Section: Pharmacology

Original Research Article

TO COMPARE THE EFFECTIVENESS OF SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIS), WITH HORMONE REPLACEMENT THERAPY (HRT), FOR MANAGING MENOPAUSAL SYMPTOMS, AND THEIR ASSOCIATED RISKS AND BENEFITS- A SYSTEMIC REVIEW AND METANALYSIS

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Abstract

Background: The menopausal symptoms i.e., hot flashes and night sweats are collectively called as the vasomotor symptoms (VMS) and are experienced by women of all ethnic groups. These are really bothersome and may negatively impact functioning and activities of daily living, including work, social, and leisure activities. The current study was commenced to review the literature systematically to compare the effectiveness of selective serotonin reuptake inhibitors (SSRIs), with hormone replacement therapy (HRT), for managing menopausal symptoms, and their associated risks and benefits. **Materials and Methods:** The inclusion criteria were framed as per internationally standardized PICOS framework, as recommended by PRISMA guidelines. The study population included women who experienced menopausal symptoms and were treated either with selective serotonin reuptake inhibitors (SSRIs) or with hormone replacement therapy (HRT). **Result:** After evaluation of 59 papers, only 12 studies were ascertained for analysis after these papers fulfilled both inclusion and exclusion criteria. The patient consisted of women who experienced menopausal symptoms and were treated with either selective serotonin reuptake inhibitors (SSRIs) or with hormone replacement therapy (HRT) over a time duration of 8 weeks to 5.2 years. Considering the high rate of success of the treatment of the hot flushes with citalopram, escitalopram, sertraline, fluoxetine and paroxetine and few side effects of these drugs, they can be regarded as good alternatives to hormone therapy and for those who are not willing to take estrogen. **Conclusion:** The present study concludes that the most common side effects reported for SSRIs are nausea and constipation, with most resolving within the first week of treatment. Therefore, considering the treatment of the hot flushes with fluoxetine, citalopram, escitalopram, paroxetine and sertraline can be regarded as good alternatives to hormone therapy as its health risks of HRT exceeds benefits and for those who are not willing to take estrogen. Treatment choice should be patient-specific and begin with the lowest dose available.

INTRODUCTION

Hot flashes are the most common complaint among women entering menopause and, for many women, may continue to occur for up to 5 years even though approximate 20% of women may experience them for up to 15 years.[1] About 75% of perimenopausal women will experience some hot flashes, with 10% to 20% of those having severe symptoms.[2]

The hot flashes and night sweats are collectively called as the vasomotor symptoms (VMS) and are experienced by women of all ethnic groups.[3] VMS can be bothersome and may negatively impact functioning and activities of daily living, including

work, social, and leisure activities. Furthermore, VMS have been linked to increased prevalence of sleep disturbances and nighttime awakenings during menopause. Because sleep disturbance is a risk factor for impaired daytime functioning, development of medical and affective disorders, and increased health care costs, sleep disturbances associated with menopause may negatively affect the health and safety of postmenopausal women and persons with whom they interact.[4] They are caused by changes in the central nervous system associated with estrogen withdrawal and are best treated with estrogen replacement therapy.[3] However, during the past few years, many women and doctors have revised their opinions of hormone replacement therapy (HRT) for menopausal symptoms, and a substantial number of individuals have discontinued its use because of concerns about side-effects.[5] Antidepressants, specifically selective serotonin reuptake inhibitors, have been evaluated and utilized internationally for alternative treatment for VMS.[6] Therefore, for those who wish to avoid hormonal treatments, there are few effective options and selective serotonin reuptake inhibitors might be effective in the very short term (less than 12 weeks) and are well tolerated. Hence, the present study was undertaken to compare the effectiveness of selective serotonin reuptake inhibitors (SSRIs), with hormone replacement therapy (HRT), for managing menopausal symptoms, and their associated risks and benefits by systematically and thoroughly assessment of the available literature.

