Effect of escitalopram on hot flash interference: a randomized, controlled trial

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Objective: To estimate the effect of escitalopram (10–20 mg/d) versus placebo for reducing hot flash interference in daily life and understand correlates and predictors of reductions in hot flash interference, a key measure of quality of life.
Design: Multisite, randomized, double-blind, placebo-controlled clinical trial.
Setting: MsFLASH clinical sites in Boston, Indianapolis, Oakland, and Philadelphia.
Patient(s): A total of 205 midlife women (46% African-American) who met criteria participated.
Intervention(s): After baseline, women were randomized to one pill of escitalopram 10 mg/d (n = 104) or placebo (n = 101) with follow-up at 4 and 8 weeks. At week 4, those not achieving 50% fewer hot flashes were increased to two pills daily (20 mg/d or 2 placebo pills).
Main Outcome Measure(s): The Hot Flash Related Daily Interference Scale; correlates were variables from hot flash diaries; predictors were baseline demographics, clinical variables, depression, anxiety, sleep quality, and hot flashes.
Result(s): Compared to placebo, escitalopram significantly reduced hot flash interference by 6.0 points at week 4 and 3.4 points at week 8 more than placebo. Reductions in hot flash interference correlated with changes in hot flash diary variables. However, baseline variables did not significantly predict reductions in hot flash interference.
Conclusion(s): Escitalopram (10–20 mg/d) for 8 weeks improves women's quality of life and this benefit did not vary by demographic, clinical, mood, sleep, or hot flash variables.
Clinical Trial Registration Number: NCT00894543. (Fertil Steril® 2012;97:1399–404. ©2012 by American Society for Reproductive Medicine.)
Key Words: Menopause, hot flashes, night sweats, selective serotonin reuptake inhibitor

The only current US Food and Drug Administration approved therapy for vasomotor symptoms in menopausal women is menopausal hormone therapy (HT). Evidence for the efficacy of selective serotonin reuptake inhibitors (SSRI) in alleviating vasomotor symptoms is growing. However, the range of outcomes in existing reports is limited. Only a few SSRI studies have examined improvements in hot flash interference (1, 2) or the degree to which hot flashes are disruptive to a woman's daily life. Hot flash interference is an essential factor in women's quality of life at menopause (3). Studies have shown that hot flash interference can be reduced with pharmacologic treatments, dietary supplements, and behavioral therapies (1, 2, 4–6), thus it is likely to improve with SSRI therapies. Identifying the therapeutic effects of SSRIs for hot flash interference could help guide clinical practice and outcome measurement in future trials.

The MsFLASH investigative group recently published the primary report of a randomized, double-blind, placebo-controlled clinical trial of escitalopram for vasomotor symptoms in perimenopausal and postmenopausal women. Escitalopram reduced the mean hot flash frequency, severity, and bother relative to placebo, but hot flash interference on daily life was not examined (7).

The main objective of the present study was to estimate the effect of escitalopram relative to placebo for reducing hot flash interference. The hypothesis was that escitalopram would reduce hot flash interference compared to placebo. Exploratory objectives were to 1) examine correlations between

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reductions in hot flash interference and other hot flash variables and 2) determine whether baseline demographic, clinical, and symptom variables predicted reductions in hot flash interference. The a priori hypotheses were that 1) reductions in hot flash interference would correlate with changes in vasomotor symptom variables and 2) age, body mass index (BMI), race, menopausal status, smoking status, alcohol use, depressive symptoms, anxiety, sleep quality, and vasomotor symptoms might predict the effect of escitalopram on hot flash interference.

MATERIALS AND METHODS

Design Overview

This was a multisite, randomized, placebo-controlled, double-blind clinical trial of a SSRI for menopausal hot flashes, with enrollment stratified by clinical site and self-reported race. Women who were eligible after daily ratings of hot flash frequency and severity for 3 screening weeks were randomized in equal proportions to receive 10 mg of escitalopram or a matching placebo pill daily for 8 weeks. Follow-up visits were conducted at 4 and 8 weeks. A telephone contact was made a week after randomization to assess protocol adherence and adverse events. Another telephone contact occurred at week 11 (3 weeks after stopping study treatment) to evaluate return of symptoms, adverse events, and withdrawal symptoms. Participants were compensated after completed visits up to $180.

The study was approved by the institutional review board at each participating site and the data coordinating center. All participants provided written informed consent and authorization to use health information.

