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Escitalopram Reduces Hot Flashes in Non-depressed Menopausal Women: A Pilot Study

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Abstract

Background—Hot flashes are one of the most troubling manifestations of menopause, affecting about 80% of women. Due to recent controversies about hormone replacement therapy (HRT), many women are seeking alternative treatments. The use of antidepressants to treat hot flashes and other menopausal symptoms has been an active area of investigation. However, the majority of past research in this area has included women with significant medical or psychiatric histories that may influence treatment response. This was the first study to examine the impact of escitalopram on hot flashes, mood, sleep, and quality of life in a healthy sample of non-depressed menopausal women.

Methods—Twenty-five menopausal women, with no significant psychiatric or medical history, were enrolled. All women were treated with escitalopram (10-20mg flexibly dosed) for 8 weeks. The active treatment phase was preceded by a single blind placebo lead-in period.

Results—Over the course of the study, women reported significant decreases in both hot flash frequency and severity and improvements in dysphoria, anxiety, quality of life, and sleep.

Conclusions—These preliminary findings suggest that escitalopram may be a feasible and effective option for treating hot flashes and other menopausal symptoms in healthy women who might not ordinarily consider antidepressant treatment.

Keywords

escitalopram; hot flashes; non-clinical sample

INTRODUCTION

Menopause is a physically and emotionally challenging transition phase in a woman's life. The cessation of menstrual periods is frequently accompanied by hot flashes, night sweats, fatigue, insomnia, depression, anxiety, memory loss, and urogenital symptoms, often resulting in a significant disturbance of quality of life (1,2). Of these, hot flashes have been reported to be one of the most troubling menopausal symptoms, affecting up to 80% of women (3,4).

Because many of the physiological changes that occur during menopause result from decreased levels of estrogen, hormone replacement therapy (HRT) has historically been considered a first-line treatment for hot flashes (5,6). However, a number of recent studies have raised concerns about the adverse effects of HRT. For example, the Women's Health Initiative

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Randomized Controlled Trial was stopped early based on evidence that the increased risk of breast cancer, coronary heart disease, stroke, and pulmonary embolism associated with HRT use far outweighed the possible benefit of decreasing the risk for hip fractures and colorectal cancer (6). Later, the women's international study of long duration oestrogen after menopause (WISDOM) confirmed that HRT increased cardiovascular and thromboembolic risk when started many years after menopause (7). Additional studies have also linked the long-term use of HRT with increased risk of ovarian cancer (8) and dementia in postmenopausal women aged 65 years or older (9). The numerous risks and side effects (e.g., vaginal bleeding, edema) associated with HRT often result in a failure to initiate, poor adherence to, or an abrupt discontinuation of HRT regimens (10-18).

Therefore, many women are seeking novel interventions to help them cope with menopausal hot flashes. For example, complementary and alternative medicine (CAM) approaches (i.e., acupuncture, reflexology, Chinese herbs, dong quai, evening primrose oil, ginseng, kava or red clover extracts, black cohosh) for the treatment of menopausal symptoms have received some empirical attention (19-22). However, results on the effectiveness of these treatments have been mixed and data on the long-term safety of their use are lacking (20-22,23). Other prescription medications such as clonidine and gabapentin have also been investigated as a treatment for menopausal hot flashes but have again yielded inconsistent results (24).

Due to the potential interaction between estrogen and neurotransmitters such as serotonin, the use of antidepressants (i.e., paroxetine, fluvoxamine, sertraline, venlafaxine, mirtazapine, citalopram, fluoxetine, desvenlafaxine) to treat hot flashes and other menopausal symptoms has become a very important area of investigation (5,25-36). While some pilot studies, case reports, and randomized controlled trials have linked the use of antidepressants to significant reductions in hot flashes, dysphoria, anxiety, and insomnia, as well as improvements in quality of life (25-33,36), other studies have reported null findings (34,35). However, most of this research has been conducted with oncology patients (e.g., breast cancer survivors) for whom HRT is contraindicated (25-27,29,31). Of the non-oncology studies that have been conducted, very few have examined the use antidepressants to treat hot flashes in a psychologically healthy sample of women (32,34-36). Therefore, it is important to continue to examine the impact of antidepressants on menopausal symptoms in populations of women without medical and psychiatric histories that may influence treatment response.

Escitalopram, the newest of the SSRIs, has not been previously evaluated as an alternative therapy for hot flashes in a healthy sample of non-depressed women. The purpose of this pilot study was to explore the use of escitalopram (10-20mg flexibly dosed) for the treatment of hot flashes, as well as emotional distress, sleep, and quality of life, in non-depressed menopausal women, with no history of cancer.

