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Effect of Menopausal Symptom Treatment Options on Palpitations: A Systematic Review

Ying Sheng, PhD, RN[1], **Janet S. Carpenter, PhD, RN, FAAN**[1], **Charles D. Elomba, MSN, RN**[1], **Jennifer S. Alwine, BSN, RN**[1], **Min Yue, BS**[2], **Chen X. Chen, PhD, RN**[1], **James E. Tisdale, PharmD**[2,3]

[1]Indiana University School of Nursing, Indianapolis, IN 46202, USA

[2]Purdue University College of Pharmacy, West Lafayette, IN 47907, USA

[3]Indiana University School of Medicine, Indianapolis, IN 46202, USA

Abstract

This systematic review provides an overview of the effects of menopausal symptom treatment options on palpitations, defined as feelings of missed or exaggerated heart beats, reported by peri- and postmenopausal women. Guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, searches were conducted in PubMed, CINAHL, and PsycINFO to identify articles meeting pre-specified inclusion criteria. Of 670 unique articles identified, 37 were included in the review. Treatments included drug therapies and non-drug therapies. Palpitations were studied as an outcome in 89% of articles and as an adverse effect in 11%. Articles provided mostly level II/III evidence due to their design and/or small sample sizes. Based on available evidence, no therapies can be fully recommended for clinical practice. Only some hormonal agents (e.g., estradiol) can be recommended with caution based on some positive evidence for reducing palpitations prevalence or severity. However, other drug therapies (e.g., moxonidine, atenolol), dietary supplementary treatments (e.g., isoflavones, *Rheum rhaponticum*, sage), cognitive-behavioral intervention, and auricular acupressure cannot be recommended giving the existing evidence. Additional well-designed randomized controlled treatment trials focusing on palpitations during the menopause transition as an inclusion criteria and outcome are needed to advance the field.

Keywords

Menopausal therapy; palpitations; menopause; postmenopause; perimenopause; menopausal symptoms; systematic review

Introduction

About 21 million women living in the US today and 1.2 billion women worldwide will experience menopausal symptoms by 2030 [1–5], and most (75%) will seek help from a health care provider [6]. Menopausal symptoms are more likely to occur during

Corresponding author: Ying Sheng, PhD, RN, Indiana University School of Nu.

perimenopause and postmenopause as a result of estrogen decline caused by ovarian insufficiency [7,8]. The average age of menopause in women is about 51 years [8,9]. Women experience menopausal symptoms for 10 years or more [9]. Menopause symptoms affect women's life and work [7,8]. Research to date has focused mainly on vasomotor symptoms (e.g., hot flashes, night sweats) [10] and strong efficacy evidence is available for drug and non-drug treatment options [11,12].

When compared to the vast literature available on vasomotor symptoms, palpitations during the menopause transition appear to be seldomly studied. Palpitations are reported by 20% to 42% of perimenopausal women and 16% to 54% of postmenopausal women as sensations of skipped, missed, or exaggerated heartbeats [13]. Distress from palpitations during the menopause transition has been associated with more severe insomnia, worse depressive symptoms, and poorer menopausal quality of life [14]. Whether palpitations are associated with electrocardiogram (ECG) abnormalities is not fully known. In the Tromsø population-based study (n=22,815), the sensation of palpitations (e.g., sudden changes in heart rate or rhythm) in the past year was associated with greater risk of developing incident, ECG-verified, atrial fibrillation (OR_{women}=1.62 [1.29–2.02]) when controlling for other known risk factors [15]. Atrial fibrillation is one of several arrhythmias that increases morbidity and mortality [16]. Similar to untreated vasomotor symptoms, untreated palpitations may increase direct care costs and lead to poorer health, lower work productivity, and greater healthcare utilization and costs [17–20].

Although evidence-informed reviews of therapies for vasomotor symptoms regularly appear in the literature [11,12], the same is not true for palpitations. To date, the effect of menopausal symptom treatment options on palpitations have not been reviewed and summarized to create recommendations for practice. Palpitations are often measured with vasomotor and other menopausal symptoms [21]. Menopausal symptom treatments may have potential benefits on palpitations or may cause palpitations as an adverse effect. A systematic review could help assist (1) clinicians in engaging women in shared decision making about treatment options and (2) researchers in understanding gaps in treatment efficacy/effectiveness research to help design future articles. Therefore, given this large gap in the literature, the purpose of this review was to evaluate the effects of menopausal symptom treatment options on palpitations.

Methods

The systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [22].

Review strategy

The review was not registered and did not require institutional review board approval. Articles were included if they were full-length, peer-reviewed, English-language, randomized, non-randomized, controlled, and uncontrolled trials of menopausal symptom therapies that included data on palpitations as an outcome or adverse effect. The latter criteria permitted summarization of evidence on treatments that could alleviate as well as exacerbate palpitations. Articles were excluded if they (1) included transgender or gender

transitioning populations, men, or animals due to different menopausal experience from biologically female women, or (2) did not specify menopausal status for the study sample.

