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ESCITALOPRAM TREATMENT OF MENOPAUSAL HOT FLASHES

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Abstract

Objective—To determine the effects of 10 mg and 20 mg/day of escitalopram on objectively-recorded hot flashes and on the rectal temperature threshold for sweating.

Method—Two studies were performed: 16 women received 10 mg/day and 26 women received 20 mg/day escitalopram for eight weeks. They were randomly assigned in equal numbers to receive active drug or placebo in double-blind fashion. Hot flash frequency was measured with an ambulatory recorder during the first three weeks and during the eighth week of the study. The rectal temperature threshold for sweating was measured during the first and eighth weeks of the study using published methods.

Results—In the first study, there were no significant effects whatsoever for any measure. In the second study, the escitalopram group showed an average decline in hot flash frequency of 14.4%, whereas, the placebo group showed an average increase of 6.7% ($P < .05$). However, there were no significant effects across time for either group. There were no significant effects whatsoever for rectal temperature sweating thresholds.

Conclusions—Escitalopram at 10 mg or 20 mg/day is not effective in the treatment of menopausal hot flashes.

Keywords

Hot flashes; escitalopram; thermoregulation; menopause

INTRODUCTION

Hot flashes (HFs) are triggered by small elevations in core body temperature (T_c) acting within a greatly reduced thermoneutral zone, i.e., the range of T_c within which neither sweating nor shivering occur.¹ This reduction is due to increased sympathetic activation and estrogen withdrawal, among other factors.² The first mechanism is supported by the following data. First, plasma MHPG (3 methoxy-4hydroxyphenyl-glycol) is greater at baseline in symptomatic vs. asymptomatic menopausal women and increases significantly further during HFs.^{3,4} Second, drugs that increase sympathetic activation, such as yohimbine, provoke HFs, whereas those that inhibit it, such as clonidine, ameliorate them.

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5:6 From these studies, we infer that levels of central norepinephrine (NE) are higher in symptomatic compared to asymptomatic women.

Research in animals has shown that NE and serotonin (5HT) work in opposite fashion,⁷ suggesting that drugs that increase brain 5HT will ameliorate HFs. Selective serotonin-reuptake inhibitors (SSRIs) increase 5HT in the synaptic junction by inhibiting its reuptake. Several such drugs, such as citalopram, have shown some efficacy in reducing HFs.⁸⁻⁹

Citalopram is a racemate consisting of a 1:1 mixture of the R (–) and S (+) enantiomers. *In vitro* studies have shown that the serotonin reuptake inhibitory activity is entirely attributable to the S-enantiomer, escitalopram. In fact, these studies have also shown that the R-citalopram in citalopram actually inhibits the effect of the S-enantiomer. For these reasons, escitalopram is more potent than citalopram for a given dose and is, therefore, a better therapeutic choice.¹⁰

We, therefore, sought to determine the effects of escitalopram upon HFs using an ambulatory recorder and to examine some of its underlying mechanisms by measuring the Tc sweating threshold, which is the upper bound of the thermoneutral zone. We performed a preliminary study and a larger study using successively higher doses of this compound.

METHODS

Participants

Forty-two postmenopausal (at least one year amenorrhea) women participated in these studies. There were 16 women in the preliminary study and 26 women in the larger study. They were recruited using ads in local newspapers requesting participants for research on menopause.

Sample size was determined in the following manner. The recent controlled trial of citalopram found a 60% reduction in hot flash frequency for this drug.⁸ In our previous studies, we have found no placebo effects on HFs using ambulatory SCL monitoring.^{11,12} To be conservative, for the present study, we assumed a 25% reduction in ambulatory HF frequency for the placebo group. We used the standard deviations from the published citalopram study.⁸ Using these assumptions in a power analysis, $n = 16/\text{group}$ will yield a power of .99 for both Time (pre/post) and Treatment $\times$ Time at $\alpha = .05$.

Procedures

Potential participants were first interviewed by one of us (M.E.T., a board-certified psychiatrist) to determine their suitability for the study. Participants were required to report at least six HFs/day, be in the age range of 44–59 years, be free of any antidepressant drugs, hot flash treatment drugs or supplements (soy, herbs), have BMI under 32, and be nondepressed as determined by Dr. Tancer using the M.I.N.I. International Neuropsychiatric Interview, a short, structured, psychiatric interview. Dr. Tancer obtained written informed consent from all participants and all procedures were approved by the Wayne State University Human Investigation Committee.

The women were paid for their participation.