Setting and Participants

Participants were recruited primarily by mass mailings from July 2009 to June 2010 at four MsFLASH research network clinical sites in Boston, MA; Indianapolis, IN; Oakland, CA; and Philadelphia, PA.

Eligible women were aged 40–62 years, postmenopausal ($\geq$12 months since the last menstrual period or bilateral oophorectomy) or in the late menopausal transition (amenorrhea $\geq$60 days in the past year), and were in good general health, as determined by medical history, brief physical examination, and standard blood tests. The study criteria for hot flashes were at least 28 hot flashes or night sweats per week recorded on daily diaries for 3 weeks; hot flashes or night sweats rated as bothersome or severe on 4 or more days per week; and hot flash/night sweat frequency in week 3 did not decrease by more than 50% from the mean weekly levels in weeks 1 and 2. Criteria were for overall total hot flashes (daytime plus nighttime).

Exclusion criteria included psychotropic medications or any hot flash treatments including herbals and over-the-counter in the past 30 days, HT, hormonal contraceptives, selective estrogen receptor (ER) modulators or aromatase inhibitors in the past 2 months; current severe medical illness or major depressive episode, drug or alcohol abuse in the past year, suicide attempt in the past 3 years, lifetime diagnosis of bipolar disorder or psychosis; uncontrolled hypertension, history of endometrial or ovarian cancer; or myocardial infarction, angina, cerebral vascular events, or other preexisting medical conditions.

Randomization and Interventions

At the second screening visit, eligible women were randomized using a dynamic algorithm, stratified by clinic and self-reported race, in a 1:1 ratio to treatment groups of escitalopram (10 mg/d) or identical-appearing placebo for 8 weeks. Participants, investigators, and clinical center staff were blinded to participants' treatment assignment. A dose escalation occurred after 4 weeks to two pills daily (e.g., 20 mg/d or 2 placebo pills) for women who did not achieve at least 50% reduction in hot flash frequency or had no decrease in severity, unless precluded by unacceptable side effects. After 8 weeks of treatment, women taking one pill per day stopped taking pills and those taking two pills per day tapered the dose during 1 week.

Outcomes and Follow-up

Hot flash interference was assessed using the 10-item Hot Flash Related Daily Interference Scale (HFRDIS) (3) at baseline and 4 and 8 weeks of treatment. Participants rated the degree to which hot flashes interfered with nine daily life activities (work, social activities, leisure activities, sleep, mood, concentration, relations with others, sexuality, enjoyment of life) and overall quality of life during the previous week. Women rated each item from 0 (do not interfere) to 10 (completely interfere). This unidimensional scale is best represented by an overall total score with possible range of 0 to 100. Cronbach's alphas in this study were 0.95 for African-American women and 0.91 for white women.

Secondary outcomes included correlations between hot flash interference and daytime and nighttime hot flash frequency, severity, bother, and the number of flash-free days and flash-free nights. These variables were created from daily diary reports. Daytime flashes were recorded at bedtime before falling asleep. Nighttime flashes were recorded upon awakening in the morning. Daytime and nighttime severities were assessed using a scale of 1 mild, 2 moderate, and 3 severe. Daytime and nighttime bother were assessed using a scale of 1 none, 2 a little, 3 moderately, and 4 a lot. Daytime hot flash variables were calculated as the mean for each day in the first 2 screening weeks (baseline) or during the 7 days before each visit (4 and 8 weeks). Nighttime hot flash variables were calculated in the same manner. The number of flash-free days and nights was calculated as the number of days or nights with recording of no hot flashes. Participants who did not complete the hot flash diary on 1 or more days in the week had their number of flash-free days or nights set to missing.

Potential predictors were taken from daily diaries as described and questionnaires assessing baseline demographics, menopausal characteristics, depressive symptoms, anxiety, and sleep quality. Well-validated measures included the nine-item depression scale from the Patient Health

TABLE 1

Baseline characteristics by treatment group.