MATERIALS AND METHODS

The inclusion criteria were framed as per internationally standardized PICOS framework, as recommended by PRISMA guidelines:

Participants/population: The study population included women who underwent treatment for menopausal symptoms by selective serotonin reuptake inhibitors (SSRIs) and hormone replacement therapy (HRT)

Intervention: Reported benefits, risks, clinical outcomes and adverse effects were included in the review.

Comparator(s)/control: Studies of any of the above-mentioned interventions was included, including studies with no comparator group.

Outcome: the key outcomes consider were reported benefits, risks, clinical outcomes and adverse effects from the treatment of menopausal symptoms by selective serotonin reuptake inhibitors (SSRIs) and hormone replacement therapy (HRT) was considered.

Study design: The review included all types of experimental studies, observational studies and case series which have reported the procedures and outcomes of the above-mentioned procedures

Inclusion Criteria

Studies conducted anywhere in the world and articles published after 2000 through April 2023 was included in the study.

Only those studies published in academic peer-reviewed journals were included in the review.

Exclusion Criteria

Exclusion criteria included any articles that failed to involve items described in the inclusion criteria or any article that described repetitive data from another included article was excluded. Additionally, articles on Serotonin-norepinephrine reuptake inhibitors (SNRIs) and other non-pharmacological treatment for menopausal symptoms were also excluded.

Literature Search

A systematic literature search was performed in PubMed, Scopus, Embase, Google scholar databases clinical trial.gov and Cochrane Library were performed to gather literature published between 2000 and April 2023. The search terms used were [“menopause” OR “climacteric” OR “perimenopause” OR “postmenopause” OR "midlife women" OR "middle-aged”] AND [“selective serotonin reuptake inhibitors (SSRIs)” OR “Fluoxetine” OR “Sertraline” OR Fluvoxamine” OR “Citalopram” OR “Escitalopram” OR “Paroxetine”] AND [“Randomized Controlled Trial” OR “Randomized Placebo-controlled Trial” OR “Randomized Double-Blind Controlled Trial OR “Interventional Studies” OR “Pilot Randomized Trial”] AND [“Hot Flashes” OR “Vasomotor Symptoms” OR “Menopausal Symptoms” OR “Climacteric Symptoms”].

The searches were screened by the references of selected articles to find those that did not appear in the search databases. Additional references were not obtained by free internet search from Google as the number of studies were large. The detail search strategy is given in [Table 1].

Process of screening and selection of articles: The search strategy for this review involved three stages: reviewing titles, abstracts, and final selection of articles for full text analysis. Articles selected from the database search were sorted independently by 2 reviewers, and any differences in selection were discussed until a consensus was reached. Upon the reviewers’ agreement, articles that did not meet the predetermined inclusion criteria were excluded. Abstracts of the articles selected at the second stage were independently evaluated by the same reviewers, and articles selected for final analysis were obtained in full text.

All the citations along with the title and abstract was added to a specified endnote library and final list of studies to be screened for inclusion in the study was prepared by removing the duplicates. Attempts were made to obtain full-text articles for all these shortlisted studies, and thorough assessment was done for the satisfaction of inclusion and exclusion criteria. At the third and final stage, the full text of the obtained articles was analyzed.

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The list of excluded studies and the reasons for exclusion were presented in the "characteristics of excluded studies" table. "PRISMA flow chart" was used to evidently represent the screening and selection technique [Figure 1].