Participants then had the Tc (rectal) sweating threshold determined using the following methods. All sessions were conducted between 1300 and 1800 hours. Participants wore cotton hospital scrub suits and data were recorded in a sound-proofed, temperature- and humidity-controlled (25°C, 50% RH) room. They were placed in a semirecumbent (45°)

position in a large reclining chair. This session was performed during weeks one and eight at the same time of the day.

Rectal temperature was recorded with a disposable Yellow Springs thermistor (YSI, Yellow Springs, OH) inserted 10 cm into the rectum. The probes are 3 mm in diameter, are flexible, and were well-tolerated in the present and previous studies. The probe remained in place for the entire session, typically about 2 hours. Sweating activity was recorded by capacitance hygrometry with a 3.5-cm diameter plastic chamber attached over the sternum. Compressed air, regulated at 200 mL/min, was dried over CaCO₂ and passed through the chamber. The minimum level of sweat detection was 0.001 mg/cm²/min¹ as described elsewhere.^{2,4}

These signals were digitized at 100 Hz by a Data Translation A/D converter and recorded on a PC computer. The Tc sweating threshold was defined as the rectal temperature at the first measurable detection of sweating.

Hot flashes were assessed using a recorder developed by one of us (RF) (Flashmark Pro; Pending U.S.A. Patent No. 60,741,3760).¹³ The device counts HFs by measuring humidity on the chest. There is no electrical connection to the body. The device contains a humidity sensor, microcontroller, flash memory, and 1.5 volt hearing aid battery. The adhesive collars are made from an FDA-approved material (3M #5122). When compared to hot flashes recorded using sternal skin conductance level, the positive predictive value was 95.6%, the specificity was 95.2%, and the sensitivity was 90.9%.

Participants were instructed to wear the recorder continuously except while bathing. They were then sent home for one week.

After one week, participants returned to the laboratory, where the HF data were downloaded from the recorder. They wore the recorder for the next two weeks and for the eighth week of the study. The participants were then given a blinded bottle of 56 capsules, to be taken once per day at bedtime at the beginning of week 2. In the preliminary study, 10 mg/day was used as the maintenance dose. In the larger study, 20 mg/day was used as the maintenance dose. The corresponding tapering doses were 5 mg/day and 10 mg/day, respectively. The tapering doses were given for two weeks, when the women had completed the eight weeks at the maintenance dose. Assignment to the drug groups was random.

Escitalopram was obtained from the manufacturer (Forest Labs) and rebottled, blinded, coded, and randomized by Nathan Worthing, PharmD. (Clark Professional Pharmacy, Ypsilanti, MI) who kept the blinding code. Randomization was done using SPSS. The placebo and active drug capsules were identical.

Data Analysis

Group differences in demographic variables that were continuous (age, BMI, years in menopause) were analyzed with independent samples T-tests; categorical variables (race, type of menopause) were analyzed with Chi-square tests. Sweating threshold data were analyzed using 2-way (Group $\times$ Time), repeated measures analyses of variance.

Hot flash frequencies were obtained from the ambulatory recorder; a hot flash was defined as a change in humidity of at least 3%/minute.¹³ Data from the preliminary study were analyzed using a 2-way, repeated-measures, analysis of variance. Data from the second study were analyzed with a 2-way (Group $\times$ Time), repeated-measures analysis of covariance using BMI as a covariate. To control for differences in HF frequency at baseline (week 1), data from subsequent weeks were expressed as percentages of the week one data. The minimum level of statistical significance for all analyses was $P = .05$.

RESULTS

For the preliminary study, 19 participants were screened; 3 discontinued (1-illness, 1-lost interest, 1-moved away). Thus, 16 participants completed this study.

There were no significant group differences on any demographic variable (Table 1). There were no group differences approaching statistical significance in hot flash frequencies or sweating thresholds. Therefore, the second study was initiated.

For the second study, 31 participants were screened. Four participants discontinued (2-lost interest; 2-insufficient time). One participant was screened out at interview due to depression. Thus, 26 participants completed this study.

In this study, the active drug group had a significantly ($P < .05$) higher BMI than the placebo group. Therefore, BMI was used as a covariate in the following analyses. There was a significant effect for Group in the analysis of covariance ($P < .05$, Table 3). The average decline in HF frequency at week eight was 14.4% for the active drug group vs. a 6.7% increase for the placebo group. There were no other significant effects from this analysis. The raw hot flash frequencies are shown in Table 4. There were no significant effects, whatsoever, from the analysis of these data or for the analyses of the sweating threshold data.