Baseline characteristic[a]	Escitalopram (N = 104) N (%)		Placebo (N = 101) N (%)	
Age (y), mean ± SD	53.45 (4.20)		54.36 (3.86)	
<50	16	15.4	8	7.9
50–54	48	46.2	47	46.5
55–59	30	28.8	36	35.6
60+	10	9.6	10	9.9
Race				
White	53	51.0	49	48.5
African American	47	45.2	48	47.5
Other/unknown	4	3.8	4	4.0
Site				
Boston	24	23.1	19	18.8
Indianapolis	17	16.3	18	17.8
Oakland	31	29.8	26	25.7
Philadelphia	32	30.8	38	37.6
BMI (m/kg^2), mean ± SD	28.58 (6.59)		29.70 (6.42)	
<25	32	30.8	22	21.8
25–<30	34	32.7	38	37.6
≥30	38	36.5	40	39.6
Education				
≤High school diploma or GED	15	14.4	23	22.8
School/training after high school	46	44.2	41	40.6
College graduate	43	41.3	37	36.6
Employment status				
Full-time	48	46.2	46	45.5
Part-time	19	18.3	16	15.8
Not currently working	32	30.8	34	33.6
Other	5	4.8	5	5.0
Marital status				
Never married	18	17.3	13	12.9
Divorced	18	17.3	26	25.7
Widowed	4	3.8	6	5.9
Married or living with partner	64	61.5	56	55.4
Menopausal status				
Postmenopause	84	80.8	83	82.2
Late transition	17	16.3	15	14.9
Early transition	3	2.9	3	3.0
Smoking status				
Never	53	51.0	46	45.5
Past	30	28.8	29	28.7
Current	21	20.2	26	25.7
Alcohol use				
0	41	39.4	41	40.6
1–<7	51	49.0	41	40.6
7+	12	11.5	17	16.8
PHQ-9 depression score, mean ± SD	3.24 (3.06)		2.94 (3.24)	
No depression (0–4)	76	73.1	77	76.2
Mild depression (5–9)	24	23.1	15	14.9
Moderate+ depression (10–13)	4	3.8	8	7.9
GAD-7 anxiety score, mean ± SD	2.50 (3.34)		2.19 (3.33)	
No anxiety (0–4)	80	76.9	82	81.2
Mild anxiety (5–9)	19	18.3	15	14.9
Moderate+ anxiety (10–19)	5	4.8	4	4.0
PSQI sleep index, mean ± SD	8.23 (3.56)		7.78 (3.92)	
Good sleep quality (PSQI <5)	15	14.4	25	24.8
Poor sleep quality (PSQI ≥5)	77	74.0	64	63.4

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TABLE 1

Continued.

Baseline characteristic[a]	Escitalopram (N = 104) N (%)		Placebo (N = 101) N (%)	
Daytime hot flash frequency, mean ± SD	5.90 (4.00)		5.60 (3.20)	
≤5	58	55.8	48	47.5
>5	46	44.2	52	51.5
Nighttime hot flash frequency, mean ± SD	3.83 (2.82)		4.08 (2.32)	
≤3.5	60	57.7	53	52.5
>3.5	43	41.3	48	47.5

Note: BMI = body mass index; GAD = Generalized Anxiety Disorders; GED = General Equivalency Diploma; PSQI = Pittsburgh Sleep Quality Index; SD = standard deviation.

[a] $P>.10$ for all comparisons by treatment group as tested by t test or χ^2 test.

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Questionnaire (8–10), the seven-item Generalized Anxiety Disorders scale with cut points of 5, 10, and 15 representing mild, moderate, and severe anxiety symptoms (11, 12), and the 19-item Pittsburgh Sleep Quality Index with global scores >5 indicative of poor sleep quality and >8 poor sleep quality and daytime fatigue (13–15).

After a brief telephone screen, eligible volunteers were mailed a baseline questionnaire to assess self-reported health and demographics and a daily diary to record hot flash frequency, severity, and bother each morning and evening for 2 weeks. Women who remained eligible were scheduled for two screening visits within a 2- to 3-week interval and continued to rate hot flashes in the daily diaries for a total of 3 screening weeks.

At the study visits, written consent was obtained, symptoms and health were reviewed, a urine pregnancy test, and blood samples were obtained for safety laboratory tests, and a brief physical examination was conducted. After randomization, a telephone contact was made at 1 week (to assess protocol adherence and adverse events) and clinic visits were conducted at 4 and 8 weeks.

