

# The Efficacy and Safety of Selective Serotonin Reuptake Inhibitors and Serotonin-Norepinephrine Reuptake Inhibitors in the Treatment of Menopausal Hot Flashes: A Systematic Review of Clinical Trials

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## What's Known

- Several studies have examined the effect of selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) on the frequency and severity of menopausal hot flashes.
- According to the literature, SSRIs and SNRIs are more widely used to treat menopausal hot flashes than hormone replacement therapy.

## What's New

- This systematic review will help psychiatrists to identify the most effective therapeutic options for the treatment of menopausal HF.
- The safety of SSRIs and SNRIs drugs is clearly described, allowing psychiatrists to choose the safest drug for their patients.

## Abstract

**Background:** Hot flashes (HF) are a common symptom during the menopausal transition. It is therefore important to identify effective drugs that can alleviate HF. This study aimed to systematically review published clinical trials on the efficacy and safety of selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) in the treatment of HF in healthy menopausal women.

**Methods:** In this systematic review, articles published during 2003-2019 in PubMed, MEDLINE, Web of Science, Scopus, Science Direct, PsycINFO, CINAHL, the Cochrane Central Register of Controlled Trials, and Google Scholar as well as Iranian databases such as SID, and Magiran were searched. The quality of the selected articles was assessed using the Jadad score calculation.

**Results:** Thirty-six articles on randomized controlled trials were included in this study, out of which 27 articles had acceptable, and nine had weak methodological quality. Findings on SSRIs class of drugs indicated that escitalopram, paroxetine, and fluoxetine have higher efficacy and safety in the treatment of menopausal HF than other drugs. Studies on the effectiveness of sertraline, citalopram, and fluvoxamine are limited in number or show inconsistent results. Therefore, further high-quality studies are required to confirm their effectiveness in alleviating HF. Within the SNRIs class, venlafaxine and desvenlafaxine showed significant efficacy in the treatment of menopausal HF. However, studies on the effectiveness of duloxetine are also limited, which requires further research.

**Conclusion:** Most studies have indicated the efficacy and safety of some antidepressants, such as SSRIs and SNRIs, in decreasing the frequency and severity of HF. These drugs are therefore recommended for the treatment of menopausal HF.

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## Introduction

Hot flashes (HF) are among the most common vasomotor symptoms (VMS) experienced by many women during the menopausal transition.<sup>1-4</sup> HF are sudden episodes of vasodilation

and intense heat around the head, face, neck, chest, and upper back, which may last for 1-5 minutes. HF might be accompanied by severe sweating, confusion, anxiety, and irritability.<sup>1, 5, 6</sup> The frequency, duration, and severity of HF vary between individuals. Although the duration of HF usually lasts from six months to two years, in some women, it may last for 10 years after the occurrence of menopause.<sup>7</sup> According to some studies, the estimated prevalence of HF is 30-75%.<sup>8-11</sup> HF can disrupt and impair the quality of life of many women.<sup>12</sup> Severe HF is significantly associated with fatigue, social isolation, embarrassment, decreased self-esteem, loss of control, panic, and depression.<sup>13, 14</sup>

Studies have shown that short-term hormone therapy (HT) is the most effective treatment for HF in perimenopausal and postmenopausal women.<sup>3, 15</sup> HT reduces HF frequency by 50-100% in women without a history of breast cancer and women who carry BRCA genes.<sup>16</sup> However, some women with thromboembolic diseases and estrogen-sensitive carcinomas are not suitable candidates for HT.<sup>17-19</sup> Because of the increased risk of cardiovascular disease and breast cancer due to long-term HT,<sup>2, 19</sup> non-hormonal treatment options such as clonidine, vitamin E, methyl dopa, alkaloids, gabapentin, propranolol, and soy products are recommended to alleviate HF symptoms.<sup>15, 18, 20</sup>

Recently, selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) have been proposed as acceptable alternative treatments for the management of menopausal HF.<sup>21-24</sup> However, clinical trials have shown contradictory results regarding the effect of SSRIs and SNRIs on alleviating menopausal HF.<sup>3, 25</sup> Most clinical trials have demonstrated that SSRIs and SNRIs reduce the frequency and severity of HF compared to the placebo.<sup>2, 3, 12, 21, 23, 26-28</sup> However, some other studies have reported no significant difference between the efficacy of such drug combinations in the treatment of menopausal HF compared to the placebo.<sup>29, 30</sup>

Various review studies have evaluated SSRIs and SNRIs, such as paroxetine,<sup>31-34</sup> venlafaxine, and desvenlafaxine.<sup>35-37</sup> However, we only have found one systematic review and meta-analysis study on the efficacy of SSRIs and SNRIs in the treatment of menopausal HF.<sup>38</sup> The main limitations of that review study were the sole inclusion of English articles and studies that did not assess duloxetine and fluvoxamine. In addition, some other studies have shown the efficacy of psychiatric drugs in the treatment of menopausal HF. However, there is no up-to-date

and comprehensive systematic review to which psychiatrists can refer to for the best therapeutic options for the treatment of menopausal HF in terms of their efficacy and safety. Therefore, we aimed to systematically review all published clinical trials related to the efficacy and safety of SSRIs and SNRIs in the treatment of menopausal HF or VMS in healthy women.

## Materials and Methods

This systematic review was conducted in 2020 in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.<sup>39</sup>

### Data Source and Search Strategy

A comprehensive literature search was conducted using the following databases and gateways: PubMed, MEDLINE, Web of Science, Scopus, Science Direct, PsycINFO, Cumulative Index to Nursing and Allied Health Literature (CINAHL), the Cochrane Central Register of Controlled Trials (CENTRAL), and Google Scholar. We also searched Iranian databases such as Scientific Information Database, and Magiran.

The terms and word variations used in the search 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 ["Serotonin-norepinephrine reuptake inhibitors (SNRIs)" OR "Venlafaxine" OR "Desvenlafaxine" OR "Duloxetine"] 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"]. Articles published during 2003-2019 in both Persian and English were included in the study. The last search was conducted in February 2020. The reference lists of the selected studies were also visually scanned to identify additional relevant articles.

### Study Selection

Two researchers (MA and FE) independently screened the titles and abstracts of the articles. If a study appeared to be relevant, the full text was obtained and reviewed for further assessment according to the inclusion and exclusion criteria. The inclusion criteria were randomized controlled trials and pilot randomized controlled trials

**Table 1:** Summary of the selected articles on the selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors drugs for the treatment of menopausal hot flashes.

Author, year	Sample size (n)	Age (mean±SD)	Study arms	Menopausal status or mean time since menopause	Measurement tools used	Primary outcomes	Frequency of HF at baseline, (mean±SD)	Reported adverse drug effects	Maximum treatment duration (weeks)	Main results
Carpenter, <sup>12</sup> USA	205	IG: 53.45±4.20 PG: 54.36±3.86	Arm 1: Escitalopram (10-20 mg/d) Arm 2: Placebo	IG: 81% PM, 16% LT, 3% ET PG: 82% PM, 15% LT, 3% ET	HFRDIS, HF diaries	Frequency and severity of HF	IG: 5.90±4.00 PG: 5.60±3.20	-	Eight weeks	Compared with placebo, escitalopram significantly reduced HF after 8 weeks
Freeman, <sup>21</sup> USA	205	IG: 53.45±4.20 PG: 54.36±3.86	Arm 1: Escitalopram (10-20 mg/d) Arm 2: Placebo	IG: 81% PM, 16% LT, 3% ET PG: 82% PM, 15% LT, 3% ET	Perspective daily diaries	Frequency and severity of bothersome daily HF	IG: 9.88±6.24 PG: 9.66±4.88	Dizziness or lightheadedness, vivid dreams, nausea, excessive sweating	Eight weeks	The use of escitalopram compared with placebo resulted in fewer and less severe HF at 8 weeks follow-up
Freedman, <sup>29</sup> USA	42	IG: 53.00±3.40 PG: 52.90±3.00	Arm 1: Escitalopram (20 mg/d) Arm 2: Placebo	IG: 5.30±4.90 PG: 5.40±5.60	Ambulatory recorder	Frequency of daily HF	IG: 20.60±5.20 PG: 20.00±5.40	-	Eight weeks	Escitalopram 10 mg/day or 20 mg/day was not effective in the treatment of menopausal HF
DeFronzo Dobkin, <sup>2</sup> USA	22	-	Arm 1: Escitalopram (10-20 mg/d) Arm 2: Placebo	-	HF diaries, MENQOL, GCS	The frequency and severity of HF	-	Fatigue, decreased libido, constipation, dry mouth, muscle tension, shoulder pain, leg cramps, irritability, anxiety, mild nausea, weight gain	Eight weeks	Escitalopram might be an effective option to treat HF and other menopausal symptoms in healthy women
Lofly, <sup>65</sup> Egypt	104	-	Arm 1: Escitalopram (10 mg/d) Arm 2: Black cohosh (20 mg/d)	100% PM	GCS	Frequency and severity of HF	IG: 6.20±1.40 PG: 6.40±1.30	Nausea or vomiting	Eight weeks	Escitalopram 10-20 mg/day was more effective in reducing HF than the black cohosh 20-40 mg/day
Ensrud, <sup>53</sup> USA	205	IG: 53.45±4.20 PG: 54.36±3.86	Arm 1: Escitalopram (10-20 mg/d) Arm 2: Placebo	IG: 80.8% PM, 16.3% LM, 2.9% EM PG: 82.2% PM, 14.9% LM, 3.0% EM	Daily diaries	frequency and severity of HF	IG: 9.88±3.34 PG: 9.66±4.88	Fatigue/tiredness, difficulty sleeping/insomnia, drowsiness	Eight weeks	Treatment with escitalopram compared with placebo reduced insomnia symptoms and improved subjective sleep quality in menopausal women with HF.
Simon, <sup>50</sup> USA	42	IG1: 54.60±2.80 IG2: 53.00±3.20 PG: 51.20±5.40	Arm 1: Raloxifene (60 mg/d) Arm 2: Paroxetine (25 mg/d) Arm 3: Placebo	100% PM	HF diaries	frequency and severity of HF	IG1: 30.20±15.80 IG2: 29.70±23.60 PG: 29.40±11.90	-	16 weeks	Reduction of HF frequency and severity in the paroxetine and placebo groups were greater than raloxifene