METHODS

Participants

Women were recruited from the community via newspaper ads, as well as through physician referral at UMDNJ-Robert Wood Johnson Medical School (RWJMS). All participants received the study medication and all study related evaluations free of charge. Women were paid $30 for each completed study visit to compensate for travel expenses and time.

A total of 25 non-depressed menopausal women who reported at least 14 hot flashes per week were enrolled in the trial. One additional woman withdrew consent after the screening appointment. All women had experienced a natural cessation of menstrual periods for at least 12 months, did not possess any current psychiatric diagnosis per *DSM-IV* (37) criteria as confirmed by the Structured Clinical Interview for DSM-IV (SCID) (38), and had absent or

minimal levels of depressive symptoms as defined by a Hamilton Depression Rating Scale (HAM-D) (39) score < 11. None of the women included in the study had taken HRT within the past 6 months or had a prior history of poor response to HRT.

Women with a history of breast or other types of cancer and/or any current, medically unstable condition were excluded from the study. Other exclusion criteria included: a history of substance abuse or dependence within the past year; lifetime history of major depressive disorder, suicide attempts, or self injurious behavior; initiation of psychotherapy within the past 3 months; and any major sleep disturbances.

Procedure

Screening Appointment—After completing a preliminary phone screen, potential participants were scheduled for an in-person evaluation. All women provided written informed consent prior to completing any study procedures. The study had full approval from the UMDNJ-RWJMS Institutional Review Board.

At the initial appointment, psychiatric and medical eligibility was determined via clinical interview, review of the patient's medical and psychiatric histories, and the administration of the SCID (38), the HAM-D (39), and the Pittsburgh Sleep Quality Index (PSQI) (40). Hot flash diaries were distributed to the eligible women to complete on a daily basis at home during the following week.

Single-Blind Placebo Lead-in Appointment—Given the high rate of placebo response in hot flash studies (41), the active treatment phase was preceded by a single blind placebo lead-in. At this appointment (one week after screening), hot flash diaries were reviewed and eligible women (i.e., those with 14 or more hot flashes per week) were given a placebo to take for one week, while continuing to complete hot flash diaries. All women were aware that they would be given placebo for one week during the trial. However they did not know which week placebo would be administered. Placebo was an identical match to the escitalopram tablets.

Baseline Appointment—At the baseline appointment (2 weeks after screening), hot flash diaries were reviewed. Participants who were found to be placebo responders (e.g., >25% reduction in hot flash frequency) were excluded from the active treatment trial and referred for appropriate treatment.

Intervention—Women who were not placebo responders received escitalopram for 8-weeks (10mg/day weeks 1-4; 10-20mg/day weeks 5-8 depending on participant and investigator assessment of efficacy and side effects).

Assessments/Visits—All participants completed hot flash diaries on a daily basis throughout the duration of the study. On the diaries, women recorded the number of hot flashes experienced each day, the severity of each hot flash (1=mild, 2=moderate, 3=severe, 4=very severe), and the total hours of sleep obtained each night. Hot flash diaries were reviewed with women on a weekly basis. A composite score reflecting both the frequency and severity of hot flashes was also calculated for each weekly hot flash assessment. Hot flash frequency, as well the hot flash composite score, were designated as the *co-primary outcomes* for the study. In addition, treatment response was defined *a priori* as a 50% or greater decrease in hot flash frequency from baseline (after the placebo run-in) to end of treatment.

The following self-report questionnaires and clinician administered measures were completed at the baseline appointment and at the end of weeks 3, 6, and 8 of the active trial for the assessment of *secondary outcomes*: the HAM-D (39), the Hamilton Anxiety Rating Scale (HAM-A) (42), the Menopause Quality of Life Scale (MENQOL) (43), the PSQI (40), and the

Greene Climacteric Scale (44). Adverse events were collected at each visit by directly questioning the patient.

Statistical Analysis

Data was analyzed using Repeated Measures ANOVA, with SPSS 15 for Windows. Data analysis included all patients who started the trial and took at least one dose of escitalopram. For those who did not complete the study, the last observation was carried forward. A significance level of alpha=.01 was employed in all statistical analyses. Baseline data was obtained after the placebo run-in period. Data was collected from October 2004 to July 2006.

RESULTS

Characteristics of the Sample

A total of 25 non-depressed women (20 Caucasian, 5 African-American, 1 Hispanic) were enrolled in the active treatment phase. There were no “placebo responders,” as defined above, during the run-in period. On average, women experienced a 2% reduction in the frequency of hot flashes after taking placebo for one-week and Repeated Measures ANOVA indicated that this change was not significant.

Sixty-four percent of the sample (n=16) remained on 10 mg of escitalopram throughout the trial. Thirty-six percent of the sample (n = 9) increased the dosage of escitalopram after week 4; 8 women titrated up to 20mg and 1 up to 15mg. Of the 8 women who increased to 20mg, one chose to taper back down to 10mg. However, she did not report any side effects while taking either dose.

