SSRIs for Hot Flashes: A Systematic Review and Meta-Analysis of Randomized Trials

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BACKGROUND: Hot flashes are the most commonly reported vasomotor symptom during the peri- and early post-menopausal period.

OBJECTIVES: To systematically review, appraise and summarize the evidence of the impact of different SSRIs on peri-menopausal hot flashes in healthy women in randomized, controlled trials.

METHODS: A comprehensive literature search was conducted of MEDLINE™, EMBASE, the Cochrane Central Register of Controlled Trials, Web of Science and Scopus through March 2013. Two independent reviewers selected studies and extracted data. Random effects meta-analysis was used to pool outcomes across studies, and Bayesian mixed treatment methods were used to rank SSRIs in terms of effectiveness.

RESULTS: We included a total of 11 randomized controlled trials with good methodological quality enrolling 2,069 menopausal and post-menopausal women (follow-up 1–9 months, mean age 36–76 years, mean time since menopause 2.3–6.6 years). Compared with placebo, SSRIs were associated with a statistically significant decrease in hot flash frequency (difference in means −0.93; 95 % CI −1.46 to −0.37; I^2 = 21 %) and severity assessed by various scales (standardized difference in means −0.34; 95 % CI −0.59 to −0.10; I^2 = 47 %). Adverse events did not differ from placebo. Mixed treatment comparison analysis demonstrated the superiority of escitalopram compared to other SSRIs in terms of efficacy.

CONCLUSION: SSRI use is associated with modest improvement in the severity and frequency of hot flashes but can also be associated with the typical profile of SSRI adverse effects.

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Received December 6, 2012
Revised April 19, 2013
Accepted May 14, 2013
Published online July 26, 2013

KEY WORDS: SSRI; hot flashes; menopause.
J Gen Intern Med 29(1):204–13
DOI: 10.1007/s11606-013-2535-9

INTRODUCTION

Hot flashes remain the most commonly reported vasomotor symptom during peri- and early post-menopausal period.[1] For some women, they can lead to significant physical distress and functional impairment requiring medical intervention.[2] Hot flashes are described as spontaneous sensations of warmth affecting the face, neck and upper chest, and are often associated with palpitation, sweating and anxiety. Although the exact pathophysiology is unknown, estrogen withdrawal, rather than low circulating estrogen levels, has been thought to cause central thermoregulatory center dysfunction, which eventually will lead to hot flashes.[3] This process is regulated by multiple neurotransmitters, norepinephrine being the primary neurotransmitter responsible for lowering the thermoregulatory set point and triggering the heat loss mechanisms as described before.[4]

Hormone replacement therapy (HRT) is the most effective and standard treatment for vasomotor symptoms of menopause.[5] However, a randomized controlled trial of 16,608 post-menopausal women receiving estrogen and progesterone HRT versus placebo showed an increased hazard ratio of coronary heart disease and breast cancer, which were present across racial/ethnic and age strata and were not influenced by the antecedent risk status or prior disease. HRT also showed increased risk of stroke and pulmonary embolism. The risk was not counterbalanced by the smaller reduction in the number of hip fractures and colorectal cancer.[6] Because of the concerns regarding the safety of HRT, the interest in alternative therapies for improving menopausal symptoms was increased. Such alternatives include stress management, chiropractic interventions, soy supplements and acupuncture; however, evidence of their efficacy is inconclusive.[7]

Other pharmacological interventions with possible benefit include clonidine, selective serotonin reuptake inhibitors (SSRIs), selective nor-epinephrine reuptake inhibitors and anticonvulsants.[8] SSRIs seem to be an attractive alternative in this setting because of their wide use and favorable safety profile demonstrated in various settings. Nevertheless, studies of SSRIs have demonstrated mixed results; some studies demonstrated benefit by reducing hot flashes by 50–60 % while others reported no effect.[9–11]

Therefore, we conducted a systematic review to synthesize and summarize the best available evidence on the use of SSRIs to treat hot flashes in healthy menopausal women. The aim of this comparative effectiveness review is to evaluate the efficacy and side effect profile to aid in decision making.

METHODS

The study was performed following procedures recommended by the Cochrane collaboration[12] and is reported in accordance with the recommendations set forth by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[13]

Eligibility Criteria

We included randomized controlled trials that enrolled healthy peri-menopausal women at the beginning of the study who received any SSRI medications (e.g., citalopram, escitalopram, fluoxetine, paroxetine, sertraline, etc.), compared them against placebo or other SSRIs, and evaluated vasomotor symptoms (daily hot flash frequency or improvement in vasomotor scores). We specifically excluded studies that enrolled cancer patients and patients receiving selective estrogen receptor modulators (SERMs) because hot flashes and night sweats are common complaints (up to 80 %) of patients receiving tamoxifen for breast cancer,[14–16] women taking hormonal replacement therapy and patients with diagnoses of depression.