Author, year	Sample size (n)	Age (mean±SD)	Study arms	Menopausal status or mean time since menopause	Measurement tools used	Primary outcomes	Frequency of HF at baseline, (mean±SD)	Reported adverse drug effects	Maximum treatment duration (weeks)	Main results
Pinkerton, <sup>49</sup> USA	1174	IG: 54.60±5.73 PG: 54.50±6.01	Arm 1: Paroxetine (7.5 mg/d) Arm 2: Placebo	IG: 80.2% NM, 19.8% SM PG: 82% NM, 18% SM	HFRDIS, GCS	Nighttime awaking attributed to VMS	IG: 11.32±4.43 PG: 11.29±4.21	-	24 weeks	Nighttime awaking attributed to VMS was significantly reduced at week 4 and sustained at weeks 12 and 24
Stearns, <sup>43</sup> USA	165	IG1: 53.60 IG2: 55.00 PG: 53.60	Arm 1: Paroxetine (12.5 mg/d) Arm 2: Paroxetine (25 mg/d) Arm 3: Placebo	IG1: 10% Peri, 82% PM IG2: 10% Peri, 79% PM PG: 16% Peri, 73% PM	GCS	Frequency and severity of daily HF	IG1: 7.1±0.00 IG2: 6.4±0.00 PG: 6.6±0.00	Headache, nausea, insomnia	Six weeks	Paroxetine might be an effective and acceptable option to treat menopausal HF than HRT or other therapies
Simon, <sup>22</sup> USA	453	-	Arm 1: Paroxetine (7.5 mg/d) Arm 2: Placebo	-	Electronic HF diary	Frequency and severity of moderate to severe HF	IG: 10.83±3.86 PG: 10.90±3.96	Muscle cramps, spasms, and twitching, restless feeling in the legs, insomnia, nausea, fatigue, dizziness	24 weeks	Paroxetine 7.5 mg was well-tolerated and effective in reducing the frequency and severity of menopausal VMS
Soares, <sup>23</sup> Canada	56	IG: 55.60±3.30 PG: 57.00±2.10	Arm 1: Paroxetine controlled release (12.5-25 mg/d) Arm 2: Placebo	IG: 7.2% PeriM, 67.8% PM PG: 3.6% PeriM, 64.2% PM	GCS	change in VMS and total score and sub score of VMS	-	Headache, dizziness	Six weeks	Treatment with paroxetine controlled-release might be an efficacious alternative for symptomatic periM and PM women
Zareen, <sup>66</sup> Pakistan	180	-	Arm 1: Paroxetine (12.5 mg/d) Arm 2: Paroxetine (20 mg/d) Arm 3: Placebo	100% PM	GCS	Frequency of HF	IG1: 2.64±0.29 IG2: 2.76±0.23 PG: 2.76±0.24	-	12 weeks	Paroxetine 20 mg and 12.5 mg significantly reduced HF frequency in PM women than the placebo
Grady, <sup>30</sup> USA	99	IG: 50.50±5.00 PG: 52.60±4.20	Arm 1: Sertraline (100 mg/d) Arm 2: Placebo	IG: 3.90±5.20 PG: 3.10±3.60	Daily diary, GCS	Frequency and severity of daily HF	IG: 8.60±4.40 PG: 9.30±7.20	Dry mouth, upper respiratory infection, gastrointestinal, fatigue or daytime sleepiness, mood change, dizziness, pain, insomnia	Six weeks	Treatment with sertraline did not improve HF frequency or severity in healthy PeriM and PM women

Author, year	Sample size (n)	Age (mean±SD)	Study arms	Menopausal status or mean time since menopause	Measurement tools used	Primary outcomes	Frequency of HF at baseline, (mean±SD)	Reported adverse drug effects	Maximum treatment duration (weeks)	Main results
Gordon, <sup>25</sup> USA	87	IG: 52.60±4.80 PG: 52.40±5.40	Arm 1: Sertraline (50 mg/d) Arm 2: Placebo	-	HF data collection instrument	Frequency and severity of HF daily and its occurrence time	IG: 45.4±27.90 PG: 49.0±31.50	Severe nausea	Eight weeks (four weeks for each crossover period)	Sertraline might reduce the number of HF and improved HF score than the placebo
Kerwin, <sup>44</sup> USA	87	-	Arm 1: Sertraline (50 mg/d) Arm 2: Placebo	-	Daily HF diary	Frequency and severity of HF	IG: 46.70±23.90 PG: 42.80±34.70	-	Four weeks	Treatment with sertraline significantly reduced the mean HF
Suvanto-Luukkonen, <sup>62</sup> Finland	150	-	Arm 1: Citalopram Arm 2: Fluoxetine Arm 3: Placebo	-	Daily diaries, Modified KI	Frequency of daily HF	-	Nausea, dry mouth	36 weeks	Compared to placebo, citalopram and fluoxetine had little effect on HF and not recommended for HF treatment
Kalay, <sup>61</sup> Turkey	100	IG1: 53.50±5.30 IG2: 52.50±4.30 PG1: 51.70±4.60 PG2: 53.60±4.70	Arm 1: Citalopram (10 mg/d) Arm 2: Citalopram (10 mg/d)+HT Arm 3: Placebo Arm 4: Placebo+HT	IG1: 6.90±5.10 IG2: 7.30±5.40 PG1: 6.10±3.40 PG2: 6.00±4.10	Modified KI, MENQOL	Frequency of HF/day and mean HF score	-	Somnolence, increased perspiration, palpitation, dry mouth	Eight weeks	Citalopram was an effective alternative treatment for women, who cannot undergo HT to alleviate climacteric symptoms
Amin, <sup>56</sup> Iran	47	IG1: 47.78±5.50 IG2: 46.40±4.90	Arm 1: Melissa officinalis extract, Nigella saliva powder, and fennel fruits Arm 2: Citalopram (20 mg/d) No placebo group	100% PM	MENQOL	Control of menopausal symptoms such as VMS	-	Nausea, vomiting, irritability	Eight weeks	There was no significant difference in the improvement of menopausal symptoms in the combined product group than the citalopram group
Molaei, <sup>57</sup> Iran	46	IG: 49.91±5.77 PG: 50.52±6.68	Arm 1: Combination of Nigella sativa and Vitex agnus-castus with citalopram Arm 2: Placebo	100% PM	MENQOL	control of HF	IG: 5.75±1.46 PG: 4.91±1.39	No adverse event	Eight weeks	Herbal combination with citalopram significantly decreased the three domains of MENQOL questionnaire (VMS, physical, and psychosocial)