Statistical Analysis

All randomized participants with data available at follow-up times, which were collected irrespective of adherence to study medication, were included in the models for intent-to-treat analysis. Baseline characteristics were compared between treatment groups using t-tests or χ^2 tests. The primary analysis consisted of the treatment arm contrast from a linear regression model summarizing hot flash interference at weeks 4 and 8 as a function of treatment assignment and baseline hot flash interference, and adjusted for race and clinical site. Robust standard errors were calculated by generalized estimating equations to account for correlation between repeated measures from each participant. Pearson's correlation coefficients were used to test association between changes in hot flash interference and changes in vasomotor symptom variables. Change was calculated as the difference between baseline and 8 week scores. Tests of interaction between

TABLE 2

Treatment arm differences at weeks 4 and 8.

	Escitalopram		Placebo		Difference	
	N	Mean (95% CI)	N	Mean (95% CI)	Mean (95% CI)	*P* value[a]
HFRDIS total[b]						.012
Baseline	99	37.3 (32.8 to 41.8)	94	38.6 (33.4 to 43.7)	1.3 (−8.1 to 5.5)	
Week 4 to baseline	96	−18.0 (−22.3 to −13.6)	93	−12.0 (−16.2 to −7.8)	−6.0 (−12.0 to 0.1)	
Week 8 to baseline	96	−18.1 (−22.5 to −13.6)	88	−14.6 (−19.6 to −9.6)	−3.4 (−10.1 to 3.2)	

[a] *P* values from comparison of escitalopram versus placebo in a linear model of the outcome as a function of intervention arm and adjusted for race, clinical center, baseline outcome, and visit (week 4 or 8).
[b] Hot Flash Related Daily Interference Scale (HFRDIS) total possible range is 0–100.

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treatment assignment and predictors were performed within the linear regression models estimating mean week 4 and 8 HFRDIS as a function of treatment arm, the covariate of interest and the interaction between treatment assignment and covariate; models were adjusted for baseline hot flash interference, race (except in race subgroups), and site.

The planned sample size of the trial (90 women per treatment group) was determined by the primary trial end points (hot flash frequency and severity) to provide 90% power with alpha at 0.025 and 0.52 effect size. Reported *P* values are based on the Wald statistic. Analyses were conducted using SAS version 9.2 (SAS Institute) with two-sided *P* value $<.05$ considered statistically significant. Secondary analyses are considered exploratory and should be interpreted with caution.

RESULTS

Supplemental Figure 1 (available online) shows that of 205 women randomized to escitalopram or placebo treatment, 201 (98%) provided HFRDIS and diary data, with 190 (93%) having HFRDIS scores at follow-up for analysis. There were no statistically significant differences in baseline characteristics between treatment groups (Table 1).

Escitalopram significantly reduced hot flash interference during the course of the trial compared with placebo after adjusting for race, site, and baseline interference ($P=.012$; effect size = 0.15). The mean hot flash interference score was reduced 18 points in the escitalopram group or 6.0 points more in the escitalopram group compared with the placebo group at week 4 and 3.4 points more at week 8 (Table 2).

Reductions in hot flash interference were significantly correlated with reductions in daytime and nighttime hot flash frequency, severity, and bother (Table 3). Reductions in hot flash interference were also significantly correlated with more flash-free days but not with flash-free nights (Table 3). The greatest absolute correlation value was between hot flash interference and daytime hot flash severity ($r = 0.42$), followed by daytime bother ($r = 0.37$).

Baseline participant characteristics did not significantly modify the effect of escitalopram on reductions in hot flash interference (Table 4). There was no significant interaction between treatment assignment and age, BMI, race, menopausal status, smoking status, depressive or anxiety symptoms, sleep quality, or baseline hot flashes ($P\geq.15$). There was a nonsignificant trend for greater reduction in hot flash interference with escitalopram among women who reported a greater number of drinks per week ($P=.05$).

DISCUSSION

Findings that escitalopram (10–20 mg/d) significantly reduced hot flash interference in daily life, a key marker of quality of life, extend knowledge from previous SSRI studies and other non-SSRI treatment studies. Other studies of SSRIs have not included the HFRDIS (16–19) or did not report mean change in HFRDIS total scores. When compared to published reports of selective norepinephrine reuptake inhibitor (SNRI) or behavioral therapies, the effect of escitalopram on hot flash interference in this study was larger than that for 37.5 mg/d of venlafaxine versus placebo (1), smaller than that for 75 mg/d of venlafaxine versus placebo (1), and smaller than that for hypnosis versus no treatment (4). There were no published estrogen (E) trials using the HFRDIS as an outcome measure, although one study of tibolone reported decreased hot flash interference using a 5-point scale (20). The mean change in hot flash interference with escitalopram treatment in this study (mean 18.1 points change) was similar to changes seen with omega-3 supplementation (mean 18.5 points change) (6) and mindfulness-based stress reduction (mean 15 point change) (21).