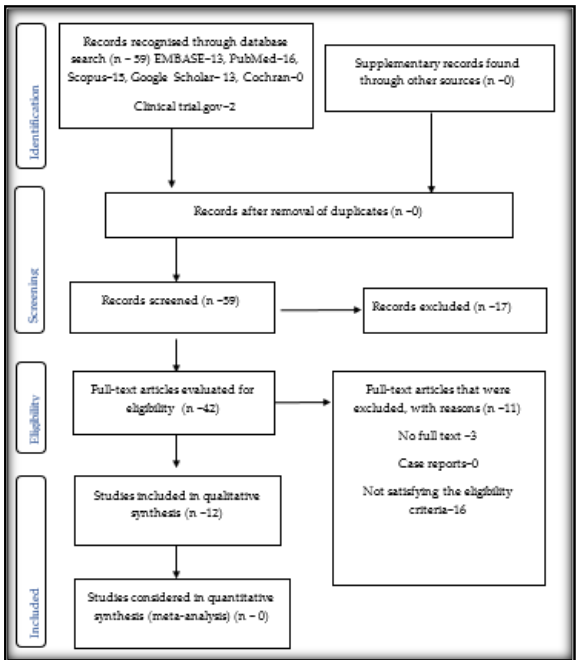

Figure 1: PRISMA 2009 Flow Diagram

Data Extraction

Data was thoroughly read through and were extracted from included studies and was extracted manually on to a structured data extraction form. Reported benefits, risks, clinical outcomes and adverse effects from the treatment of menopausal symptoms by selective serotonin reuptake inhibitors (SSRIs) and hormone replacement therapy (HRT) was considered.

Risk of Bias in Individual Studies

The methodological quality of studies included in the systemic review was considered according to Fowkes and Fulton quality assessment.[7]

Study Outcome

After evaluation of 59 papers, only 12 studies were ascertained for analysis after these papers fulfilled both inclusion and exclusion criteria. The present study compared treatment of menopausal symptoms with selective serotonin reuptake inhibitors (SSRIs) and hormone replacement therapy (HRT). The patient consisted of women who experienced menopausal symptoms and were treated with selective serotonin reuptake inhibitors (SSRIs) and hormone replacement therapy (HRT) over a time duration of 8 weeks to 5.2 years (Table 1). The total patients evaluated in the present study was approximately more than 21,812 patients as one study did not report the total number of patients and two studies were part of one trial reporting various analytic results in two parts.

[Table 2] reports applied therapy and clinical outcome as reported across the studies. [Table 3] reports benefits of selective serotonin reuptake inhibitors (SSRIs) and hormone replacement therapy (HRT) and [Table 4] reports associated risks with SSRIs and HRT. The frequency of hot flashes with paroxetine 20mg and 12.5mg, was significantly reduced in post-menopausal women as compared to placebo. The use of escitalopram (10-20 mg/d) compared with placebo resulted in fewer and less severe menopausal hot flashes at 8 weeks of follow-up. Considering the effectiveness of fluoxetine in the treatment of hot flash in postmenopausal period with few side-effects, inexpensiveness and availability, it can be used instead of hormonal replacement therapy. Sertraline reduced the number of hot flashes and improved the hot flash score relative to placebo and may be an acceptable alternative treatment for women experiencing hot flashes. Paroxetine CR may be an effective and acceptable alternative to hormone replacement and other therapies in treating menopausal hot flash symptoms. On the contrary, one study reported that citalopram and fluoxetine have little effect on hot flushes as compared to placebo and that study suggested that these cannot therefore be recommended for the treatment of menopausal symptoms, if vasomotor symptoms are the main complaint. Overall health risks exceeded benefits from use of combined estrogen plus progestin for an average 5.2-year follow-up among healthy postmenopausal US women.

One randomized clinical trial compared four groups including fluoxetine, citalopram, hormone therapy and placebo groups on effect on hot flushes and reported that there were no significant differences between the groups in the mean duration of menopause, history of any chronic disease, drug use and frequency of hypertension before intervention ($p<0.05$). The mean frequency of hot flushes decreased by 57%, 74.7%, 81.8% and 80% after intervention in estrogen + progesterone, fluoxetine, citalopram and placebo groups respectively ($P<0.001$).