Information Sources and Search Methods

A comprehensive literature search was conducted by an expert reference librarian. We searched the electronic databases (MEDLINE™, EMBASE, the Cochrane Central Register of Controlled Trials CENTRAL, Web of Science and Scopus) using various combinations of controlled terms: "menopause," post-menopause," "peri-menopause", "hot flushes," "hot flashes," "SSRIs," "climacteric" and "vasomotor." No limits were applied for publication date or language, and foreign papers were translated. We searched through March 2013.

Study Identification

Previously described data sources were searched by two independent reviewers (TS & BF); they reviewed the abstracts, agreed on a-priori eligibility criteria including the inclusion and exclusion criteria of each study and decided which of the eligible studies to include. Disagreements between reviewers were resolved by consensus. The kappa statistic for agreement on study selection was 0.87. If a study was deemed relevant, the manuscript was obtained and reviewed in full text versions for further assessment. The final search identified 61 RCTs; of these, 11 fulfilled the inclusion criteria (Fig. 1).

Data Collection and Extraction

Data from included studies were extracted by two independent reviewers (TS and FH) using a standardized, piloted data extraction sheet. We abstracted data on patient demographics and baseline characteristics (including age, menopause status, race, smoking status and body mass index); study design; sample size; intervention type [including type and dose of the SSRI (selective serotonin reuptake inhibitor) versus placebo or versus the type and dose of another SSRI]; type of outcome measure (including the frequency of hot flashes, improvement in the vasomotor score of a validated scale).

One review author extracted the data from included studies, and a second author verified the extracted data. Disagreements were resolved by discussion between the two review authors. The number of events in each trial was extracted, when available, on the basis of the intention-to-treat approach. For collected and abstracted data, please see Table 1.

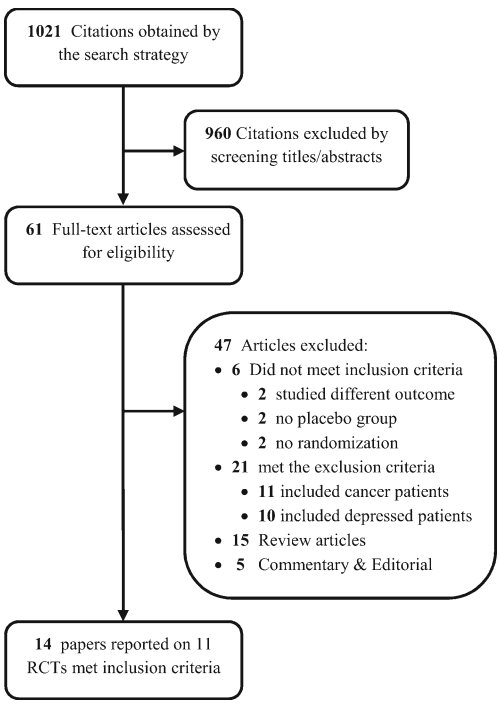

Figure 1. Flow chart of the study.