Author, year	Sample size (n)	Age (mean±SD)	Study arms	Menopausal status or mean time since menopause	Measurement tools used	Primary outcomes	Frequency of HF at baseline, (mean±SD)	Reported adverse drug effects	Maximum treatment duration (weeks)	Main results
Davari-Tanha, <sup>59</sup> Iran	60	51.02±3.51	Arm 1: Venlafaxine (75 mg/d) Arm 2: Citalopram (20 mg/d) Arm 3: Placebo	100% PM	Daily diary	Frequency of HF in a day and its severity	IG1: 3.85±2.05 IG2: 3.85±2.34 PG: 3.70±2.08	Vomiting, nausea, constipation, lethargy, headache	Eight weeks	The severity of HF in both venlafaxine and citalopram groups was significantly lower than the PG group
Ghomian, <sup>54</sup> Iran	80	IG: 50.03±1.50 PG: 51.33±1.20	Arm 1: Fluoxetine (20 mg/d) Arm 2: Placebo	IG: 1.50±0.60 PG: 1.60±0.40	Daily diary	Frequency and duration of HF and HF severity	-	Headache	Eight weeks	Fluoxetine was effective in the treatment of HF in PM women
Oktem, <sup>60</sup> Turkey	80	IG: 52.70±6.40 PG: 53.10±5.60	Arm 1: Fluoxetine (20 mg/d) Arm 2: Black cohosh No placebo group	-	Daily diaries, Modified KI	The daily number and severity of HF	-	Dry mouth, tiredness, sleep disturbance, headache, allergic skin reactions	24 weeks	Compared with fluoxetine, black cohosh was more effective in treating HF and NS
Rahmanian, <sup>56</sup> Iran	79	IG1: 51.70±2.50 IG2: 51.10±2.40	Arm 1: Fluoxetine (20 mg/d) Arm2: Gabapentin (300 mg/d) No placebo group	100% PM	GCS	Frequency and severity of VMS	IG1: 1.68±0.73 IG2: 1.85±0.80	Lack of Appetite	Eight weeks (four weeks for each crossover period)	In two rounds of treatment, gabapentin resulted in a greater reduction of HF severity than the fluoxetine
Akhavan, <sup>28</sup> Iran	80	IG1: 49.40±3.30 IG2: 50.50±3.90 IG3: 52.40±2.70 PG: 53.10±4.30	Arm 1: Fluoxetine (20 mg/d) Arm 2: Citalopram (20 mg/d) Arm 3: Estrogen-progesterone (0.625 mg/d) or Medroxy progesterone acetate (5 mg/d) Arm 4: Placebo	IG1: 3.70±1.20 IG2: 3.40±1.30 IG3: 2.70±1.10 PG: 3.40±1.40	Daily diary	Frequency of daily HF	IG1: 15.00±3.40 IG2: 14.30±3.10 IG3: 13.70±3.50 PG: 15.70±2.50	No adverse effects	Eight Weeks (four weeks for each crossover period)	Fluoxetine and citalopram were effective therapeutic options for treating HF and were an appropriate alternative to HT in women with contraindications for HT

Author, year	Sample size (n)	Age (mean±SD)	Study arms	Menopausal status or mean time since menopause	Measurement tools used	Primary outcomes	Frequency of HF at baseline, (mean±SD)	Reported adverse drug effects	Maximum treatment duration (weeks)	Main results
Yazdizadeh, <sup>65</sup> Iran	71	IG: 52.63±4.29 PG: 51.05±3.38	Arm 1: Fluoxetine (20 mg/d) Arm 2: Placebo	-	Checklist for recording HF	Frequency and severity of HF	IG: 7.05±3.36 PG: 6.97±3.33	Headache, heartburn	Four weeks	Fluoxetine was effective in improving HF
Oishi, <sup>63</sup> Japan	22	IG: 52.90±7.60	Arm 1: Fluvoxamine (500 mg/d) No placebo group	36.3% Peri, 63.6 % PM	SMI	The mean level of VMS	-	Nausea, mouth dryness, dizziness	Six weeks	Fluvoxamine was effective in treating vasomotor and psychological symptoms
Evans, <sup>45</sup> USA	80	IG: 52.70±4.90 PG: 51.60±6.10	Arm 1: Venlafaxine (75 mg/d) Arm 2: Placebo	IG: 4.90±4.40 PG: 4.00±3.50	Daily diaries	Daily HF severity scores	-	Dry mouth, sleeplessness, and decreased appetite	12 weeks	Extended-release of venlafaxine 75 mg/day was an effective treatment in PM women with HF
Caan, <sup>46</sup> USA	339	IG1: 54.90±4.10 IG2: 54.80±3.70 PG: 54.30±3.80	Arm 1: Estradiol low dose (0.5 mg/d) Arm 2: Venlafaxine (75 mg/d) Arm 3: Placebo	IG1: 14.4% Peri, 76.3% PM, 9.3% NOS IG2: 17.7% Peri, 74.0% PM, 8.3% NOS PG: 15.1% Peri, 75.3% PM, 9.6% NOS	Daily diaries, MENQOL	Frequency and severity VMS	IG1: 5.70±0.00 IG2: 5.90±0.00 PG: 5.60±0.00	-	Eight weeks	Both the low-dose E2 and venlafaxine were effective pharmacologic drugs for improving menopause-related QOL in healthy women with VMS
Pinkerton, <sup>52</sup> USA	365	IG: 54.00±5.00 PG: 54.00±5.00	Arm 1: Desvenlafaxine (100 mg/d) Arm 2: Placebo	IG: 82% NM, 16% SM PG: 77% NM, 23% SM	GCS	changes in frequency and severity of HF	IG: 11.70±5.60 PG: 11.90±5.70	No adverse effects	52 weeks	Treatment with desvenlafaxine reduced the frequency and the mean severity of VMS after 12 weeks and its effect was maintained for one year.
Pinkerton, <sup>51</sup> USA	390	IG: 54.00±5.00 PG: 54.00±5.00	Arm 1: Desvenlafaxine (100 mg/d) Arm 2: Placebo	IG: 82% NM, 18% SM PG: 75% NM, 25% SM	GCS	the daily number and severity of HF	IG: 11.70±5.60 PG: 11.90±5.70	Supine systolic blood pressure, diastolic blood pressure	12 weeks	Desvenlafaxine reduced the number of moderate to severe HF
Bouchard, <sup>67</sup> South Africa and USA	451	IG1: 54.00±4.00 IG2: 53.00±5.00 PG: 54.00±5.00	Arm 1: Desvenlafaxine (100 mg/d) Arm 2: Tibolone (2.5 mg/d) Arm 3: Placebo	IG1: 5.00±4.00 IG2: 5.00±4.00 PG: 6.00±4.00	GCS	average daily number of moderate and severe HF	IG1: 10.10±4.20 IG2: 10.10±4.30 PG: 9.60±2.90	Nausea, headache	12 weeks	Desvenlafaxine did not significantly decrease the number of daily HF than the placebo. Tibolone decreased the number of daily HF more than placebo

Author, year	Sample size (n)	Age (mean±SD)	Study arms	Menopausal status or mean time since menopause	Measurement tools used	Primary outcomes	Frequency of HF at baseline, (mean±SD)	Reported adverse drug effects	Maximum treatment duration (weeks)	Main results
Archer, <sup>27</sup> USA	458	IG1: 53.29±4.70 IG2: 53.43±4.64 PG: 53.36±5.05	Arm 1: Desvenlafaxine (100 mg/d) Arm 2: Desvenlafaxine (150 mg/d) Arm 3: Placebo	IG1: 4.39±3.69 IG2: 4.53±4.25 PG: 4.23±3.71	Daily diary entries, GCS	Daily number of moderate to severe HF and average daily HF severity score	IG1: 11.10±4.50 IG2: 10.50±3.40 PG: 10.90±4.60	Nausea, dry mouth, mydriasis	12 weeks	Desvenlafaxine is an effective non-hormonal treatment for menopausal HF
Archer, <sup>47</sup> USA	567	IG1: 53.30±5.20 IG2: 53.90±5.14 PG: 54.00±4.74	Arm 1: Desvenlafaxine (100 mg/d) Arm 2: Desvenlafaxine (150 mg/d) Arm 3: Placebo	IG1: 4.50±4.01 IG2: 4.70±4.19 PG: 5.30±4.66	Daily diaries, GCS	Daily number of moderate to severe HF and severity score	IG1: 10.8±4.20 IG2: 10.3±4.10 PG: 10.6±4.00	Dry mouth, nausea, vomiting, dizziness, insomnia, nervousness, somnolence, mydriasis, Asthenia, chills, anorexia, constipation, diarrhea	26 weeks	Desvenlafaxine is an effective treatment for menopausal HF
Speroff, <sup>48</sup> USA	707	IG1: 53.20±4.44 IG2: 53.50±5.33 IG3: 53.30±4.59 PG: 54.20±5.44	Arm 1: Desvenlafaxine (100 mg/d) Arm 2: Desvenlafaxine (150 mg/d) Arm 3: Desvenlafaxine (200 mg/d) Arm 4: Desvenlafaxine (150 mg/d) Arm 5: Placebo	IG1: 8.00±5.98 IG2: 10.8±7.42 IG3: 11.00±9.82 IG4: 13.10±11.61 PG: 11.20±9.54	Daily diaries	Frequency and severity of HF	IG1: 10.80±4.10 IG2: 10.55±4.10 IG3: 11.20±6.40 IG4: 11.10±4.30 PG: 11.00±4.60	Nausea, dry mouth, hypertension, somnolence, nervousness, anorexia, dizziness, insomnia, vomiting, decreased libido, asthenia, constipation, abnormal behavior	52 weeks	Desvenlafaxine is an effective non-hormonal treatment for VMS in PM women
Freeman, <sup>26</sup> USA	19	IG: 52.10±5.40	Arm 1: Duloxetine (60 mg/d) No placebo group	IG: 37.90% PeriM, 42.10% PM	HFRDIS, GCS,	Frequency and severity of HF	-	Nausea, headache, dizziness, possible drug rash	Eight weeks	Overall, the number and severity of HF improved significantly, but further research is required
Joffe, <sup>64</sup> Canada	30	IG: 52.30±4.10 PG: NOS	Arm 1: Duloxetine (60-120 mg/d) Arm 2: Placebo	100% PM	GCS, MENQOL, HFRDIS	Changes in VMS	-	Constipation, headache, dry mouth	10 weeks	VMS decreased significantly after duloxetine therapy

