectomy with serum FSH > 40 mIU/mL.	pressure, hepatic/renal disease, presence of major depressive, bipolar, psychotic, or generalized anxiety disorder, untreated malabsorption disorder; persistent elevated blood pressure, other clinically important abnormalities at screening	106 (42= placebo, 64= 100mg Desvenlafaxine)	Desvenlafaxine 100 mg orally once daily
Pinkerton et al., 2013 (8)	Double Blind RCT	365	46-71	Same as above inclusion criteria. Plus: Age ≥ 45 y/o, BMI ≤ 34.0 ; GCS total score of ≥ 12 & a GCS hot flash Score of ≥ 2 ; Menopause defined as a hysterectomy with serum FSH > 40 mIU/mL.	pressure, hepatic/renal disease, presence of major depressive, bipolar, psychotic, or generalized anxiety disorder, untreated malabsorption disorder; persistent elevated blood pressure, other clinically important abnormalities at screening	67 (30= placebo, 37 = 100mg Desvenlafaxine)	Desvenlafaxine 100 mg orally once daily

OUTCOMES MEASURED

Each of the RCTs used in this systematic review evaluated patient oriented evidence that matters (POEMs) and assessed the efficacy of Desvenlafaxine in reducing the frequency of daily hot flashes. Patients in each trial completed daily diary cards on which they recorded the number and severity of daily hot flashes from the screening period through the 12 weeks of therapy.

Mild hot flashes were characterized by a fleeting warm sensation without perspiration or disruption to activity; moderate hot flashes were defined as a warm sensation with sweating without a disruption to activity; severe hot flashes disrupted activity with a hot sensation and sweating.⁶ The average daily number of moderate to severe hot flashes was calculated as the sum of moderate to severe hot flashes on each day divided by the days in the week with data.^{7, 8}

Patients completed self-administered questionnaires at baseline and after 12 weeks of treatment.

Speroff et al. used the Profile of Mood States (POMS), Work Limitations (WLQ), Menopause Symptoms Treatment Satisfaction, Sexual Functioning and EuroQuality of Life Visual Analog Scale to monitor improvement throughout the treatment phase.⁶ Archer et al. utilized the POMS, WLQ and Greene Climacteric Scale (GCS)⁷

RESULTS

Dichotomous data was used in all three trials and was used to calculate both the efficacy and safety of the interventions. Each of the trials evaluated the efficacy of 100mg of Desvenlafaxine daily for 12 weeks in reducing the average daily number of moderate to severe hot flashes compared to a placebo. There were no statistically significant demographic differences noted between the treatment and control groups at baseline. Results were based on daily diaries the patients kept, which noted the frequency and severity of daily hot flashes.

The RCT conducted by Speroff et al. showed a statistically significant decrease from baseline in the average number of daily hot flashes for the 100mg Desvenlafaxine group compared to placebo after 12 weeks ($p = .005$).⁶ Treatment with Desvenlafaxine yielded a 64% decrease from baseline whereas the treatment with placebo only showed a 51% decrease.⁶ Likewise, the RCT conducted by Archer et al. showed a similarly significant decrease from baseline in the average number of hot flashes after 12 weeks of therapy; a 60% reduction was noted in the treatment group compared to a 47% reduction with the placebo group ($p \leq .002$).⁷ Finally, the RCT by Pinkerton et al. showed similar findings, with a 62% reduction in daily hot flashes for the Desvenlafaxine group in contrast with a 38% decrease for the placebo group ($p \leq .001$) (Table 2)

Table 2: Percentage Decrease from Baseline in Average Daily Number of Hot Flashes

STUDY	Desvenlafaxine 100 mg	Placebo
Speroff et al. ⁶	64%	51%
Archer et al. ⁷	60%	47%
Pinkerton et al. ⁸	62%	38%

Additionally in Speroff et al., the Desvenlafaxine group had 50% of women achieve at least a 75% reduction from baseline in average daily number of hot flashes compared to 29% in the placebo group after 12 weeks of therapy ($p = .003$).⁶ Archer et al. demonstrated that 41.4% of patients treated with Desvenlafaxine achieved at least a 75% reduction in the number of hot flashes compared to the 26.4% treated with placebo over the 12-week period ($p = .004$).⁷ Pinkerton et al. showed a significantly larger percent of women in the Desvenlafaxine group achieving a minimal clinically important difference when compared to the placebo group, 63.6% compared to 41.4% respectively ($p < .001$). The minimal clinically important difference was determined to be a reduction of 5.35 hot flashes from baseline.⁸ Treatment effects from the 3

RCTs are presented in **Table 3**. The control event rate (CER) and experimental event rate (EER) were used to calculate the relative benefit increase (RBI) and absolute benefit increase (ABI). The ABI was subsequently used to determine the numbers needed to treat (NNT). The NNT represents the number of patients that need to be treated with 100mg of Desvenlafaxine for one additional patient to benefit from the intervention compared to a placebo. The benefit in this case is a reduction in average daily number of hot flashes.