Table 1. Characteristics of Included Studies

Study ID	Origin	Sample size	Study arms	Primary outcomes	Age (years; range or mean ± SD)	Frequency of hot flashes at baseline	Time since menopause (years; mean)	Race (%)	Smoking (%)	BMI (mean ± SD)	Treatment max duration
Paroxetine (3 trials)											
Simon 2012	USA	568	Arm 1: low-dose mesylate salt of paroxetine (LDMP) 7.5 mg/day Arm 2: Placebo	Frequency and severity of HF	54.4±5.6	10.86±3.91	-	75.5 % white; 21.5 % AA; 3 % others	-	28.14±5	24 weeks
Kaunitz 2012	USA	606	Arm 1: LDMP 7.5 mg/day Arm 2: Placebo	Frequency and severity of HF	54.7±6.1	11.72±4.63	-	64.7 % white; 32.8 % AA; 2.5 % others	-	29.5±6.1	12 weeks
Stearns 2003	USA	165	Arm 1: paroxetine 12.5 mg /day Arm 2: paroxetine 25 mg /day Arm 3: placebo	Frequency of HF, disability score and adverse events	36-76	-	-	78 %≥12 months	-	-	6 weeks
Escitalopram (2 trials)											
Freeman 2011	USA	205	Arm 1: escitalopram 10–20 mg/day Arm 2: placebo	Frequency of HF/day and HF severity score	40-62	9.77±5.62	Postmenopause 81 %; late transition 15 %; early transition 3 %	50 % white; 46 % AA; 6 % others	23	29.1±6	8 weeks
Freedman 2011	USA	26	Arm 1: escitalopram 10–20 mg/day Arm 2: placebo	Frequency of HF/day	49-59	20.28±5.31	5.8±4	26 % white; 71 % AA; 0.2 % Hispanic	-	26.8±3	8 weeks
Citalopram (3 trials); fluoxetine (1 trial)											
Akhavan 2011	Iran	80	Arm 1: cipram Arm 2: cipram plus HT Arm 3: placebo Arm 4: placebo plus HT	Frequency of HF/day	51.4±3.5	15.0±3.0	3.3±1	-	-	-	8 weeks
Kalay 2007	Turkey	50	Arm 1: cipram Arm 2: cipram plus HT Arm 3: placebo Arm 4: placebo plus HT	Frequency of HF/day and MENQOL HF score	53±4.5	7.39±0.8	6.6±4	-	15	27.8±4	8 weeks
Suvanto-Luukkonen 2005	Finland	150	Arm 1: citalopram Arm 2: fluoxetine Arm 3: placebo	Frequency of HF/day and Modified Kupperman-index	45-66	5.51±2.25	4±4	-	25	-	36 weeks
Sertraline (3 trials)											
Aedo 2011	Chile	33	Arm 1: sertraline 50 mg/day Arm 2: placebo	Somatic menopause score	45-60	-	2.3±4	-	6	28.3±3	13 weeks
Grady 2007	USA	89	Arm 1: sertraline 100 mg/day Arm 2: placebo	Frequency of HF/day and hot flash score	40-60	8.95±5.78	3.5±4	57 % white; 26 % AA; 17 % others	23	-	6 weeks
Gordon 2006	USA	97	Arm 1: sertraline 50 mg/day Arm 2: placebo	Frequency of HF/day and hot flash score	40-65	6.7±4.26	-	80 % white; 13 % Hispanic; 6 % others	16	-	8 weeks (4 weeks each crossover period)

Risk of Bias Assessment

Methodological quality was defined as the control of bias assessed through the reported methods in each individual trial. Two reviewers independently assessed trial quality by examining several components: generation of allocation sequence (classified as adequate if based on computer-generated random numbers, tables of random numbers or similar), concealment of allocation (classified as adequate if based on central randomization, sealed envelopes or similar), blinding (patients, care givers or outcome assessors), baseline imbalance and lost to follow-up. Disagreements between the reviewers were resolved by discussion or arbitrated with a third coauthor. We used the Cochrane Collaboration's risk-of-bias tool to assess the quality of included randomized trials.[17] The two reviewers extracting risk of bias data were blinded to the study authors, institution and journal name.

Summary of Measures

Our primary outcome measure was the daily frequency of hot flashes. We also extracted hot flashes/vasomotor symptoms assessed by scores (e.g., hot flash score,[10] vasomotor score,[11] modified Kupperman index,[20] Rand mood score,[21] hot flash-related daily interference scale[22] and menopausal rating score[23]) whenever available and from those studies that did not report daily hot flash frequency.

Statistical Analysis

From each trial, we calculated the mean difference (MD) and 95 % confidence intervals (CI) as the measure of effect. When the mean response is not measured on the same scale, the standardized mean difference (SMD) was calculated allowing for pooling across trials on the same scale.[18] The average effects for the outcomes across trials was estimated using a random effects model, as described by DerSimonian.[19] We chose the random effects method as primary analysis because of its conservative summary estimate and incorporation of between- and within-study variance. We also tested the fixed-effect method to ascertain robustness of findings, and this model is mentioned only if it changed the conclusions. To assess the heterogeneity of treatment effect among trials, we used the I^2 statistic. The I^2 statistic represents the proportion of heterogeneity of treatment effect across trials that were not attributable to chance or random error. Hence, a value of 50 % reflects significant heterogeneity due to real differences in study populations, protocols, interventions and outcomes.[20] The p-value threshold for statistical significance was set at 0.05 for the effect size. The level of agreement between the reviewers was estimated using Cohen's kappa statistic, a measure of inter-rater agreement. Publication bias was evaluated using the Begg-Mazumdar rank correlation[21] and Egger's linear regression[22,23] method. Analyses were conducted using RevMan v5.1 (The Nordic Cochrane Center, Copenhagen, Denmark).

Mixed Treatment Comparison

We anticipated that the majority of the trials would include comparisons with placebo, with only few head-to-head trials. Therefore, we conducted a mixed treatment comparison (MTC) analysis. This analysis pools evidence from direct and indirect comparisons to facilitate simultaneous inference regarding all treatments.[24] MTC analysis was conducted using Bayesian methods. The goodness of fit was checked using the incoherent value. When incoherent value of the fixed-effect model or random-effect model was obtained, the model with the lower value was used. When residual deviance was similar between the two models, a random-effect model was used. The mean effect and standard error in the treatment and placebo groups of each eligible trial were conducted simultaneously using the fixed- and the random-effect Bayesian method.