DISCUSSION

In our preliminary study, we found no significant effects of escitalopram upon HF frequency at a dose of 10 mg/day. At a dose of 20 mg/day, we found a significant overall effect of Group (escitalopram vs. placebo). At week 8, the escitalopram group showed an average decline in HF frequency of 14.4%, whereas the placebo group demonstrated an average increase of 6.7%. However, there were no significant effects across time in either group. From these data, we conclude that, in the present study, escitalopram had little clinical utility in the treatment of HFs in nondepressed women.

Our study is important because it is the first controlled investigation published, to date, of the treatment of menopausal HFs in women screened to be free of clinical depression. A pilot study found significant declines in self-reported hot flash frequency and severity, but there was no placebo control group.¹⁴ A flexible-dose study of escitalopram in depressed women found improvement in menopausal symptoms on the Greene Climacteric Scale; but, again, there was no placebo control group.¹⁵

Consistent with its lack of effects upon HFs, escitalopram had no significant effects upon the sweating threshold for rectal temperature. A previous study of estrogen conducted in our laboratory showed that 1 mg/day, p.o., 17 β -estradiol significantly increased the rectal temperature sweating threshold and decreased HF frequency, whereas no such effects were obtained in women who received placebo.¹⁶

We recently performed a study in which 5HTP (5-hydroxytryptophan), the immediate precursor of 5HT (serotonin) also had no effect upon objectively-recorded HFs.¹⁷ Another recent investigation found no significant effects of acute tryptophan depletion upon HFs.¹⁸ Taken together, these results, along with our findings for escitalopram, raise questions regarding the role of the serotonin system in the etiology of HFs.

Our study is distinguished by the fact that HFs were recorded objectively using a miniature, electronic recorder requiring no interventions from the participant. Most HF studies have used diaries as the main endpoint. However, diaries are subject to compliance problems,

which result in bias and errors.¹⁹ Additionally, HFs are not accurately reported during sleep because awakenings do not always occur. Finally, large placebo effects occur with diary measures, but not with objective ones.¹⁹

CONCLUSIONS

In conclusion, we found that two doses of escitalopram had no significant effects over eight weeks on objectively-recorded HFs in two groups of nondepressed symptomatic women. Additionally, we found no significant effects of this drug on the rectal temperature sweating threshold. These results question the clinical utility of escitalopram in the treatment of HFs in this population. However, our findings are limited by our relatively small sample size and should be tested in larger groups using longer treatment periods.

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TABLE 1

Demographic data – preliminary study

Variable	Group (means $\pm$ SD)	
	Drug (n = 8)	Placebo (n = 8)
Age	53.0 $\pm$ 2.9	52.0 $\pm$ 3.2
BMI	25.0 $\pm$ 2.7	27.8 $\pm$ 3.9
Years Menopausal	5.4 $\pm$ 1.6	7.8 $\pm$ 6.0
Race		
African-American	Drug = 3	Placebo = 6
Caucasian	Drug = 5	Placebo = 2
Type of Menopause		
Natural	Drug = 7	Placebo = 6
Surgical	Drug = 1	Placebo = 2

TABLE 2

Demographic data – second study

Variable	Group (means $\pm$ SD)	
	Drug (n = 12)	Placebo (n = 14)
Age	53.0 $\pm$ 3.4	52.9 $\pm$ 3.0
BMI	28.5 $\pm$ 3.5	25.9 $\pm$ 3.0 ^a
Years Menopausal	5.3 $\pm$ 4.9	5.4 $\pm$ 5.6
Race		
African-American	Drug = 11	Placebo = 10
Caucasian	Drug = 1	Placebo = 3
Hispanic	Drug = 0	Placebo = 1
Type of Menopause		
Natural	Drug = 8	Placebo = 9
Surgical	Drug = 4	Placebo = 5

^a $P < .05$, T-test.

TABLE 3

Hot flash frequencies by week as percent of baseline adjusted for BMI

Week	Group (means $\pm$ SD)	
	Active Drug (n = 12)	Placebo (n = 14)
1	100%	100%
2	91.8% $\pm$ 35.0	120.4% $\pm$ 20.5
3	96.3% $\pm$ 41.5	104.2% $\pm$ 22.6
8	85.6% $\pm$ 28.3	106.7% $\pm$ 30.4

TABLE 4

Hot flash frequencies by week (number of hot flashes/24h)

Week	Group (means $\pm$ SD)	
	Active Drug (n = 12)	Placebo (n = 14)
1	20.6 $\pm$ 5.2	20.0 $\pm$ 5.4
2	19.1 $\pm$ 6.5	23.3 $\pm$ 6.3
3	19.4 $\pm$ 7.0	19.9 $\pm$ 4.8
8	16.9 $\pm$ 4.5	21.4 $\pm$ 8.5