TABLE 3

Correlations between change in hot flash interference and change in other hot flash variables.

	Change in hot flash interference
Change in daytime frequency	0.24[a]
Change in nighttime frequency	0.28[b]
Change in daytime severity	0.42[b]
Change in nighttime severity	0.36[b]
Change in daytime bother	0.37[b]
Change in nighttime bother	0.33[b]
Change in flash-free days	−0.28[b]
Change in flash-free nights	−0.14

Note: All changes are calculated as the difference between baseline and 8 weeks.
[a] $P<.01$.
[b] $P<.001$.

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TABLE 4

HFRDIS differences at weeks 4 and 8 as a function of treatment assignment, subgroups, and their interactions.

Subgroup	Escitalopram (n)	Placebo (n)	Estimate[a]	95% CI[a]		*P* value[a]
Age (y)						.15
<55	60	50	−7.31	−13.36	−1.26	
≥55	36	38	−3.66	−9.42	2.10	
BMI						.82
<25	29	21	−6.24	−13.85	1.36	
25–<30	29	30	−6.01	−12.92	0.91	
≥30	38	36	−5.78	−13.47	1.91	
Race[b]						.37
White	51	43	−7.73	−13.49	−1.96	
African American	41	42	−3.55	−10.65	3.56	
Other/unknown	4	3	−5.83	−17.12	5.46	
Menopausal status						.68
Postmenopausal	77	71	−5.38	−10.30	−0.46	
Transition	19	17	−7.38	−15.70	0.95	
Smoking status						.45
Never	48	41	−5.26	−11.13	0.62	
Past	30	27	−8.99	−16.32	−1.65	
Current	18	20	−0.83	−11.36	9.69	
Alcohol use						.05
0	35	36	0.27	−6.82	7.35	
1–<7	49	36	−7.94	−14.22	−1.65	
7+	12	16	−14.85	−24.38	−5.32	
PHQ depression						.27
0–4	70	67	−7.35	−12.07	−2.63	
5–13	26	21	−2.14	−11.76	7.47	
GAD-7 anxiety						.40
0–4	73	70	−6.65	−11.25	−2.05	
5–19	23	18	−4.20	−13.94	5.55	
PSQI sleep						.20
<5	13	21	−8.31	−15.78	−0.84	
≥5	73	60	−4.88	−10.47	0.72	
Daytime flash severity						.65
≤2.00	52	42	−5.20	−10.71	0.31	
>2.00	44	44	−5.72	−12.60	1.16	
Nighttime flash severity						.63
≤2.21	47	46	−8.76	−13.60	−3.91	
>2.21	48	42	−3.21	−10.54	4.12	
Daytime flash bother						.40
≤3.00	55	48	−4.02	−9.22	1.18	
>3.00	41	38	−7.70	−15.09	−0.30	
Nighttime flash bother						.68
≤3.15	48	47	−7.21	−12.35	−2.07	
>3.15	47	41	−4.61	−11.78	2.55	

Note: BMI = body mass index; HFRDIS = Hot Flash Related Daily Interference Scale; PHQ = Perceived Health Questionnaire; GAD = Generalized Anxiety Disorders; PSQI = Pittsburgh Sleep Quality Index.

[a] Treatment effect estimates, corresponding confidence intervals (CI), and interaction *P* values are from a repeated measures linear model of weeks 4 and 8 HFRDIS as a function of treatment assignment and baseline HFRDIS score, adjusted for ethnicity, clinical center, and visit (week 4 or 8). When possible, *P* values were computed from separate interaction models with the interaction between treatment arm and the continuous form of the subgroup.

[b] *P* value calculated for difference between white and African-American participants.

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As hypothesized, changes in hot flash interference during the course of the trial were significantly correlated with changes in other hot flash variables. In addition to evaluating hot flash variables that are commonly reported in other studies (22), this report evaluated correlations between hot flash interference and newly conceptualized variables—the number of flash-free days and flash-free nights. In general, hot flash interference scores were more highly correlated with the daytime measure of each variable than with the nighttime measure (e.g., severity, bother, flash-free times). The greater correlation with daytime measures may reflect the central role that hot flash interference plays in a woman's quality of life, with items inclusive of mainly daytime activities (work, social activities, leisure activities, mood, concentration, relations with others, sexuality, and enjoyment of life) rather than nighttime activities (sleep).