For all outcomes, a burn-in of 30,000 simulations was discarded and the results presented based on a further 270,000 simulations. For each comparison, we estimated the 95 % credible intervals (CrI, the Bayesian version of the confidence intervals) of the estimates.[25] Analyses were performed using WinBUGS 1.4 statistical software (MRC Biostatistics Unit, Cambridge, UK).

RESULTS

Search Results and Study Description

A total of 1,021 potentially relevant references were identified by the electronic search strategy, of which 61 full-text articles met the eligibility for assessment. A total of 11 trials (reported in 14 papers) met the inclusion criteria and were pooled in the meta-analysis;[10,11,26–37] 47 articles were excluded. Figure 1 depicts the results of the search strategy and study selection. All included randomized trials had a parallel design and only one had a crossover design,[27] for which we only included the first arm of the crossover.

The 11 trials included 2,069 menopausal and post-menopausal women. In these trials, women were followed for a period of 1 to 9 months. Their mean age ranged from 36 to 76 years old. The mean time since menopause prior to enrollment in those trials ranged from 2.3 to 6.6 years. The most prevalent races among trials' populations are Caucasian and African American. Smoking rate ranged from 6 % to 25 %. Table 1 describes and summarizes the characteristics of the included studies.

There were four papers reported on one trial;[34–37] we referred to them as Freeman et al. Included trials reported

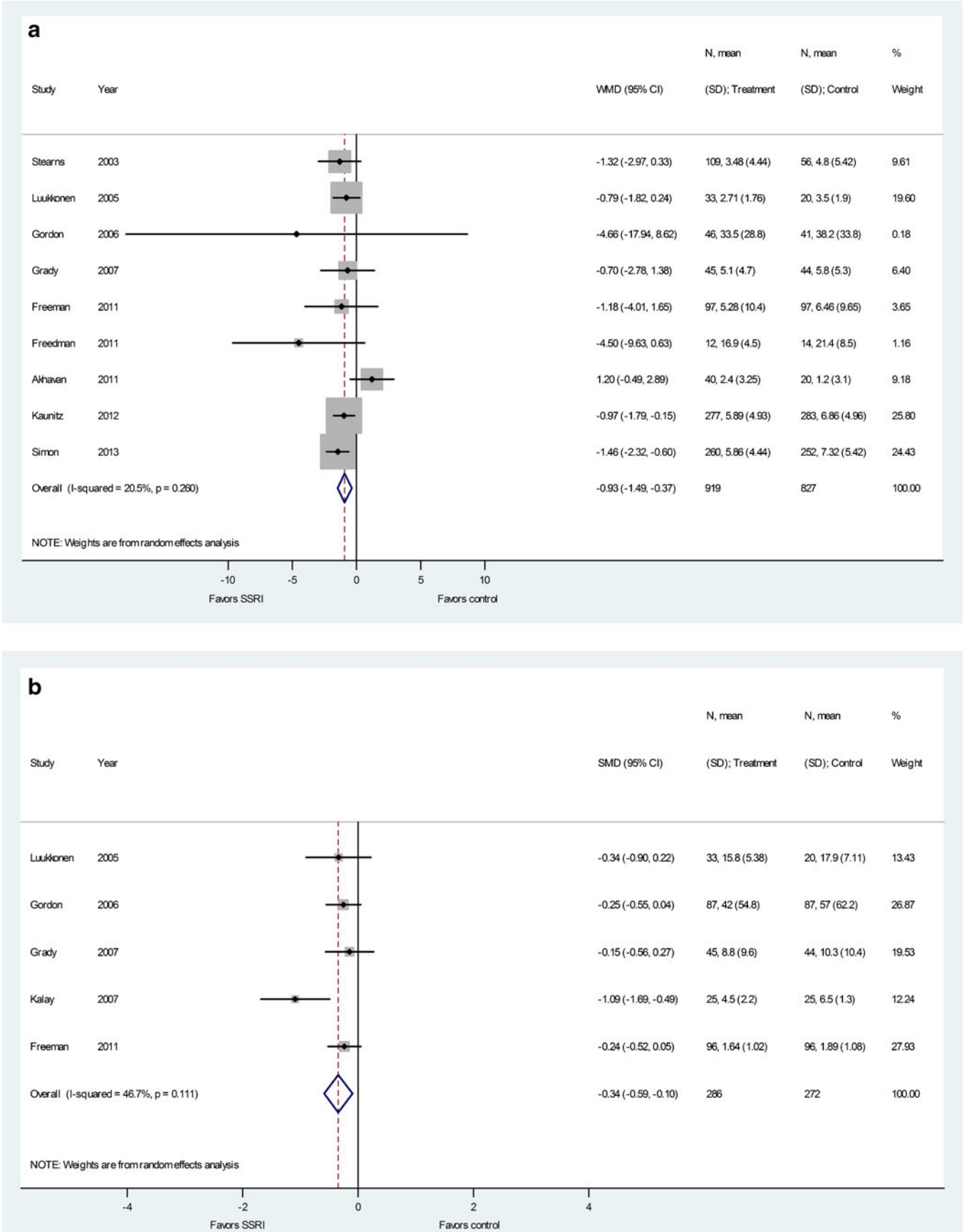

Figure 2. Meta-analyses. Panel a: Improvement in hot flash frequency per day. Panel b: Improvement in standardized hot flash scale scores. Panel c: Adverse events.