HF: Hot flashes; NS: Night sweats; IG: Intervention group; PG: Placebo group; PM: Postmenopausal; LT: Late transition; ET: Early transition; MENQOL: Menopause specific quality of life questionnaire; GCS: Greene climacteric scale; KI: A modified Kupperman index; SMI: Simple menopausal index; HFRDIS: Hot flash-related daily interference scale; HRT: Hormone replacement therapy; PeriM: Perimenopausal; PM: Postmenopausal; NOS: Not specified; NM: Natural menopause; SM: Surgical menopause

conducted on healthy perimenopausal or postmenopausal women who had received SSRIs or SNRIs (e.g., citalopram, fluoxetine, paroxetine, sertraline, escitalopram, fluvoxamine, venlafaxine, desvenlafaxine, and duloxetine) to reduce the frequency and the severity of HF and comparing the results with women who had received a placebo or other non-hormonal drugs. We excluded studies that investigated the effects of SSRIs or SNRIs in the treatment of HF in patients with cancer. Note that HF and night sweats are common complaints in patients taking tamoxifen for breast cancer or receiving HT.

#### Data Extraction

The full text of the selected articles was read carefully and the required information was extracted and summarized in a descriptive table and cross-checked by one of the authors (FE). Disagreements were resolved in group discussions between the authors. The extracted data included authors' names, year of publication, country, sample size, age of participants, study arms, menopausal status or the mean time since menopause, measurement tools used, primary outcomes, frequency of HF or VMS at baseline, reported drug side effects, maximum treatment duration, and main results (table 1).

#### Quality Assessment of the Selected Articles

The Jadad score calculation was used to assess the methodological quality of the clinical trials.<sup>40, 41</sup> The Jadad scale comprises two sets of questions, namely three direct and eight indirect questions. The three direct questions were whether the study was described as randomized, whether it was described as double-blind, and whether there was a description of withdrawals and dropouts. For the first direct question, one point was given to a study, if randomization was mentioned and an additional point, if the method of randomization was described. Studies in which the method of randomization was inappropriate did not receive the additional point. For the second direct question, one point was awarded, if the study mentioned blinding and an additional point was given, if the appropriate method of blinding was mentioned. For the third direct question, one point was given, if the withdrawals or dropouts were described. The overall score of the first set of questions ranged from 0-5, higher scores indicated a high-quality study. Scores  $\geq 3$  were considered to be acceptable and appropriate quality studies, while studies scoring  $< 3$  were considered to be of poor quality.<sup>41, 42</sup>

The second section of the Jadad scale

contains eight indirect questions about the study objectives, obvious outcome measures, a clear description of the inclusion and exclusion criteria, an explanation of sample size, a clear description of the interventions, the existence of at least one control (comparison) group, a description of the method used to assess the adverse effects, and a description of the statistical analysis methods. In the present review study, we assessed the selected articles only based on the three direct questions (table 2).

#### Ethical Approval

The study was conducted in accordance with the Ethical Principles and the National Norms and Standards for Conducting Medical Research in Iran (code: IR.MAZUMS.REC.1397.099).

## Results

The search resulted in 1,933 original research studies out of which 355 articles were excluded, as they contained duplicate results. From the remaining 1,578 articles, 980 were further excluded after screening their title and abstract. Detailed analysis of the full text resulted in the exclusion of cross-sectional studies, cohort, or review studies (n=172), including patients with cancer (n=242), or in which non-hormonal drugs other than SSRIs and SNRIs were used to alleviate menopausal HF (n=148). Finally, 36 articles were selected and systematically reviewed (figure 1).

#### Description of the Studies

The results of the selected articles are shown in table 1. Of the 36 selected articles, 20 studies were conducted in the United States,<sup>2, 12, 21, 22, 25-27, 29, 30, 43-53</sup> seven in Iran,<sup>28, 54-59</sup> two in Turkey,<sup>60, 61</sup> one in Finland,<sup>62</sup> one in Japan,<sup>63</sup> two in Canada,<sup>23, 64</sup> one in Egypt,<sup>65</sup> one in Pakistan,<sup>66</sup> and one joint study in South Africa and the USA.<sup>67</sup> The above-mentioned articles were all published between 2003 and 2019. The 36 studies included a total of 7,347 menopausal women and the sample sizes varied from 19 to 1,174 individuals. Of the 36 studies, 21 were randomized placebo-controlled trials with a double-blind design,<sup>12, 21-23, 27-30, 43, 46-54, 59, 62, 67</sup> four were double-blind or non-blind cross-over controlled trials,<sup>25, 44, 55, 58</sup> eight were single-blind or non-blind design,<sup>45, 55, 56, 60, 61, 64-66</sup> and three studies were pilot randomized trials.<sup>2, 57, 63</sup> The assessed drugs within the SSRIs class included escitalopram (six articles),<sup>2, 12, 21, 29, 53, 65</sup> paroxetine (six articles),<sup>22, 23, 43, 49, 50, 66</sup> sertraline (three articles),<sup>25, 30, 44</sup> citalopram (five articles),<sup>56, 57, 59, 61, 62</sup> fluoxetine (five articles),<sup>28, 54, 55, 58, 60</sup> and

**Table 2:** Quality assessment of the selected studies was presented according to the Jadad score calculation

Row	First author	Items (three directly related markers)			Total score
		Was the study described as randomized? (if the method of randomization mentioned receive 1 additional point)	Was the study described as double-blind? (if the method of blinding was appropriate receive 1 additional point)	Was there a description of withdrawals and dropouts?	
1	Carpenter <sup>12</sup>	2	2	0	4
2	Freeman <sup>21</sup>	2	2	1	5
3	Freeman <sup>29</sup>	2	1	1	4
4	DeFronzo Dobkin <sup>2</sup>	0	0	1	1
5	Lofty <sup>65</sup>	2	0	1	3
6	Ensrud <sup>53</sup>	2	2	1	5
7	Simon <sup>50</sup>	2	2	0	4
8	Pinkerton <sup>49</sup>	2	2	1	5
9	Stearns <sup>43</sup>	2	1	1	4
10	Simon <sup>22</sup>	2	2	1	5
11	Soares <sup>23</sup>	0	1	1	2
12	Zareen <sup>66</sup>	0	0	0	0
13	Grady <sup>30</sup>	2	2	0	4
14	Gordon <sup>25</sup>	2	2	0	4
15	Suvanto-Luukkonen <sup>62</sup>	2	2	1	5
16	Kalay <sup>61</sup>	2	0	0	2
17	Amin <sup>56</sup>	2	0	1	3
18	Molaie <sup>57</sup>	1	2	1	4
19	Davari <sup>59</sup>	2	2	1	5
20	Kerwin <sup>44</sup>	2	2	0	4
21	Ghomian <sup>54</sup>	1	2	0	3
22	Oktem <sup>60</sup>	1	0	0	1
23	Rahmanian <sup>58</sup>	2	0	1	3
24	Akhavan <sup>28</sup>	2	2	0	4
25	Yazdizadeh <sup>55</sup>	1	0	1	2
26	Oishi <sup>63</sup>	0	0	1	1
27	Evans <sup>45</sup>	2	0	1	3
28	Caan <sup>46</sup>	2	2	0	4
29	Pinkerton <sup>52</sup>	2	2	1	5
30	Pinkerton <sup>51</sup>	2	2	1	5
31	Bouchard <sup>67</sup>	2	2	1	5
32	Archer <sup>27</sup>	2	2	1	5
33	Archer <sup>47</sup>	2	2	1	5
34	Speroff <sup>48</sup>	2	2	0	4
35	Freeman <sup>26</sup>	0	0	1	1
36	Joffe <sup>64</sup>	0	0	1	1