The fact that treatment effects did not vary by baseline demographic, clinical, or symptom variables is important clinically as it suggests that escitalopram's effect may be similar across diverse menopausal patient populations. Clinicians can use these findings to educate women about anticipated treatment effects for quality of life. The modest but nonsignificant effect of higher alcohol use on escitalopram may reflect a potential interaction between escitalopram and alcohol. Escitalopram labeling warns that alcohol may potentiate the central nervous system effects of escitalopram. Although

alcohol is a known inducer of CYP2E1, escitalopram is not metabolized by CYP2E1 and instead is metabolized through CYP2D6, 2C19, and 3A4 (23). Thus, any interaction is likely due to direct central nervous system effects rather than changes in drug metabolism.

Escitalopram and other SSRI antidepressants do not reduce bone loss like menopausal HT. Menopausal symptom management decision making should take into consideration a woman's individual preferences, values, and total health care goals.

Limitations

Findings should be interpreted in light of study strengths and limitations. Equal numbers of African-American and white women were included in this study, but findings may not be generalizable to other racial or ethnic groups. The strengths of using multiple sites to increase representativeness are offset by the fact that subjects were a select group of community-based volunteers. The advantage of using a stepped dosing approach is offset by the relatively short, 8-week duration of the trial. There may be additional moderators of treatment response that were not considered in our data collection of analyses.

In summary, this report expands on the available data related to the effects of SSRI for menopausal symptoms. Escitalopram reduced hot flash interference, a key component of women's quality of life at menopause. Including a measure of hot flash interference in future clinical trials may be useful in understanding improvements in quality of life with various vasomotor symptom therapies.

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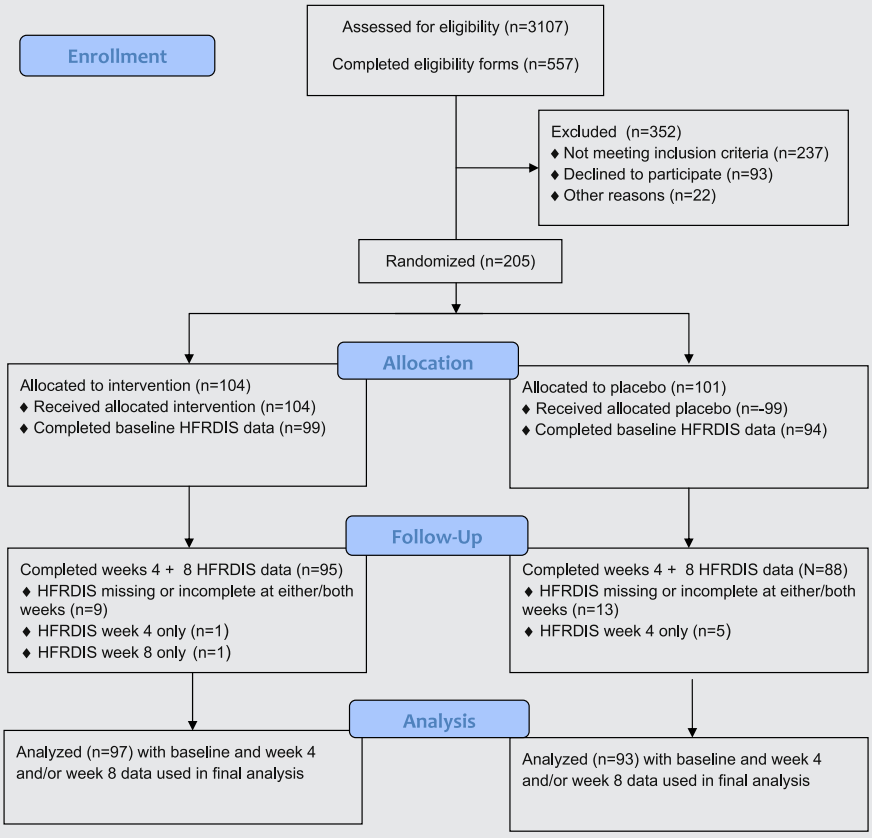
SUPPLEMENTAL FIGURE 1



CONSORT diagram showing the flow of participants through the study.

Carpenter. Escitalopram for hot flash interference. Fertil Steril 2012.