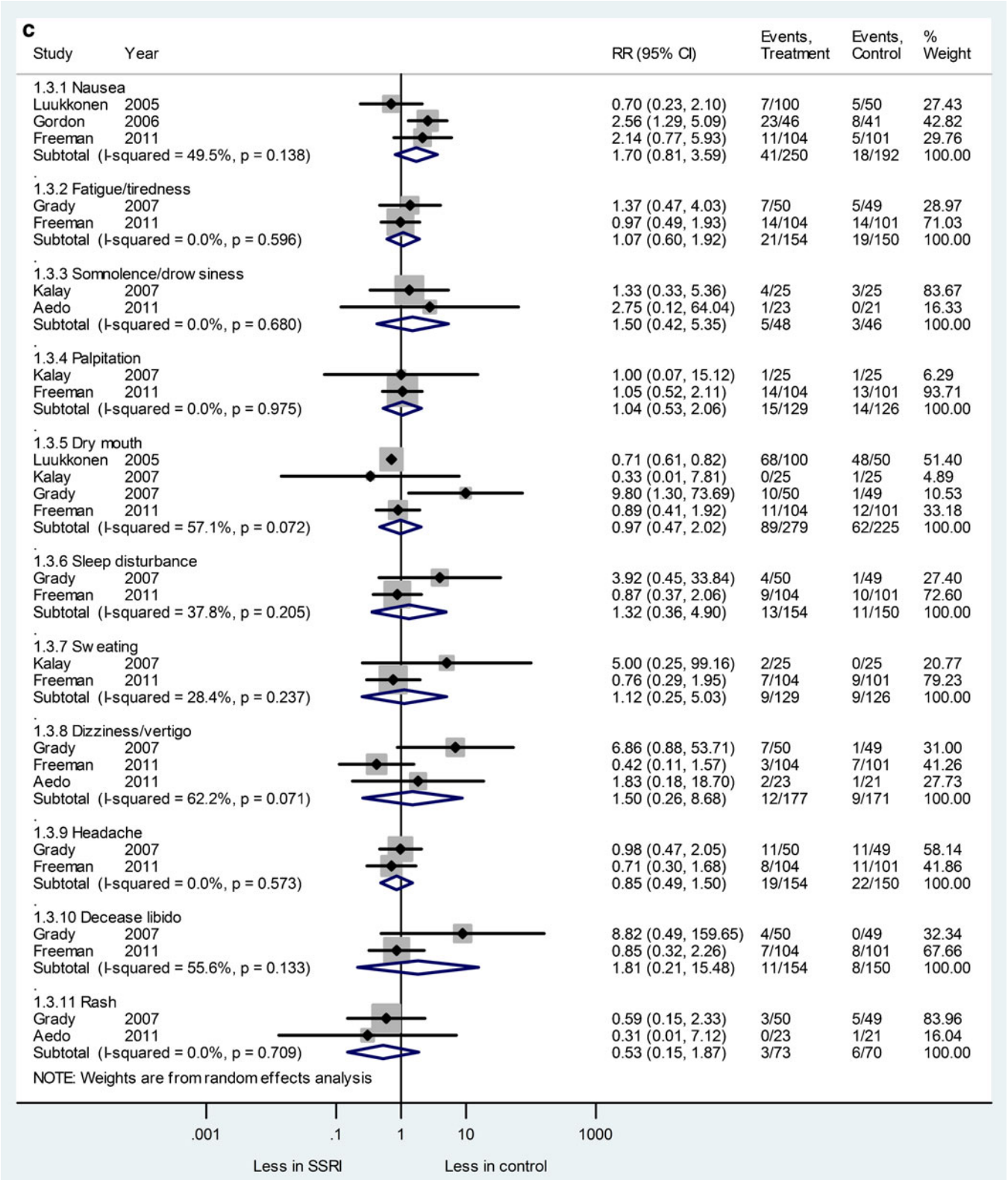

Figure 2. continued.