[Table 4] reports adverse effects in the literature. Citalopram was well-tolerated, with no significant negative adverse effects. The most common side effects reported for SSRIs are nausea and constipation, with most resolving within the first week of treatment. For coronary artery disease and coronary artery insufficiency, the relative risk with BZA/CE vs placebo was 1.29 (95% CI, 0.16–10.34), or an incidence of 2.02 vs. 1.56 per 1,000 women–years. Estimated hazard ratios (HRs) (nominal 95% confidence intervals [CIs]) were as follows: CHD, 1.29 (1.02-1.63) with 286 cases; breast cancer, 1.26 (1.00-1.59) with 290 cases; stroke, 1.41 (1.07-1.85) with 212 cases; PE, 2.13 (1.39-3.25) with 101 cases; colorectal cancer, 0.63 (0.43-0.92) with 112 cases; endometrial cancer, 0.83 (0.47-1.47) with 47 cases; hip fracture, 0.66 (0.45-0.98) with 106 cases; and death due to other causes, 0.92 (0.74-1.14) with 331 cases. Considering the high rate of success of the treatment of the hot flushes with citalopram and

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fluoxetine and few side effects of these drugs, they can be regarded as good alternatives to hormone therapy and for those who are not willing to take estrogen.

The commonest side effects reported for SSRIs are nausea and constipation, with most resolving within the first week of treatment. Therefore, considering the high rate of success of the treatment of the hot flushes with fluoxetine, citalopram, escitalopram, paroxetine, sertraline they can be regarded as good alternatives to hormone therapy as its health risks exceeded benefits and for those who are not willing to take estrogen.

RESULTS

Table 1: Study characteristics

	Author	Year	Study design	Time duration	Sample Postmenopausal women with menopausal symptoms (at least 2 to 3 daily hot flushes)	Age
1	Naz Z et al,[8]	2019	Prospective open label control clinical trial	12 months	180	Middle aged
2	Simon JA et al,[9]	2013	Multicenter, double-blind, placebo-controlled study	24 weeks	591	Middle aged
3	LaCroix AZ et al,[10]	2012	A double-blind, placebo-controlled randomized trial	8 weeks	205	40-62 years
4	Akhavan S et al,[11]	2011	Randomized clinical trial (RCT).	8 weeks	80	46 to 55 years
5	Freeman EW et al,[12]	2011	A multicenter, randomized, double-blind, placebo-controlled, parallel group trial	8 weeks	205	40-62 years
6	Barton DL et al,[13]	2010	A randomized, double-blind trial	6 weeks	254	Middle aged
7	Lobo RA et al,[14]	2009	Multicenter, double-blind, placebo- and active-controlled phase trial	2 years	3,397	40 to 75 years
8	Ghomian N et al,[15]	2008	A randomized clinical trial	8 weeks	80	Middle aged
9	Gordan PR et al,[16]	2006	A double-blind, placebo-controlled	8 weeks	102	40 to 65 years
10	Suvanto-Luukkonen E et al,[17]	2005	Randomized placebo-controlled double-blind study	9 months	150	Middle aged
11	Stearns V et al,[18]	2003	Randomized, double-blind, placebo-controlled, parallel group study	6 weeks	165	Middle aged
12	Rossouw JE et al,[19]	2002	a randomized controlled primary prevention trial	5.2 years	16608	aged 50-79 years

Table 2: Applied Therapy and clinical outcome as reported across the studies

Author	Applied Therapy	Clinical outcome	Conclusion
Naz Z et al (2019),[8]	12.5mg, 20mg Paroxetine on frequency of hot flashes	Mean Greene Climacteric Score Scaling (GCS) scoring frequency in 12.5mg Paroxetine group at 12 week was 1.97±0.31 and the baseline 2.64±0.29. In 20mg Paroxetine mean GCS at baseline was 2.76±0.23 and 12 week 2.04±0.12. Where as in Placebo mean GCS scoring frequency at 12 week was 2.80±0.24 and at baseline 2.76±0.24.	The frequency of hot flashes with Paroxetine 20mg and 12.5mg, is significantly reduced in post-menopausal women as compared to Placebo
Simon JA et al (2013),[9]	Treatment with paroxetine 7.5 mg, and placebo	Paroxetine 7.5 mg is well-tolerated, is effective in reducing the frequency and severity of menopausal vasomotor symptoms.	Persistence of treatment benefit was demonstrated in the 24-week study.
LaCroix AZ et al (2012),[10]	Escitalopram 10-20mg/day	Treatment with escitalopram 10-20mg/day in healthy women significantly improved menopause vasomotor (hot flushes) symptoms	Largest difference seen in the Vasomotor domain (hot flushes)
Akhavan S et al (2011),[11]	hormone replacement therapy, menopause, oestrogens, progesterone, women	The mean frequency of hot flushes decreased after intervention was estrogen + progesterone: 57%, fluoxetine:74.7% citalopram: 81.8% and placebo groups: 80% (P<0.001).	Considering the high rate of success of the treatment of the hot flushes with fluoxetine, citalopram, they can be regarded as good alternatives to hormone therapy and for those who are not willing to take estrogen.
Freeman EW et al (2011),[12]	Women received 10 to 20 mg/d of escitalopram or a matching placebo for 8 weeks.	Reductions in hot flash severity scores were significantly greater in the escitalopram group (-0.52; 95% CI, -0.64 to -0.40 vs -0.30;	Among healthy women, the use of escitalopram (10-20 mg/d) compared with placebo resulted in fewer and less