fluvoxamine (one article).<sup>63</sup> The assessed drugs within the SNRIs class included venlafaxine (two articles),<sup>45, 46</sup> desvenlafaxine (six articles),<sup>27, 47, 48, 51, 52, 67</sup> and duloxetine (two articles).<sup>26, 64</sup> All but five studies had at least one comparison group (placebo).<sup>26, 56, 58, 60, 63</sup> The menopausal status of women was reported as percentages in 19 articles,<sup>12, 21-23, 26, 43, 46, 49, 51-53, 56-59, 63-66</sup> while ten articles reported the age (mean±SD).<sup>27-30, 45, 47, 48, 54, 61, 67</sup> In 29 of the studies, the primary outcomes were the measurements of the frequency and severity of HF. The primary outcomes in seven studies were the measurements of VMS (HF and night sweats).<sup>23, 46, 49, 56, 58, 63, 64</sup> All studies evaluated HF using a validated self-reported

diary in which the women recorded the daily frequency and severity of HF. To assess the four domains of menopausal symptoms (vasomotor, psychological, physical, and sexual), 15 studies used the Greene Climacteric Scale (GCS).<sup>2, 23, 26, 27, 30, 43, 47, 49, 51, 52, 58, 64-67</sup> and six studies used the menopause specific quality of life (MENQOL) questionnaire.<sup>2, 46, 56, 57, 61, 64</sup> The GCS score ranged from 0-63, where a high score indicated more severe symptoms. Four studies used the HF-related daily interference scale, which is a validated scale measuring the impact of HF on daily activities.<sup>12, 26, 49, 64</sup> Three studies used the modified Kupperman Index (KI) to score menopausal symptoms such as HF, sweating, insomnia, nervousness,

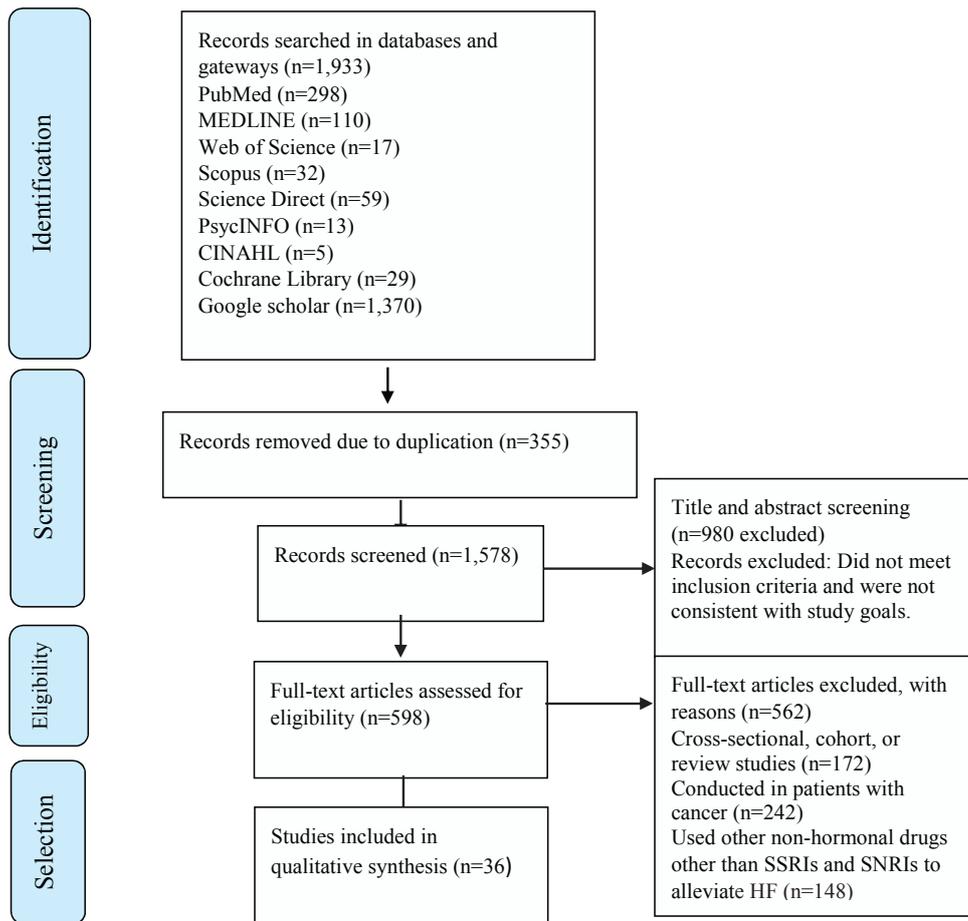


Figure 1: Flow chart of study selection according to PRISMA guidelines is presented. PsycINFO: Psychological information database, CINAHL: Cumulative index to nursing and allied health literature

depression, vertigo, fatigue, joint pain, headache, palpitation, and vaginal dryness; each symptom was given a value from 0-3.<sup>60-62</sup> Ten studies did not report HF frequency at baseline.<sup>2, 23, 26, 45, 54, 56, 60, 62-64</sup> The duration of treatment in the studies was 4-52 weeks.

### Selective Serotonin Reuptake Inhibitors (SSRIs) Escitalopram

Six studies assessed the efficacy of escitalopram in the treatment of HF. Five studies reported that escitalopram significantly reduced the frequency and severity of HF in healthy women compared to the placebo.<sup>2, 12, 21, 53, 65</sup> Carpenter and colleagues reported that compared with placebo, escitalopram significantly reduced HF interference by 6.0 points at week four to baseline and 3.4 points at week eight to baseline ( $P=0.012$ ). No significant side effects were reported in the treatment group compared to those on placebo.<sup>12</sup>

In a study by Freeman and colleagues, 55% of the escitalopram group and 36% of the placebo group reported at least a 50% decrease in the HF frequency ( $P=0.009$ ).<sup>21</sup> The escitalopram group also experienced a greater reduction

in the severity of HF ( $-0.52$ ; 95% CI,  $-0.64$  to  $-0.40$ ) than in the placebo group ( $-0.30$ ; 95% CI,  $-0.42$  to  $-0.17$ ;  $P<0.001$ ). In the same study, the dropout rate due to drug side effect was 4%. The most common side effects reported by the participants were dizziness or lightheadedness, vivid dreams, nausea, and excessive sweating.

The results of a pilot study showed the efficacy of escitalopram versus placebo in the treatment of HF and other menopausal symptoms.<sup>2</sup> They reported that both the frequency and severity of HF decreased compared to the control group ( $P<0.0001$ ). However, 12% of the participants discontinued treatment because of side effects such as anxiety and insomnia.

In a study by Lofty and colleagues, the effectiveness of escitalopram versus black cohosh on the frequency and severity of HF in postmenopausal women was compared at weeks four and eight.<sup>65</sup> Results showed that both the frequency and severity of HF were significantly reduced in the escitalopram group compared to the black cohosh group ( $P=0.0001$ ). Moreover, the participants did not have serious side effects that required medical intervention or led them to withdraw from the study.

However, mild to moderate side effects such as vomiting and nausea were reported in the escitalopram group.

Another study assessed the effect of escitalopram on menopausal HF-related insomnia symptoms. They showed escitalopram to be effective in reducing the frequency and severity of HF during eight weeks, which in turn significantly reduced insomnia symptoms and improved subjective sleep quality compared to the placebo ( $P < 0.001$ ).<sup>53</sup>

In contrast with the findings of the above-mentioned studies, a previous study reported that escitalopram 10-20 mg/day was not effective in the treatment of menopausal HF.<sup>29</sup> However, the low sample size could have negatively affected the results. The study included two groups; a group of 16 women receiving escitalopram 10 mg/day and another group of 26 women receiving escitalopram 20 mg/day, both for eight weeks. In each group, the participants were randomly assigned to equal groups to receive active drug or placebo. In the first group, the results did not show any significant effect of the drug. However, in the second group, escitalopram resulted in an average decrease of HF frequency (14.4%) compared to the placebo group (6.7%,  $P < 0.05$ ). Nonetheless, the overall effectiveness of this drug was minimal.

### *Paroxetine*

Among the six studies that evaluated the effectiveness of paroxetine in the treatment of HF, five studies reported that it was an effective and acceptable therapy for the management of menopausal HF.<sup>22, 23, 43, 49, 66</sup>

In a study by Stearns and colleagues, participants were given paroxetine 12.5 mg/day, paroxetine 25 mg/day, or placebo.<sup>43</sup> They reported that the mean reduction in HF frequency was 3.3, 3.2, and 1.8 for the 12.5 mg/day group, the 25 mg/day group, and the placebo group, respectively. Most of the participants (89%) in the treatment groups reported mild to moderate side effects. The most common side effects were headache, nausea, and insomnia.