outcome measures at different periods: two trials reported at 6 weeks, five trials reported at 8 weeks and four trials reported at >12 weeks. We used data reported at 6- to 8-week periods. The trial by Gordon et al., reported in two papers,[27,38] is a crossover trial; outcomes were both prior to crossover (at 4 weeks) and at the end of the study (8 weeks). For frequency of hot flashes, we used data before crossover had occurred, at end of a 4-week period, which is optimal. For hot flash severity scores, data before crossover were not available, and we used the available data at the end of the

Table 2. Quality Assessment of Included Studies*

Study ID	Adequate sequence generation	Allocation concealment	Blinding	Baseline characteristics imbalance	Lost to follow-up (%)	Intention to treat analysis applied	Source of study funding	Other source of bias
Simon 2012	Yes; method not mentioned	Unclear	Double-blind at first, then single-blind after 12 days	None	12 at week 8; 102 at week 24	Mentioned	For-profit organization	Both Simon et al. and Kauntiz et al. has same co-authors from Yale Medical Group and Noven Pharmaceuticals
Kaunitz 2012	Yes; method not mentioned	Unclear	Double-blind at first, then single-blind after 12 days	None	44 at week 8; 62 at week 12	Mentioned	For-profit organization	
Freedman 2011	Yes; generated through a computer software	Yes; a distant institute kept the blinding code	Yes; the placebo and active drug capsules were identical	The active drug group had a significant higher BMI	14	Not mentioned	Non-for-profit organization	• Adverse effect of medication was not mentioned • Participant were paid for their participation
Freeman 2011	Yes; through a dynamic randomization algorithm	Yes; they used a secure web-based database	Yes; participant ants and study site personnel	None	5.4	Not mentioned	Non-for-profit organization	The dose increase if HF was not reduced ≥50 %
Akhavan 2011	Yes, they used blocked randomization	Unclear	Yes; methods unclear	There is significant difference in mean age of study groups	Unclear	Mentioned	Unclear	-
Suvanto-Luukkonen 2005	Yes; the randomization done at distant institute	Yes; opaque boxes were used	Yes; randomization codes opened only after all women had completed the study	None	36	Not mentioned	Non-for-profit organization	Some adverse effect of medication was not mentioned (only nausea and dry mouth were mentioned)
Kalay 2007	Yes; generated through a computer software	No	Yes; only participants were blinded	Kupperman index for climacteric symptoms score was higher in the Citalopram group than in placebo group	0	Not mentioned	Unclear; not reported	• The dose was increased to 40 mg/day in cases where insufficient improvement was observed. • Investigators know the treatment and the placebo groups
Grady 2007	Yes; through randomly permuted blocks	Yes; see next cell	Yes; all investigators, study staff and participants were blinded to study medication status until the trial was completed	Treatment group participants were younger, had higher percentage of African American race, and were less educated than Placebo group	10.1	Not mentioned	For-profit organization	-
Gordon 2006	Yes; method not mentioned	Yes; randomization code was not unmasked until the collection of data was completed	Yes; The randomization code was not unmasked until the collection of data was completed	None	25	Mentioned	Unclear; not reported	-
Gordon 2006	Yes; generated through a computer software	Yes; a pharmacist who had no contact with study participants determined the sequence numbers	Yes; all study participants and study personnel were blinded	None	14.7	Not mentioned	For-profit organization	Participant were paid for their participation
Stearns 2003	Yes; patients randomized in 1:1:1 ratio; method not mentioned	Unclear	Yes; methods unclear	None	0	Not mentioned	For-profit organization	-

**We used the Cochrane risk-of-bias tool [17] for assessing the quality of included randomized clinical trials*

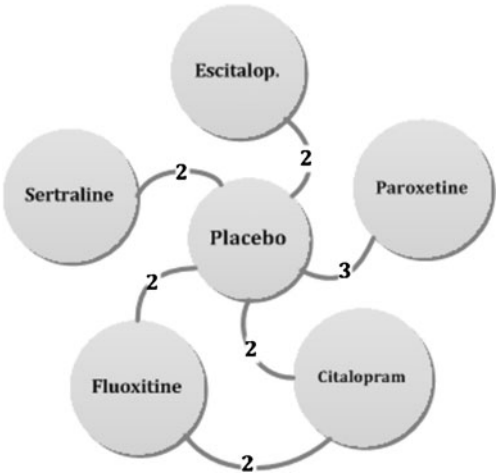

Figure 3. SSRI network: Each edge (circle) represents a treatment; connecting lines indicate pairs of treatments that have been directly compared in randomized trials. The numbers on the lines indicate the numbers of trials making that comparison.

study, an 8-week period. Simon et al. and Kaunitz et al. are both conference abstracts presented at the 23rd Annual Meeting of The North American Menopause Society in October 2012 at Orlando, FL. The authors were contacted and provided us with the presentation and further information about those studies; we included data reported at 8 weeks. Aedo et al. only reported on hot flash severity scores, although they was not included in the analysis as the reported data are dichotomous. Our inclusion criteria initially excluded all studies containing >10 % of breast cancer patients or >10 % of patients on hormonal therapy. We included Stearns et al. as breast cancer patients comprise only 7 % of the patient population, and 7 % were also on hormonal therapy. Only 9 of the 11 included trials reported the frequency of hot flashes per day; only six trials reported the severity scores of hot flashes (see Fig. 2).