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		95% CI, -0.42 to -0.17 for placebo; P < .001).	severe menopausal hot flashes at 8 weeks of follow-up.
Barton DL et al (2010),[13]	Citalopram at target doses of 10, 20, or 30 mg/d versus placebo for 6 weeks	Reductions in mean hot flash scores were 2.0 (23%), 7.0 (49%), 7.7 (50%), and 10.7 (55%) for placebo and 10, 20, and 30 mg of citalopram, respectively (P ≤ .002)	There does not appear to be a significant dose response above 10 mg/d, but broader helpful effects of the agent appear to be more evident at 20 mg/d.
Lobo RA et al (2009),[14]	Single tablets of BZA (10, 20, or 40 mg), each with CE (0.625 or 0.45 mg); raloxifene 60 mg; or placebo taken daily for 2 years.	At week 12, the daily number of hot flushes decreased by 51.7% to 85.7% with all BZA/CE doses vs. 17.1% for placebo	BZA (20 mg)/CE (0.625 or 0.45 mg) is an effective and safe treatment for menopausal symptoms.
Ghomian et al (2008),[15]	One group (n=40) were treated with fluoxetine (20mg per day) and the other with placebos for 8 weeks.	Positive clinical response was more in fluoxetine group (75%), but in the placebo group it was less (42.5%), (P=0.01).	Considering the effectiveness of fluoxetine in the treatment of hot flash in postmenopausal period with few side-effects, inexpensiveness and availability, it can be used instead of hormonal replacement therapy.
Gordan PR et al (2006),[16]	Sertraline 50 mg for 4 weeks, -week washout and cross over to the opposite treatment for 4 weeks.	At baseline, the mean number of hot flashes reported was 45.6 per week (SD = 29.6), ranging from 2 to 148. During the sertraline phase of the study, women experienced five fewer hot flashes per week than they did on the placebo (*P* = 0.002).	Sertraline reduced the number of hot flashes and improved the hot flash score relative to placebo and may be an acceptable alternative treatment for women experiencing hot flashes.
Suvanto-Luukkonen E et al (2005),[17]	The initial dose was 10 mg of both fluoxetine and citalopram, and it was increased to 20 mg at 1 month and to 30 mg at the 6-month visit with a follow up period of 9 months	There were no statistically significant differences between the groups in respect to number of hot flushes although there was a tendency in all these parameters in favor of SSRIs versus placebo.	Compared with placebo, citalopram and fluoxetine have little effect on hot flushes and cannot therefore be recommended for the treatment of menopausal symptoms, if vasomotor symptoms are the main complaint.
Stearns V et al (2003),[18]	Placebo or received 12.5 mg/d or 25.0 mg/d of paroxetine CR (in a 1:1:1 ratio) for 6 weeks.	The mean reductions in the hot flash frequency composite score from baseline to week 6 were statistically significantly greater for those receiving paroxetine CR than for those receiving placebo.	Paroxetine CR may be an effective and acceptable alternative to hormone replacement and other therapies in treating menopausal hot flash symptoms.
Rossouw JE et al (2002),[19]	Participants received conjugated equine estrogens, 0.625 mg/d, plus medroxyprogesterone acetate, 2.5 mg/d, in 1 tablet (n = 8506) or placebo (n = 8102).	The risk of coronary heart disease, breast cancer, stroke, colorectal cancer, endometrial cancer increased with hormonal therapy	Overall health risks exceeded benefits from use of combined estrogen plus progestin for an average 5.2-year follow-up among healthy postmenopausal US women.