Simon and colleagues assessed the efficacy of low-dose paroxetine (7.5 mg) for the treatment of VMS and reported that the mean weekly frequency of VMS in the paroxetine group was significantly reduced at week four ( $P < 0.0001$ ), week 12 ( $P = 0.0090$ ), and week 24 ( $P = 0.0001$ ) compared to the placebo group.<sup>22</sup> The mean reduction in the severity of VMS during a 24-week trial of treatment with paroxetine was significantly greater than the placebo group at week four ( $P = 0.0452$ ) and week 12 ( $P = 0.0114$ ). The participants experienced mild to moderate

side effects of paroxetine such as muscle cramps, spasms, twitching of muscles, the feeling of restless legs, insomnia, nausea, fatigue, and dizziness. They reported the effectiveness of paroxetine during the 24-week of treatment. No significant difference was found between the paroxetine 7.5 mg arm and the placebo arm in terms of discontinuation symptoms (e.g., influenza-like illness, dizziness, fatigue, nausea, sensory disturbances, and paresthesia).

Soares and colleagues evaluated the effects of 12.5-25 mg/day of controlled-release paroxetine on changes in vasomotor scores.<sup>23</sup> Their results showed the efficacy of paroxetine in reducing VMS in the treatment group compared to the placebo group. The mean reduction of weekly HF was 6.1 in the treatment group and 2.8 in the placebo group ( $P = 0.03$ ). After treatment, they used the Discontinuation Emergent Signs and Symptoms (DESS) checklist and reported mild discontinuation symptoms in the paroxetine (47%) and placebo (50%) groups, which was not statistically significant. The participants of both groups stated similar severity of mild side effects such as headache and dizziness.

Zareen and colleagues conducted a study to determine the role of paroxetine in reducing HF frequency in postmenopausal women.<sup>66</sup> In their study, two groups received paroxetine 12.5 mg/day and 20 mg/day, and one group received a placebo. Based on the GCS scoring, they showed that HF frequency after 12 weeks in the first intervention group (paroxetine 12.5 mg/day) was  $1.97 \pm 0.31$  compared to the baseline frequency ( $2.64 \pm 0.29$ ). Moreover, HF frequency in the second intervention group (paroxetine 20 mg/day) was  $2.04 \pm 0.12$  compared to the baseline frequency ( $2.76 \pm 0.23$ ). In the placebo group, it was  $2.80 \pm 0.24$  after 12 weeks. They concluded the two doses of paroxetine to be significantly effective in reducing the HF frequency in postmenopausal women compared to the placebo group ( $P < 0.01$ ). The side effects of paroxetine were not mentioned in that study.

In a randomized double-blind, placebo-controlled study, Pinkerton and colleagues enrolled 1,174 postmenopausal women and assigned them to two groups.<sup>49</sup> They assessed nighttime awakenings due to VMS at weeks 12 and 24. They reported that paroxetine 7.5 mg significantly reduced the number of nighttime awakenings due to VMS in the treatment group. They did not report the side effects of the drug.

In 2014, Simon and colleagues assessed the effectiveness of paroxetine and raloxifene on the frequency and severity of weekly HF.<sup>50</sup> They reported that HF frequency in the paroxetine group was numerically lower (-49.8 vs -37.4),

but the reduction was not significantly greater than the placebo group ( $P < 0.584$ ). They also showed that raloxifene had no significant effect on reducing HF in postmenopausal women compared to the placebo (-14.2 vs -37.4,  $P = 0.152$ ). Furthermore, their results showed no significant differences between the two treatment groups ( $P = 0.120$ ).

### Sertraline

Three studies addressed the use of sertraline for the treatment of HF in menopausal women.<sup>25, 30, 44</sup> The results of two studies showed the effectiveness of sertraline in the treatment of HF.<sup>25, 44</sup>

In a study by Gordon and colleagues, 87 women were assigned to two treatment groups and a placebo group.<sup>25</sup> The results indicated that the number of HF per week during the treatment phase was significantly lower than baseline compared to the placebo group. Women in the intervention group experienced five HF less in a week (the average HF frequency based on mean  $\pm$  SD scores) than the placebo group in each week during weeks one to four ( $P = 0.002$ ). The severity of HF was not significantly different between the groups. During the first week of intervention, 49% of the participants, who received sertraline, and 19% of the participants in the placebo group showed significant severe nausea ( $P < 0.001$ ). The results showed no difference in side effects between the groups after the first week. Another clinical trial showed that the frequency and severity of HF were reduced statistically but were clinically modest in the sertraline group compared to the placebo group. No side effects during the treatment period were reported.<sup>44</sup>

In a six-week randomized controlled trial, Grady and colleagues reported that the mean HF frequency decreased similarly in both the sertraline and placebo groups ( $P = 0.94$ ). The mean HF scores also decreased similarly in both groups ( $P = 0.86$ ). The prevalence of side effects (dry mouth, gastrointestinal symptoms, and dizziness) was significantly higher in the sertraline group. They concluded that sertraline is not effective in the treatment of menopausal HF.<sup>30</sup>

### Citalopram

The five studies that investigated the efficacy of citalopram in the treatment of HF reported significantly different results.<sup>56, 57, 59, 61, 62</sup> Kalay and colleagues enrolled 100 postmenopausal women and assigned them to four groups: (1) citalopram, (2) placebo, (3) citalopram plus HT, and (4) placebo plus HT.<sup>61</sup> HF reduction rates

were 37% in group one, 13% in group two, 50% in group three, and 14% in group four. The reduction rates in groups one and three were greater than in groups two and four ( $P < 0.01$ ). Citalopram was recommended as an effective treatment option for HF. However, one of the most important limitations of this study was its single-blind design. The drug side effects in groups one and three were significantly greater than in the placebo group. The most reported symptoms included somnolence, increased perspiration, palpitation, and dry mouth.

A double-blind, randomized, placebo-controlled study in Iran assessed the effectiveness of *Nigella sativa* and *Vitex agnus-castus* combined with citalopram on postmenopausal women with HF.<sup>57</sup> They assigned the participants to two groups; the first group received a combination of both herbs and citalopram, whereas the second group received placebo. They showed that combining the herbs with citalopram significantly reduced the three domains of the MENQOL questionnaire (VMS:  $P < 0.001$ , physical:  $P = 0.036$ , and psychosocial symptoms:  $P = 0.001$ ). No serious side effect was reported in that study.

Davari-Tanha and colleagues compared the effectiveness of citalopram and venlafaxine in the treatment of sleep disturbance in menopausal aged women.<sup>59</sup> They also evaluated the frequency and severity of HF. Their results showed that both drugs reduced HF frequency ( $P < 0.05$ ) compared to the placebo group. However, citalopram was more efficacious than venlafaxine ( $P = 0.03$ ). Either drug reduced the severity of HF compared to the placebo ( $P = 0.02$ ). The reported side effects were vomiting, nausea, constipation, lethargy, and headache.

In another study, 150 healthy women with HF were assigned to three groups, namely citalopram, fluoxetine, and placebo.<sup>62</sup> The results showed that HF frequency after the intervention was not significantly different. After nine months of follow-up, the percentage of dropouts in the placebo group was 40% and 34% in both the citalopram and fluoxetine groups. Ineffectiveness of the treatment was reported as the most common reason for subject withdrawal. Nausea and dry mouth were the most frequent side effects experienced in both treatment groups. Despite a long treatment period, citalopram showed no significant efficacy in the treatment of HF.

Amin and colleagues conducted a randomized clinical trial in Iran to compare the effectiveness of combined *Nigella sativa* and *Melissa officinalis* extracts versus fennel fruit combined with citalopram on menopausal symptoms.<sup>56</sup>

They reported no significant difference in the improvement of menopausal symptoms (e.g., VMS) between the two groups ( $P=0.232$ ). The frequency of VMS did not decrease in either group compared to the baseline. The feeling of anger and fatigue in the citalopram group was greater after treatment than the *Nigella sativa* plus *Melissa officinalis* group ( $P=0.03$ ). Drug side effects such as vomiting, nausea, and irritability were the reason for nine individuals in the citalopram group to withdraw from the study.