In general, the overall quality of the 11 trials was appropriate with likely low risk of bias. Table 2 describes the methodological quality of the 11 RCTs included in this systematic review.

Improvement in Hot Flash Frequencies and Scores

Compared with placebo, SSRIs were associated with a statistically significant decrease in hot flash frequency at end of 4 to 8 weeks (MD −0.93; 95 % CI −1.49 to −0.37; I^2 = 21 %). Also, scores reflecting hot flashes assessed on different standardized scales showed improvement in SSRI groups (SMD −0.34; 95 % CI −0.59 to −0.10; I^2 = 47 %). Results are depicted in Fig. 2, panels a and b, and Fig. 3. There was no evidence of publication bias ($P > 1.0$ using the methods of both Begg-Mazumdar and Egger). This improvement in hot flashes, although statistically significant, is modest and likely has questionable clinical significance.

Aedo et al. reported a successful response, defined as reduction of 50 % or more in the sum of somatic and psychological domains of the Menopause Rating Scale (MRS), in 81.3 % of women in the sertraline group compared to 35.3 % in the placebo group at 90 days of follow-up.

Adverse Events

SSRIs had no significantly higher or significantly lower adverse events compared to placebo, but there was a trend toward more adverse effects in the SSRI group. Pooled effects for adverse events are: nausea (RR 1.7; CI 0.81 to 3.59), fatigue/tiredness (RR 1.07; CI 0.60 to 1.92), somnolence/drowsiness (RR 1.50; CI 0.42 to 5.35), palpitation (RR 1.04; CI 0.53 to 2.06), dry mouth (RR 1.29; CI 0.69 to 2.40), sleep disturbance (RR 1.32; CI 0.36 to 4.90), sweating (RR 1.12; CI 0.25 to 5.03), dizziness/vertigo (RR 1.5; CI 0.26 to 8.68), headache (RR 0.85; CI 0.49 to 1.5), decreased libido (RR 1.81; CI 0.21 to 15.48) and rash (RR0.53; CI 0.15 to 1.87). Simon et al. and Kaunitz et al. did not report adverse events at 8-week intervals. Results are provided in Fig. 2, panel c.

Mixed Treatment Comparison Analysis

In Table 3, the corresponding mean effects using Bayesian methods are presented. As expected, and when using the fixed- or random-effect Bayesian MTC, each treatment from the SSRI family performs better than placebo. Table 3 also demonstrates the relationship of SSRIs compared to each other. Escitalopram

Table 3. Results of Mixed Treatment Comparison Comparing the Efficacy of Escitalopram, Paroxetine, Sertraline, Citalopram and Fluoxetine, Conducted Using the Random-Effect Bayesian Method (Total Residual Deviance = 18.87)

Comparison	Mean effect	95% CrI	Probability treatment is best	Rank
Placebo	Reference	-	0	-
Escitalopram	−2.05	−4.82 to 0.62	61 %	1
Paroxetine	−1.23	−2.39 to −0.12	18 %	2
Sertraline	−0.83	−3.44 to 1.64	16 %	3
Citalopram	−0.54	−2.00 to 0.83	3.4 %	4
Fluoxetine	−0.14	−1.55 to 1.30	0.9 %	5
Escitalopram vs. Citalopram	1.511	−1.55 to 4.58	-	-
Escitalopram vs. Fluoxetine	1.914	−1.11 to5.06	-	-
Escitalopram vs. Sertraline	1.225	−2.44 to 4.89	-	-
Escitalopram vs. Paroxetine	0.82	−2.06 to 3.82	-	-
Citalopram vs. Fluoxetine	0.40	−1.02 to 1.92	-	-
Citalopram vs. Sertraline	−0.29	−3.32 to 2.57	-	-
Citalopram vs. Paroxetine	−0.69	−2.47 to 1.14	-	-
Fluoxetine vs. Sertraline	−0.69	−3.64 to 2.12	-	-
Fluoxetine vs. Paroxetine	−1.09	−2.94 to 0.70	-	-
Sertraline vs. Paroxetine	−0.40	−3.11 to 2.46	-	-

has the highest probability to be ranked first among other SSRIs in terms of efficacy. In sensitivity analysis, the fixed effect results were very similar to the random effect results, suggesting the robustness the of analysis to the choice of model

DISCUSSION

Main Findings

We conducted a systematic review and meta-analysis comparing the effect of SSRIs on menopausal hot flashes. The use of SSRIs is associated with a statistically significant decrease in the number of hot flashes per day after 8 weeks of use. This analysis was associated with minimal heterogeneity suggesting high confidence in this estimate. SSRI use was also associated with a significant, although heterogeneous, improvement in the scores of standardized scales for hot flashes.