Table 3: Benefits as reported across the studies

Author	Main outcome measured	Benefits
Naz Z et al (2019),[8]	The Greene Climacteric Score Scaling was applied to observe effects of Paroxetine on frequency of hot flashes as compared to Placebo.	There was a significant mean difference observed in Greene Climacteric Scale scores at baseline, 4th week, 8th week and 12th week with p-value less than 0.05.
Simon JA et al (2013),[9]	The four primary efficacy endpoints included mean changes in the frequency and severity of moderate to severe vasomotor symptoms on weeks 4 and 12; an additional endpoint was persistence of treatment benefit on week 24.	Mean weekly reduction in vasomotor symptom severity was significantly greater for paroxetine 7.5 mg than for placebo on week 4 (P = 0.0048) in the 12-week study and on week 4 (P = 0.0452) and week 12 (P = 0.0114) in the 24-week study
LaCroix AZ et al (2012),[10]	Menopause-Specific Quality of Life Questionnaire (MENQOL) and Vasomotor, Psychosocial, and Physical domain scores	Treatment with escitalopram resulted in significantly greater improvement in total MENQOL scores p<0.001), as well as Vasomotor (hot flushes), Psychosocial, and Physical domain scores with the largest difference seen in the Vasomotor domain (mean difference -0.75; 95% CI -1.28 to -0.22; p=0.02).
Akhavan S et al (2011),[11]	The effects of citalopram, fluoxetine, hormone therapy and placebo on perimenopausal flushes, were compared with one another.	The mean frequency of hot flushes was decreased after intervention in estrogen + progesterone, fluoxetine, citalopram and placebo groups.
Freeman EW et al (2011),[12]	Primary outcomes were the frequency and severity of hot flashes assessed by prospective daily diaries at weeks 4 and 8. Secondary outcomes were hot flash bother, recorded on daily diaries, and clinical improvement	The mean difference in hot flash frequency reduction was 1.41 (95% CI, 0.13-2.69) fewer hot flashes per day at week 8 among women taking escitalopram (P < .001), with mean reductions of 4.60 (95% CI, 3.74-5.47) and 3.20 (95% CI, 2.24-4.15) hot flashes per day in the escitalopram and placebo groups, respectively.
Barton DL et al (2010),[13]	Evaluated citalopram at target doses of 10, 20, or 30 mg/d versus placebo for 6 weeks.	Significant reduction in mean hot flash scores (P ≤ .002). Improvement in secondary outcomes, such as the Hot Flash Related Daily Interference Scale, was statistically superior in the 20-mg arm
Lobo RA et al (2009),[14]	Tissue-selective estrogen complex (TSEC) composed of bazedoxifene/conjugated estrogens	Significantly reduced the frequency and severity of hot flushes