#### *Fluoxetine*

Five clinical trials evaluated the effectiveness of fluoxetine in the treatment of menopausal HF in healthy menopausal women.<sup>28, 54, 55, 58, 60</sup> Three of these studies, conducted in Iran, reported that fluoxetine had a positive effect on reducing HF,<sup>28, 54, 55</sup> but the results of one trial were contradictory.<sup>58</sup>

Ghomian and colleagues assigned 80 postmenopausal women to two groups, namely the Fluoxetine group ( $n=40$ ) and placebo group ( $n=40$ ).<sup>54</sup> They reported that the severity of HF was significantly different between the treatment group and the placebo group at weeks two ( $P=0.018$ ), four ( $P=0.049$ ), and eight ( $P=0.01$ ). Positive clinical response in the fluoxetine group was 75%, which was significantly greater than in the placebo group (42.5%,  $P=0.01$ ). Drug side effects were reported in 52.5% of women in the Fluoxetine group and 58.5% of women in the control group. The difference was not statistically significant between the groups ( $P=0.105$ ). Headache and anxiety were the most common symptoms in the treatment group and the placebo group, respectively. The study did not report any subject withdrawal due to drug side effects.

Akhavan and colleagues compared the efficacy of fluoxetine and citalopram versus estrogen plus progesterone and placebo on 80 menopausal women.<sup>28</sup> They reported that HF frequency was significantly decreased in the fluoxetine and citalopram groups ( $P<0.001$ ). The severity of HF was not assessed in this trial and the participants showed no drug side effects.

Yazdizadeh and colleagues reported that HF frequency decreased by 55% in the fluoxetine group and 28% in the placebo group. HF was significantly reduced in the fluoxetine group ( $P>0.001$ ). However, 11% of the participants withdrew from the study because of side effects (headache and heartburn).<sup>55</sup>

In a crossover study by Rahmanian and colleagues, the effectiveness of gabapentin and fluoxetine for the treatment of VMS in postmenopausal women was compared. They

reported that after two rounds of therapy, gabapentin reduced the frequency ( $P<0.001$ ) and severity of HF more than fluoxetine ( $P<0.001$ ). Lack of appetite was the only side effect reported by individuals in the fluoxetine group.<sup>58</sup>

Oktem and colleagues compared the effectiveness of fluoxetine and black cohosh in the treatment of menopausal symptoms. They reported that black cohosh was more effective in alleviating menopausal symptoms. The percentage of subject withdrawal was similar in both treatment groups (33%). The absence of a placebo group was the main limitation of this study.<sup>60</sup>

#### *Fluvoxamine*

Only one pilot study investigated the effect of fluvoxamine in the treatment of climacteric symptoms (vasomotor, psychological, and skeletal).<sup>63</sup> The study had a sample size of 22 and no control group. The results indicated that fluvoxamine was effective in the treatment of vasomotor and psychological symptoms. Some side effects (nausea, mouth dryness, dizziness) were reported by four of the participants.

#### *Serotonin-norepinephrine Reuptake Inhibitors Venlafaxine*

Two randomized controlled trials investigated the use of venlafaxine in the treatment of postmenopausal HF.<sup>45, 46</sup> Evans and colleagues showed that the severity score of HF in the treatment group was lower than the placebo group, although it was not statistically significant ( $P=0.25$ ).<sup>45</sup> The study recommended venlafaxine as an appropriate option for the treatment of HF when they interfere with daily activities. Nineteen participants (23.5%), 11 individuals in the treatment group and eight individuals in the placebo group, withdrew from the study. Side effects such as dry mouth, sleeplessness, and decreased appetite were significantly more frequent in the venlafaxine group.

Caan and colleagues used venlafaxine and low-dose estrogen in the treatment of postmenopausal HF.<sup>46</sup> They reported that both venlafaxine and estrogen were effective in treating VMS associated with reduced health-related quality of life in healthy postmenopausal women. The total score of the MENQOL questionnaire in the two treatment groups was significantly lower than the total score of the placebo group ( $P<0.001$ ). Drug side effects and dropout rate were not reported.

#### *Desvenlafaxine*

Six clinical trials with large sample sizes studied

the efficacy and safety of desvenlafaxine in alleviating HF in menopausal women.<sup>27, 47, 48, 51, 52, 67</sup> Five studies reported that desvenlafaxine was an effective non-hormonal drug in the treatment of menopausal HF.

Archer and colleagues conducted two studies with different treatment durations (first study: 12 weeks, second study: 26 weeks).<sup>27</sup> In the first study, the frequency ( $P \leq 0.021$ ) and severity ( $P \leq 0.048$ ) of HF in the treatment groups (desvenlafaxine 100 mg and 150 mg) were significantly reduced at weeks four and 12 compared to the placebo group. Both desvenlafaxine groups and placebo experienced similar mild to moderate drug side effects. Nausea was the most common side effect and was more prevalent in the treatment groups (25.2%) than in placebo (7.3%,  $P < 0.001$ ). In the second study, desvenlafaxine 100 mg and 150 mg were compared to placebo at weeks four, 12, and 26. The results showed that HF frequency in both treatment groups was significantly reduced at weeks four and 12 ( $P < 0.002$ ), although only desvenlafaxine 150 mg significantly reduced HF frequency at week 26. The severity of HF improved in the treatment groups that the placebo group at weeks four and 12 ( $P < 0.002$ ). Dry mouth, nausea, vomiting, dizziness, insomnia, nervousness, somnolence, and mydriasis were the most common side effects in the treatment groups ( $P < 0.001$ ).<sup>47</sup>

Speroff and colleagues enrolled 707 healthy postmenopausal women with moderate to severe HF in a longitudinal study, increasing the validity and accuracy of the results.<sup>48</sup> They compared four different doses of desvenlafaxine with placebo. Of the 707 participants, 620 (87.7%) individuals completed four weeks of treatment, 519 (83.7%) completed 12 weeks of treatment, and 368 (59.4%) completed  $\geq 50$  weeks of treatment. There was a significant dropout rate during the first week in the desvenlafaxine groups compared to the placebo group due to the side effects of the drug ( $P < 0.04$ ). Treatment with desvenlafaxine 100 mg significantly reduced the frequency of moderate to severe daily HF compared to the placebo ( $P = 0.013$ ). Among the four doses of desvenlafaxine (50, 100, 150, 200 mg), 100 mg of desvenlafaxine reduced HF frequency more than other doses. Compared with placebo, 150 mg of desvenlafaxine reduced HF frequency at week 12 ( $P = 0.020$ ), while 50 and 200 mg of desvenlafaxine improved HF similar to placebo. Overall, compared with placebo, 100 and 150 mg of desvenlafaxine were significantly effective in reducing the daily HF frequency irrespective of the severity (mild, moderate, severe). Nausea was the most prevalent side effect in the treatment

groups. Although this symptom was dose-dependent, it was lower in the desvenlafaxine 50 mg group (18%) than 100 mg (33%), 150 mg (39%), and 200 mg (42%) groups. Significant side effects included dry mouth, hypertension, somnolence, nervousness, anorexia, dizziness, insomnia, vomiting, decreased libido, asthenia, constipation, and abnormal behavior. These were more common in the desvenlafaxine groups than in the placebo group.

Pinkerton and colleagues conducted two studies to assess the efficacy of desvenlafaxine on menopausal VMS.<sup>51, 52</sup> In their first randomized controlled trial, HF frequency at weeks 12, 24, and 52 (one year) was assessed. They reported that both the frequency ( $P < 0.001$ ) and severity of HF ( $P < 0.001$ ) reduced at week 12 and thereon remained steady until the end of the study. The participant reported no side effects during the study.<sup>52</sup> In the second study, they evaluated the effectiveness of desvenlafaxine on 365 postmenopausal women with VMS during 12 weeks. They reported that desvenlafaxine resulted in a rapid reduction of the number and severity (moderate to severe) of HF at week four. Although no severe drug side effects were observed, they reported a mild increase in supine systolic and diastolic blood pressure in some desvenlafaxine groups.<sup>51</sup>

Bouchard and colleagues evaluated the efficacy and safety of desvenlafaxine in postmenopausal women with VMS. Participants were randomly assigned to desvenlafaxine, tibolone, and placebo groups. They reported that desvenlafaxine reduced the daily number of moderate to severe HF compared to the placebo (-5.78 vs -5.82), but the difference was not statistically significant ( $P < 0.921$ ). Tibolone reduced the daily moderate to severe HF frequency compared to the placebo ( $P < 0.001$ ). Nausea was the most common drug side effect in the desvenlafaxine group.<sup>67</sup>

### *Duloxetine*

Two clinical trials investigated the use of duloxetine in the treatment of daytime and nighttime HF and depressive symptoms during the menopausal transition.<sup>26, 64</sup> In the first clinical trial, 19 participants received duloxetine 60 mg/day for eight weeks. The study did not include a control or placebo group. The results showed improvement in the frequency and severity of daily HF in women compared to the baseline ( $P = 0.009$  and  $P = 0.008$ , respectively). The study did not state the randomization method and blinding was not considered. No serious side effects were reported by the participants. Only two individuals withdrew from the study

because of side effects such as headache, nausea, dizziness, and possible drug rash.<sup>26</sup> The second clinical trial comprised of a two-week, single-blind placebo run-in phase followed by an eight-week open-label duloxetine therapy for women, who did not respond to placebo. The results showed that eight weeks of duloxetine therapy significantly improved VMS in postmenopausal women ( $P=0.003$ ). The most common side effects in the intervention group were constipation, headache, and dry mouth.<sup>64</sup>

#### *Risk of Bias Assessment*

The Jadad score calculation was used to assess the risk of bias in the studies. The guidelines for quality assessment were used in the assessment process, and the quality of the studies was scored without any bias in terms of their bibliographical characteristics (table 2). To increase the accuracy of the assessment process, the results were initially assessed by two authors and then cross-checked by the third author.