The patients enrolled in the included trials had moderate-to-severe hot flashes, with an average frequency of ten per day. In terms of hot flash frequency, our analysis showed a decrease of one hot flash per day. In comparison, this 10 % reduction is less than that noticed with estrogen. The mean reduction observed with estrogen was (−2.7; 95 % CI – 4.7 to – 0.7) for conjugated equine estrogen, (−2.4; 95 % CI –3.3 to −1.45) for oral 17 β-estradiol and (−3.2; 95 % CI –5.1 to −1.48) for trans-dermal 17 β-estradiol.[5]Therefore, the effect of SSRIs on the frequency of hot flashes compared to estrogen, the most effective treatment, is smaller. In terms of hot flash severity, we noticed an improvement of 0.70 in standard deviation units across multiple scales. This improvement is considered a moderate effect size. Therefore, SSRIs appear to be a reasonable alternative to estrogen in women who cannot take hormonal therapy or are concerned about the long-term effects of estrogen.

The results of comparative effectiveness mixed treatment analysis suggest that escitalopram may be more effective than other SSRIs. All other SSRIs (escitalopram, citalopram and fluoxetine) were more effective than placebo. The adverse effects of SSRIs when used to alleviate hot flashes were minor and did not differ significantly from placebo, but there was a trend toward more adverse effects in the SSRI group. The adverse effects reported were nausea, dry mouth, fatigue, tiredness, decreased libido, sweating, dizziness and rash. In general, inferences about adverse effects should be derived from trials and observational studies of SSRIs used in the general population and with various indications. Such studies would provide a larger body of evidence with longer follow-up than studies of a limited indications, such as the case here.

Implications for Practice and Research

In this review, we excluded studies of women who are being treated with selective estrogen receptor modulators (SERM) or other hormonal treatments, such as tamoxifen and raloxifene, as they may suffer from flashing and hot flashes caused by different mechanisms than those related to natural menopause.[16] SSRIs in these women may also speed the metabolism of tamoxifen to inactive metabolites, possibly reducing the severity of side effects, including hot flashes.[39] Therefore, our findings relate to women suffering from natural peri- and post-menopausal symptoms.

Our results are consistent with previous guidelines. The Royal College of Obstetricians and Gynecologists Scientific Advisory Committee acknowledged SSRIs as the most commonly used drugs in clinical practice for the alleviation of menopause symptoms as an alternative to HRT.[40,41] HRT was considered the most effective treatment for vasomotor symptoms including hot flashes, but its use is associated with several complications and adverse effects, particularly venous thromboembolism and stroke. The committee described side effects of SSRIs, such as nausea and reduced libido, as a possible drawback. In our analysis, there was no statistical significance in adverse event rates between SSRI and placebo, although rates of nausea and libido appeared to be higher in the SSRI arm. It is likely that analysis of a small number of RCTs is underpowered to detect these adverse effects, and data from larger observational studies in menopausal women or trials in conditions other than menopausal treatment are needed for more precise harm outcomes.

The limitations of this review include the short follow-up period in most of the included studies; only one study followed patients up to 9 months, whereas most of the studies had less than 3 months of follow-up. Other limitations are the small sample size in each individual study, which ranged from 26 to 606 patients. The quality of the overall evidence (confidence in the estimates) was moderate to high for efficacy vs. placebo, low to moderate for side effects (limited by imprecision) and likely low for the ranking suggesting superiority of escitalopram (limited by indirectness of comparative data).[42,43]

In conclusion, given the promising positive effects of SSRIs on hot flashes and the likely favorable side effect profile, their use seems to be an acceptable option for treating menopausal women with hot flashes and is a good alternative to HRT. Future trials should investigate different SSRIs over a long time period (e.g., 6–12 months) and should not use placebo for comparison in order to provide high-quality comparative effectiveness evidence.

CONCLUSIONS

SSRI use is associated with modest improvement in the severity and frequency of hot flashes and can also be associated with the typical profile of SSRI adverse effects.

Acknowledgement:
Source of Funding: *None*

Disclosures: *This study was made possible by support from the Center for the Science of Healthcare Delivery, Mayo Clinic, and*

CTSA grant UL1 TR000135 from the National Center for Advancing Translational Sciences (NCATS), a component of the National Institutes of Health (NIH). Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the National Institutes of Health.

Conflict of Interest: *The authors declare that they do not have a conflict of interest.*

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