Twenty-two women (88%) completed the trial. Three women dropped out of treatment due to side effects (i.e., anxiety and insomnia) of the medication. All women who dropped out of the trial were taking 10mg of escitalopram.

Primary Outcome

Table 1 illustrates the results of the Repeated Measures ANOVAs, as well as means and standard deviations, for the hot flash variables assessed in the trial. Over the course of the study, women experienced significant decreases in both the hot flash frequency and hot flash composite scores. Sixteen women (64%) were “treatment responders” (greater than 50% decrease in hot flash frequency) with an average decrease of 55% in hot flash frequency observed across all participants. Planned contrasts indicated that initial improvements in hot flashes were observed after 1 week of active treatment and were maintained throughout the 8 week treatment period.

Secondary Outcomes

Table 1 also depicts the results of the Repeated Measures ANOVAs, as well as means and standard deviations, for the assessment of dysphoria, anxiety, and quality of life throughout the study. Significant improvements in dysphoria, anxiety, and quality of life were also observed over the course of the trial. Planned contrasts indicated that these gains occurred by the third week of active treatment and were maintained throughout the 8-week treatment phase.

Several sleep parameters were also evaluated. Means, standard deviations, and the results of the Repeated Measures ANOVAs for all sleep assessments across time can be found in Table 2. On the PSQI, subjective sleep quality and sleep disturbances significantly improved over the course of the study. There was a trend towards improvement in global ratings of sleep, sleep duration, sleep latency, and sleep efficiency. No change was noted in daytime dysfunction due to insomnia, though baseline rates of this complaint were quite low at the beginning of the

study. The rate of change in use of sleep medications was not explored, as the use of concomitant psychotropic medication was prohibited. No improvements in total sleep time were noted on the hot flash diaries.

Side Effects

Women were directly asked about their experience of side-effects throughout the study. Fifty-six percent of women (n = 14) reported side effects while participating in the study. The majority of side effects were mild and transient, with the most frequently reported events being fatigue (16%, n = 4) and decreased libido (16%, n = 4). Less than 1% of women also experienced the following side effects: constipation (n = 1), dry mouth (n = 1), muscle tension (n = 1), shoulder pain (n = 1), fogginess (n = 1), diarrhea (n = 1), anorgasmia (n = 2), irritability (n = 1), anxiety (n = 1), insomnia (n = 1), mild nausea (n = 1), leg cramps (n = 1), mild spotting (n = 1), and weight gain (n = 1). Less than 1% of the sample also reported side effects (e.g., fatigue and anxiety) while on placebo.

DISCUSSION

This is the first study to evaluate escitalopram as an alternative treatment for menopausal symptoms in a medically stable sample of non-depressed women. The results of this study suggest that escitalopram is an effective non-hormonal approach for the treatment of hot flashes and other symptoms associated with menopause. Over the course of the study, women reported significant decreases in both the frequency and severity of hot flashes, in addition to significant improvements in dysphoria, anxiety, quality of life, and sleep. Speed of relief from hot flashes was rapid (within a week of beginning active drug) and gains were durable for the remainder of the trial. Escitalopram was well-tolerated, with 88% of participants completing the study. This completion rate favorably compares to the rates observed in other published trials of SSRIs (45).

Fatigue and decreased libido were the most frequently reported side effects in this trial, affecting approximately 16% of the patients. Other side effects, such as anxiety, insomnia, and irritability, were generally infrequent and were experienced by less than 1% of the women. Overall, in studies of its efficacy for depression and anxiety, escitalopram has been shown to have a favorable side effect profile, with most events being transient and mild (46). The rate of adverse events reported in this trial (i.e., 56% of the subjects) is comparable to the rates observed in double-blind, randomized, placebo-controlled trials of escitalopram for depression (e.g., 79% and 56.8%) (47,48) and no unknown adverse events emerged in this population of women. Escitalopram may be even more well-tolerated in menopausal women than in other populations as the rates of adverse events in studies of SSRIs used to treat vasomotor symptoms tend to be lower than those observed for depression (49).

A recent randomized trial of escitalopram vs. hormone therapy for the treatment of menopausal depression has suggested that escitalopram can be as efficacious as, and perhaps better than, hormone therapy in treating menopause-related symptoms (50). In this study, both escitalopram and hormone therapy significantly alleviated the impact of hot flashes on daily functioning (they did not examine the treatments' impact on frequency), with no significant difference observed between the two treatments. However, women treated with escitalopram also showed a significantly greater decrease in menopause-related symptoms in general when compared to those women treated with hormone therapy. Although the population under study was different (i.e., women in this study were clinically depressed), these findings are similar to the results of our open-label trial which suggest that escitalopram has a salubrious impact on hot flashes and other menopausal symptoms.