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	(BZA/CE) on menopausal symptoms, metabolic parameters, and overall safety.	improved measures of vaginal atrophy. BZA/CE improved lipid parameters and homocysteine levels, did not significantly change carbohydrate metabolism, and had only minor effects on some coagulation parameters.
Ghomian N et al (2008),[15]	Frequency and duration of baseline hot flashes were recorded one week before the start of the treatment and during the following eight weeks (2nd, 4th, and 8th week).	Positive clinical response was more in fluoxetine group than placebo group (P=0.01). The incidence of side-effects was the same in both groups.
Gordan PR et al (2006),[16]	Baseline hot flash data was collected before 1 week of receiving placebo or active drug. The number and severity of hot flashes were measured after 4 weeks of treatment.	During the sertraline phase of the study, women experienced five fewer hot flashes per week than they did on the placebo (P = 0.002).
Suvanto-Luukkonen E et al (2005),[17]	Evaluate the efficacy of citalopram and fluoxetine in the treatment of hot flushes	There were no statistically significant differences
Stearns V et al (2003),[18]	Mean change from baseline to week 6 in the daily hot flash composite score (frequency × severity).	By week 6, the mean daily hot flash frequency went from 7.1 to 3.8 (mean reduction, 3.3) for those in the 12.5-mg/d and from 6.4 to 3.2 (mean reduction, 3.2) for those in the 25-mg/d paroxetine CR groups and from 6.6 to 4.8 (mean reduction, 1.8) for those in the placebo group

Table 4: Reported adverse effects in the literature

Studies	Risks
Barton DL et al (2010),[13]	Citalopram was well-tolerated, with no significant negative adverse effects.
Lobo RA et al (2009),[14]	For coronary artery disease and coronary artery insufficiency, the relative risk with BZA/CE vs. placebo was 1.29 (95% CI, 0.16–10.34), or an incidence of 2.02 vs. 1.56 per 1,000 women–years.
Rossouw JE et al (2002),[19]	Estimated hazard ratios (HRs) (nominal 95% confidence intervals [CIs]) were as follows: CHD, 1.29 (1.02-1.63) with 286 cases; breast cancer, 1.26 (1.00-1.59) with 290 cases; stroke, 1.41 (1.07-1.85) with 212 cases; PE, 2.13 (1.39-3.25) with 101 cases; colorectal cancer, 0.63 (0.43-0.92) with 112 cases; endometrial cancer, 0.83 (0.47-1.47) with 47 cases; hip fracture, 0.66 (0.45-0.98) with 106 cases; and death due to other causes, 0.92 (0.74-1.14) with 331 cases.
Stearns V et al 2002,[20]	The most common side effects reported for SSRIs are nausea and constipation, with most resolving within the first week of treatment.

DISCUSSION

Despite the prevalence of the symptoms, the pathophysiology of hot flushes remains unknown. A decline in hormone concentrations might lead to alterations in brain neurotransmitters and to instability in the hypothalamic thermoregulatory setpoint. The most effective treatments for hot flushes include oestrogens and progestogens. 20 In a meta-analysis by Stubbs C et al,[21] it was reported that HRT is still considered as the most effective treatment for reducing hot flashes in menopausal and post-menopausal women. Lobo RA et al,[14] evaluated the role of elective estrogen receptor modulators (SERMs), bazedoxifene (BZA) which is conjugated estrogens for the treatment of menopausal symptoms and effects on metabolic parameters and overall safety profile and reported that mean daily number of moderate and severe hot flushes demonstrated that all doses of BZA/CE provided significantly better relief of hot flushes than placebo at most time points. Worsley R et al,[22] conducted a survey in which 2,911 agreed to participate and among all participants, 11.3% used hormone therapy, mostly oral estrogen (68.5%) and most women with severe menopausal symptoms remain untreated despite the availability of safe nonhormone therapies and safer low-dose transdermal hormone therapies. On the contrary, Rossouw JE et al,[19] studied risks and benefits of estrogen plus progestin in healthy postmenopausal women and reported overall health risks exceeded benefits from use of combined estrogen plus progestin for an average 5.2-year follow-up among healthy postmenopausal US women. However, many women and their physicians are reluctant to accept hormonal treatments. Women want non-pharmacological treatments but unfortunately such treatments are not very effective, and non-hormonal drugs are often associated with adverse effects. Results from recent studies showed that selective serotonin reuptake inhibitors and other similar compounds can safely reduce hot flushes.[20]