#### *Quality of the Selected Studies*

The results of the Jadad score calculation showed that the methodological quality of nine studies was weak<sup>2, 23, 26, 55, 60, 61, 63, 64, 66</sup> while 27 studies had an acceptable quality. Randomization was not mentioned in six studies.<sup>2, 23, 26, 63, 64, 66</sup> Four studies only mentioned the randomization method (randomized controlled trial) without describing the method.<sup>54, 55, 57, 60</sup> Twelve studies were either a single-blind study or did not mention blinding.<sup>2, 26, 45, 55, 56, 58, 60, 61, 63-66</sup> Three studies mentioned double-blind design, but did not explain the procedure.<sup>3, 23, 29</sup> Twelve studies did not mention the dropout rate.<sup>12, 25, 28, 30, 44, 46, 48, 50, 54, 60, 61, 66</sup>

## Discussion

This study systematically reviewed published clinical trials on the efficacy of SSRIs and SNRIs in the treatment of menopausal HF. The review was limited to articles on healthy menopausal women. Although HT is considered the most effective treatment for menopausal HF, according to recommendations by the Women's Health Initiatives (i.e., the risk-benefit patterns of menopausal HT), some women should not receive HT because of potential high risks. Studies in Iran and developed countries on the role of antidepressant agents in HF treatment have found that most of these drugs significantly alleviated menopausal HF.<sup>2, 12, 21, 22, 25-30, 43-48, 54</sup> The most studied antidepressants for the treatment of menopausal HF were escitalopram, fluoxetine, citalopram, paroxetine, sertraline, and desvenlafaxine. Some studies have shown

that escitalopram in the doses of 10-20 mg/day is effective in the treatment of HF without any serious side effects.<sup>2, 12, 21</sup>

In general, all of the reviewed studies on HF treatment with paroxetine reported positive results. Some dosages of paroxetine (7.5 mg, 12.5 mg, and 25 mg) were effective in alleviating moderate to severe HF. Side effects such as headache, nausea, dry mouth, insomnia, and dizziness were the most common reasons for subject withdrawal.<sup>22, 23, 43</sup> A previous 24-week study of paroxetine reported that the drug was well tolerated and reduced both the frequency and severity of HF.<sup>22</sup> Overall, the side effects of the drug were not bothersome to the patients.<sup>22, 23, 43</sup>

The majority of the reviewed studies reported that paroxetine is an effective and safe drug in reducing menopausal VMS. However, further research is required to confirm the most effective and safest dose of paroxetine for VMS.<sup>33</sup> Based on the result of a study, paroxetine decreases menopausal VMS possibly by regulating body temperature via neurotransmitters.<sup>32</sup> Other studies that used sertraline reported contradictory results. Although most studies supported the effectiveness of sertraline in reducing the frequency and severity of HF,<sup>25, 44</sup> one study reported that the drug was ineffective in treating menopausal HF.<sup>30</sup> The main side effects were severe nausea<sup>25</sup> and dry mouth.<sup>30</sup> However, overall, these studies stated that sertraline may be an acceptable option in the treatment of menopausal HF.<sup>25</sup>

The findings of some studies on the effectiveness of citalopram were also inconsistent.<sup>61, 62</sup> Considering the ambiguities and uncertainties on the efficacy of citalopram, further research is required to confirm the effectiveness of this drug in the treatment of menopausal HF.

According to studies on the efficacy of fluoxetine in the treatment of HF, this drug was recommended for alleviating menopausal HF. However, some other studies reported contradictory results on its effectiveness.<sup>58, 60</sup> Fluoxetine appeared to have no significant side effects and most of the reviewed studies reported the safety of this drug.<sup>28</sup> However, the quality of the published studies on fluoxetine was not high. Therefore, high-quality clinical trials on this drug are strongly recommended. Oktem and colleagues evaluated the efficacy of fluoxetine and black cohosh in the treatment of women with postmenopausal symptoms.<sup>60</sup> They randomly assigned the participants to fluoxetine or black cohosh group and evaluated them after one, two, three, and six months. By the end of the third month, the scores of KI and Beck's

Depression inventory significantly decreased in both groups compared to the baseline values ( $P < 0.001$  in both groups). In this period, KI scores had decreased significantly in the black cohosh group compared to the fluoxetine group ( $P = 0.02$ ). In addition, the decrease in Beck's Depression Inventory scores was significantly greater in the fluoxetine group than in the black cohosh group ( $P = 0.01$ ). After six months, black cohosh reduced monthly HF and night sweats scores more than fluoxetine ( $P < 0.001$ ). In addition, black cohosh reduced HF scores by 85% compared to the 62% for fluoxetine and the total number of side effects was significantly lower than in the fluoxetine group. Considering limited evidence on fluvoxamine, as a class of SSRIs drugs, it seems that this drug is not suitable for the treatment of menopausal HF, and more clinical trials with consistent results are required to confirm its effectiveness.<sup>63</sup>

Discontinuation of SSRIs may have some adverse side effects. Antidepressant discontinuation syndrome occurs in approximately 20% of patients after abrupt discontinuation of an antidepressant taken for at least six weeks. Typical withdrawal symptoms include influenza-like symptoms, insomnia, nausea, imbalance, and sensory disturbances. In cases with high doses of SSRIs, some studies have recommended slow tapering of antidepressants to avoid such adverse effects.<sup>68, 69</sup>

Studies on venlafaxine and desvenlafaxine have shown that doses of 75 mg and 100 mg, respectively, were effective therapeutic options for the treatment of HF.<sup>27, 46, 47</sup> However, some of the reviewed studies stated nausea and dry mouth as the most common side effect.<sup>27, 48</sup> Therefore, it is important to consider such symptoms when prescribing these drugs. Note that there were more studies of desvenlafaxine in healthy menopause women than venlafaxine.

Current literature shows that desvenlafaxine is clinically and statistically a successful non-hormonal alternative for treating menopausal HF, and its use is currently off-label. It should be avoided in patients with known hypersensitivity to desvenlafaxine and patients, who have recently used monoamine oxidase inhibitors for the treatment of psychiatric conditions. It should also be used with caution in elderly menopausal women due to the risk of hyponatremia and orthostatic hypotension. To minimize the side effects of desvenlafaxine, manufacturers recommend that discontinuation of the therapy should include slow tapering over several weeks.

Studies on the effectiveness of duloxetine in the treatment of HF were also limited in number. It is therefore recommended to conduct

further studies to confirm its effectiveness in menopausal HF.<sup>26, 64</sup>

In our systematic review, we included studies on all SSRIs and SNRIs classes of drugs and only gathered data from healthy menopausal women. Since our objective was to determine the effectiveness of these drugs on healthy women, comparable studies in women with cancer were not reviewed. Despite strong evidence on the effectiveness of these drugs, further high-quality studies are required to determine their efficacy in the treatment of HF.

## Conclusion

The findings of the present study indicated limited evidence on the effectiveness of some antidepressants (e.g., fluvoxamine and duloxetine) in treating menopausal HF. Considering their availability and the low rate of side effects, SSRIs and SNRIs can generally be considered effective replacements for HT, especially in women with contraindications for HT. Due to the side effects of HT, it is often recommended that obstetricians consider drugs within the SSRIs and SNRIs classes in the treatment of menopausal HF. However, contradictory results on some of these drugs encourage further high-quality, longitudinal, and large sample size clinical trials. Such studies provide reliable information to determine the most effective antidepressant for the treatment of menopausal HF in women with contraindications for HT.

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## Authors' Contribution

M.A: participated in collecting the data, did the literature search and independent review for eligibility, interpreted findings, drafted the manuscript and revised the manuscript; F. E: contributed in the conception of the work and definition of intellectual content, contributed in study design, did independent review for eligibility, identifying the studies and independently reviewing for eligibility, manuscript revising; S. Kh: contributed in study design, participated in independent review for eligibility and edited the final manuscript and provided critical revision for important intellectual content; M.K: contributed in study design, participated in independent review

for eligibility and edited the final manuscript and provided critical revision for important intellectual content; All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

**Conflict of Interest:** None declared.

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