Yet, there are a few important limitations to the current trial that warrant consideration. The small sample size may limit the generalizabilty of study findings. In addition, as this pilot study was uncontrolled, the role of chance as well as non-specific treatment factors could not be explored. Thus, it is possible that factors, other than the study medication, such as time, patient expectations, clinician's attention, and demand characteristics were responsible for the observed improvement in menopausal symptoms. In particular, high placebo response rates have often been found in hot flash studies (51,52). Although the current trial employed an open-label design, an attempt was made to at least partially control for placebo response with the use of a single-blind placebo lead-in period. A low rate of placebo response was noted during the lead-in period and baseline data was not obtained until women had been on placebo for one week. However, larger, randomized, placebo-controlled trials in non-depressed menopausal women are needed to further evaluate the efficacy of this intervention.

In sum, escitalopram may be a safe and an effective alternative treatment for symptomatic menopausal women who are reluctant to initiate HRT, as well as for those who need to discontinue HRT due to side effects or medical complications. For example, a recent web-based survey assessing women's attitudes regarding HRT and alternative treatments found that 95% of women would prefer to try an alternative therapy before trying HRT (53). Additional research has indicated that many women are reluctant to initiate hormone replacement because of potential risks (54), while concerns about unwanted side effects, such as weight gain and monthly bleeding, may lead some women to prematurely discontinue HRT (55). The favorable side effect profile of the medication, combined with the rapid and durable improvements in hot flashes observed in this pilot study, indicate that escitalopram may be a good treatment option for menopausal women experiencing vasomotor symptoms, who might not otherwise consider antidepressant treatment.

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Table 1

Means and Standard Deviations for Outcome Measures Across Time

*Hot Flashes (Diary)	Baseline	Week 3	Week 6	Week 8	F	p
Composite (Range unlimited)	75.56(61.36)	36.72(34.71)	30.32(29.22)	34.88(41.88)	11.37	.0001
Frequency (Range unlimited)	41.88(25.88)	22.12(18.97)	19.16(17.28)	20.00(20.99)	12.06	.0001
Depression	**Baseline**	**Week 3**	**Week 6**	**Week 8**	**F**	**p**
HAM-D (Range=0-52)	7.68(2.94)	5.04(2.8)	4.52(2.94)	3.48(3.22)	10.71	.0001
Anxitey	**Baseline**	**Week 3**	**Week 6**	**Week 8**	**F**	**p**
HAM-A (Range=0-30)	11.68(4.92)	6.60(4.16)	5.64(4.12)	4.88(5.17)	19.98	.0001
Quality of Life	**Baseline**	**Week 3**	**Week 6**	**Week 8**	**F**	**p**
MENQOL (Range=0-174)	124.32(29.38)	142.32(29.59)	143.92(30.88)	151.76(21.68)	9.22	.0001
GREENE (Range=0-63)	49.00(7.44)	54.76(7.70)	54.08(7.68)	56.48(5.16)	17.27	.0001

Key: Hamilton Depression Rating Scale (HAM-D), Hamilton Anxiety Rating Scale (HAM-A), Menopause Quality of Life Scale (MENQOL), and the Greene Climacteric Scale (GREENE).

* Please note that participants tracked hot flashes for all 8 weeks of active treatment as reflected in the results section of the paper. The table only presents means and standard deviations from the same four time points at which the other outcome measures were assessed.

Table 2

Means and Standard Deviations for Sleep Outcome Measures Across Time

Sleep	**Baseline**	**Week 3**	**Week 6**	**Week 8**	**F**	**p**
PSQI-Total (Range=0-21)	9.04(2.11)	8.32(2.39)	8.44(2.32)	7.84(2.80)	2.61	.08
PSQI- Sleep Subscales (Range=0-3)						
Quality	1.72(.68)	2.16(.62)	2.24(.60)	2.24(.83)	6.82	.002
Disturbances	2.44(.87)	1.92(1.04)	2.04(.98)	1.56(1.12)	4.60	.01
Duration	.92(.86)	.64(.70)	.48(.59)	.64(.91)	3.13	.05
Latency	1.44(.92)	1.04(.79)	1.08(.81)	.84(.94)	2.00	.14
Efficiency	.68(.90)	.60(.82)	.44(.82)	.64(.99)	1.99	.15
Daytime dysfunction	1.48(.51)	1.52(.51)	1.68(.48)	1.68(.48)	1.20	.31
Hot Flash Diary-Total Sleep	44.59 (6.95)	49.52(6.22)	49.41(7.21)	49.54(7.8)	1.00	.29

Key: PSQI- Pittsburgh Sleep Quality Index.

Hot Flash Diary Total Sleep- Total number of hours slept at night per 7 day interval.