Hence, concerns that HRT can increase the risks of estrogen-dependent pathologies have led to studies investigating other treatments for vasomotor symptoms. Based on the evidence reviewed, SSRIs reduce the frequency and severity of menopause-associated vasomotor symptoms by 10% to 64%, depending on the study. Side effects from SSRIs which included nausea, constipation, and dry mouth, were generally not severe and often subsided within the first week. SSRIs escitalopram and paroxetine ER were shown to be the most effective. Although less effective than HRT, SSRIs/SNRIs are demonstrated to reduce hot flashes and may be recommended for women who wish to avoid the risks of HRT.[21]

The present study found that as considering the treatment of the hot flushes with citalopram, escitalopram, sertraline, fluoxetine and paroxetine and due to reported few side effects of these drugs, they can be regarded as good alternatives to hormone therapy and for those who are not willing to take estrogen. However, treatment choice should be patient-specific and begin with the lowest dose

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available. Similarly, Wei D et al,[23] studied effect and safety of paroxetine for vasomotor symptoms and reported a moderate quality of evidence supporting the effectiveness of paroxetine for vasomotor symptoms; however, it causes nausea and dizziness. Stearns V et al,[18] reported paroxetine CR to be as effective and adequate alternative to hormone replacement in treating symptoms of menopausal hot flash. The most common side effects reported for SSRIs are nausea and constipation, with most resolving within the first week of treatment. Women with a history of breast cancer and taking tamoxifen should avoid SSRIs, which have been shown to interfere with tamoxifen metabolism. Treatment choice should be patient-specific and begin with the lowest dose available.[21] Hence, one of the challenging clinical issues with utilizing SSRIs is that many of the effective ones evaluated for hot flashes, namely paroxetine and fluoxetine, are potent inhibitors of CYP2D6 and cannot be used to manage tamoxifen-associated hot flashes. Tamoxifen continues to be an important treatment in reducing the risk of primary or recurrent breast cancer and adverse effects, including vasomotor symptoms, remain one of the main reasons women decide against taking this treatment. Therefore, effective hot flash options that are safe to use in this population continue to be a critical need.[13]

Freeman EW et al,[12] determined the efficacy and tolerability of 10 to 20 mg/d escitalopram and reported greater reductions in hot flash severity scores in the escitalopram group and reported that race did not significantly modify the treatment effect. In another study by Gordan PR et al,[16] sertraline reduced the number of hot flashes and improved the hot flash score relative to placebo and may be an acceptable alternative treatment for women experiencing hot flashes.

Citalopram, an antidepressant similar to fluoxetine and paroxetine, is considered to be an SSRI, readily absorbed following oral ingestion, reaching its peak serum concentration in 2 to 4 hours. Dosing commonly begins at 10-mg daily and can be increased to a maximum of 60-mg daily for treating depression. Citalopram is primarily hepatically metabolized by the CYP3A4 and CYP2C19 pathways and is a weak inhibitor of the CYP2D6 pathway. Since it is a weak inhibitor of CYP2D6, it is clinically feasible that this agent, if effective for hot flashes, would be able to be used to control hot flashes related to tamoxifen. In fact, preliminary data provide support that citalopram does not interfere with tamoxifen metabolism in a clinically significant way.[13] Thurston RC et al,[24] reported beneficial effects of sertraline on reduction of hot flushes.

Use of SSRIs 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.25 Castelli MC et al,[26] evaluated the pharmacokinetic properties, safety and tolerability of the low-dose mesylate salt of paroxetine (LDMP 7.5 mg) for the treatment of vasomotor symptoms associated with menopause and no serious AEs were reported, and no clinically meaningful changes in laboratory values, vital signs, or ECGs were observed. On multiple dosing, LDMP exhibited nonlinear pharmacokinetics and was well tolerated in these healthy postmenopausal women.

CONCLUSION

The present study concludes that the most common side effects reported for SSRIs are nausea and constipation, with most resolving within the first week of treatment. Therefore, considering the treatment of the hot flushes with fluoxetine, citalopram, escitalopram, paroxetine and sertraline can be regarded as good alternatives to hormone therapy as its health risks of HRT exceeds benefits and for those who are not willing to take estrogen. Treatment choice should be patient-specific and begin with the lowest dose available.

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