Table 3: Treatment Effects of Desvenlafaxine

STUDY	CER	EER	RBI	ABI	NNT
Speroff et al. ⁶	0.29	0.5	0.72	0.21	5
Archer et al. ⁷	0.264	0.414	0.57	0.15	7
Pinkerton et al. ⁸	0.414	0.636	0.54	0.222	5

Furthermore, CER and EER were used to calculate the relative risk increase (RRI) and absolute risk increase (ARI). The equation $1/ARI$ was used to determine the numbers needed to harm (NNH). Nausea was the most commonly reported adverse event in all three RCTs for the Desvenlafaxine group compared to the placebo group, and therefore data for nausea was used to calculate NNH.^{6,7,8} NNH represents the number of patients treated with Desvenlafaxine 100mg that would result in one more patient experiencing an adverse event, in this instance nausea, when compared to placebo. All three RCTs consistently showed a higher incidence of nausea in the Desvenlafaxine 100mg group compared to the placebo group. 38.7% of the Desvenlafaxine 100mg group in Speroff et al. reported nausea compared to 6.5% in the placebo group (95% Confidence Interval 2.62 to 14.41).⁶ Archer et al. confirmed similar findings with 45.1% of the 100mg Desvenlafaxine group reporting nausea compared to 8.3% of the placebo group ($p < .001$).⁷ Finally, Pinkerton et al. paralleled the previous two studies with 16.5% of the

Desvenlafaxine 100mg patients reporting nausea compared with only 6.3% of the placebo patients ($p = .002$).⁸ Calculations for harm for all three RCTs are summarized in **Table 4**.

Table 4: Calculations for Harm (Nausea)

STUDY	CER	EER	RRI	ARI	NNH
Speroff et al. ⁶	0.065	0.387	4.95	0.322	3
Archer et al. ⁷	0.083	0.451	4.43	0.368	3
Pinkerton et al. ⁸	0.063	0.165	1.62	0.102	10

Participants in the Desvenlafaxine groups reported more treatment related adverse effects than the placebo group in all three RCTs. In Speroff et al., 87% of women in the placebo group reported adverse effects compared to 94% of women treated with 100mg of Desvenlafaxine.⁶ The differences between groups were only noteworthy during the first week of treatment and after that point there were no statistically significant differences between groups in the incidence of new adverse effects.⁶ Discontinuations due to adverse effects did not differ between the placebo group and the 100mg Desvenlafaxine group.⁶ Nausea, dizziness and headache were the most frequently reported discontinuation complaints.⁶ Archer et al. paralleled the results found by Speroff et al. with 95.1% of the treatment group reporting at least one adverse effect compared to 88.3% of the placebo group.⁷ Commonly reported adverse effects of Desvenlafaxine patients that resulted in discontinuation were nausea and dizziness.⁷ Although there were more adverse event related discontinuations from the Desvenlafaxine group than the placebo group during the first week of therapy, there were no significant differences in reported adverse effects between the groups after week one of therapy.⁷ Speroff et al. and Archer et al. both reported 90% compliance rates with therapy for both the Desvenlafaxine group and placebo group after the first week of therapy. Compliance was determined by returned pill counts and daily diary

information; compliance with treatment was defined as taking at least 80% of dispensed doses.^{6,7} Pinkerton et al. reported 10% of Desvenlafaxine patients discontinuing due to adverse effects compared to only 3.7% of placebo patients ($p = .016$).⁸ A similar pattern was observed in the study by Pinkerton et al.; 39.5% of Desvenlafaxine patients conveyed treatment emergent adverse effects during week one in comparison to 16.8% of placebo patients ($p < .001$), however, after the first week no significantly noticeable differences existed between the two groups in regards to treatment emergent adverse effects.⁸ The most commonly reported adverse effects were nausea, constipation, dry mouth, diarrhea, fatigue and somnolence.⁸

DISCUSSION

All three RCTs used in this review concluded that 100mg of Desvenlafaxine daily significantly reduced the number of hot flashes in postmenopausal women compared with placebo. Although hormone replacement therapy still remains the most effective treatment for menopausal vasomotor symptoms, Desvenlafaxine proved to be a successful nonhormonal alternative, demonstrating both clinically and statistically significant improvements in hot flashes related to menopause. Desvenlafaxine is currently marketed primarily for its use as an antidepressant medication in major depressive disorder (MDD).⁹ The use of Desvenlafaxine in the treatment of menopausal vasomotor symptoms is currently an off-label indication.⁹ Although proven to be an effective nonhormonal treatment alternative for menopausal hot flashes, there are several contraindications to using Desvenlafaxine. Desvenlafaxine should be avoided in patients with a known hypersensitivity to Desvenlafaxine, Venlafaxine, or any other formulary component. Moreover, Desvenlafaxine should be avoided in patients who recently used a monoamine oxidase inhibitor (MAOI) for the treatment of a psychiatric condition because of the major risk of serotonin syndrome.⁹ It is important to note that Desvenlafaxine should be used

with caution in elderly patients because of the risk of hyponatremia and orthostatic hypotension.⁹ Manufacturers of Desvenlafaxine recommend tapering the drug slowly over several weeks upon discontinuation of therapy to minimize side effects. Desvenlafaxine is a prescription medication that is available as a generic medication in the United States. Most insurance companies cover Desvenlafaxine, however without insurance this medication can cost anywhere from \$174.14 to \$399.00 for a 30 day supply of the 100mg tablets.⁹

Limitations in the RCTs used in this review include a lack of diversity in the subject population and lack of dose titration and tapering protocols at the initiation and discontinuation of treatment. The majority of subject participants (> 80%) were Caucasian, so the generalizability of the results to postmenopausal women of other races is limited. The lack of dose titration and tapering is likely responsible for the majority of the adverse events and discontinuation symptoms reported in all three RCTs. These limitations prompt areas of future research to improve both the generalizability and tolerability of Desvenlafaxine as an intervention for vasomotor symptoms in menopause.

CONCLUSION

Based on the analysis of the three RCTs, this selective Evidence-Based Medicine review concludes that Desvenlafaxine is an effective nonhormonal treatment for moderate to severe hot flashes associated with menopause. A statistically and clinically significant reduction in the frequency of moderate to severe hot flashes was observed following treatment with Desvenlafaxine when compared with a visually matched placebo. The efficacy of Desvenlafaxine was comparable to other nonhormonal centrally acting medications. Desvenlafaxine was found to be generally safe and well tolerated, consistent with that of other drugs in the serotonin-norepinephrine reuptake inhibitor class.

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