Literature search strategy

Literature searches were conducted in May 2020 by a health science librarian using three online search engines with no restriction on publication date: PubMed, CINAHL, and PsycINFO. All searches used (MeSH terms) “Menopause” OR “Menopaus*”) AND (keywords) (“Palpitation*” OR “Heart racing” OR “Hear Pounding” OR “Irregular heart”). Additional articles were identified by searching for articles that used standard menopausal symptom assessment tools, including the Menopause Rating Scale (Heinemann) [23], Greene Climacteric Symptom Rating Scale [24], Midlife Women’s Symptom Index [25], Holte/Mikkelsen Menopause Checklist [26], Hunter’s Women’s Health Questionnaire [27], Neugarten and Kraines’ Symptom Checklist [28], Study of Women Across the Nation menopausal symptom checklist, Menopause Symptoms List [29], and Kupperman/Blatt Index [30–32].

Study selection

All citations from the database searches were screened independently by two authors (JSC, CDE, JA). Disagreements were resolved through discussion and erring on the side of inclusion to full-text screening, which was performed independently by two reviewers from the same group of three. All disagreements were resolved through discussion.

Data collection

Data extraction was performed by one author (JSC) and then verified by two reviewers (YS, CDE, MY, CXC, JET). Discrepancies were resolved through discussion and referral back to the article contents. The data extraction form included fields about treatment categories, the article (author, year, country), design (number of groups, masking, randomization, control, and crossover), sample characteristics (number, age, symptoms when recruited, and menopausal status), data collection and timepoints, intervention and control or comparison condition details, palpitations as outcome or adverse effect, study findings, and quality and bias ratings. Cochrane levels of evidence ratings were noted, and the ROBINS-I and ROBINS-II tools were used to assess for presence of bias and study quality [33,34]. Because this appeared to be the first review of its kind and we aimed to conduct an inclusive/comprehensive review, papers were not excluded solely on the basis of quality ratings.

Data synthesis

To aid the data synthesis, the tables were organized by author last name from the included articles within larger categories of drug and non-drug therapies. Within each category, extracted data were synthesized. Effects of the interventions on palpitations prevalence and/or severity were noted as significant or non-significant and details about the significant findings were further described. Heterogeneity across the reviewed articles prohibited meta-analysis. We included an evidence summary statement in the results pertaining to each treatment, was done in a prior vasomotor treatment position paper [35]. We included a statement about whether each treatment could be recommended (positive level 1 evidence

from multiple articles), could be recommended with caution (positive level II evidence from multiple articles), or could not be recommended at this time (insufficient, negative, or equivocal evidence) [35].

Results

This search initially identified 1574 citations. After 904 duplicates were removed, there were 670 unique articles. Of these, 62 were excluded, most because of no palpitations data or not being data-based. Of the remaining 608 articles reviewed in full text, 571 were excluded, most for not containing data on palpitations or data not separately reported. This resulted in 37 eligible articles for the review. The selection process is illustrated in the PRISMA [22] diagram (Figure 1).

Articles are summarized in tables and figures. Table 1 contains descriptive information about all articles, organized by treatment option category of drug therapies followed by non-drug therapies. Table 2 pertains to 2- and 3-group trials and shows comparative effects on palpitations. Additional details on results for treatments on palpitations prevalence and/or severity are in Supplement A. Bias assessment for articles is shown in Supplement B.

Drug therapy options (n=19)

Drug therapies (n=19) for menopausal symptoms included: (1) hormonal agents (n=15); (2) non-hormonal drug therapies (n=4) including selective serotonin reuptake inhibitor/serotonin-norepinephrine reuptake inhibitor (SSRI/SNRI) (n=3), and antihypertensives (n=1). Each category is discussed below.

Hormonal agents (n=15)—As shown in Table 1, 15 articles focused on various hormonal agents (e.g., estrogen, progesterone, tibolone, raloxifene) with differing mechanisms of action [36–50]. Articles were from 19 different countries. Most articles included a control or comparison group (86.7%) [36–39,41–47,49,50]. Most articles focused on peri- and postmenopausal women reporting one or more menopausal symptoms. Sample sizes varied with 60% below 100 (n=9) [36–38,40,42,44,46,49,50], 20% between 100 and 200 (n=3) [39,41,43], and 20% over 200 (n=3) [45,47,48]. Palpitations were measured using a single self-reported item in 10 different measures, such as “palpitations” in the Kupperman index [36] and “heart discomfort” in the Menopause Rating Scale (MRS) [38,42]. Intervention doses and treatment periods varied across all the articles. For example, one article [36] used transdermal 17 β-estradiol plus medroxyprogesterone on days 14 and 25 for 6 months, while another [43] applied transdermal 17 β-estradiol 50ug daily with micronized progesterone 200mg daily for first 12 days of the month for 48 months. Most data collection periods were within one year and slightly more than half of the articles collected data at three or more timepoints [36,39–41,43,44,47,50]. Palpitations were studied as an adverse effect in one article, where one subject withdrew from transdermal estradiol due to palpitations [37]. In the remaining 14 articles, palpitations were an outcome usually assessed as severity (Supplement A). Of these 14, none (0%) were level I, 57.1% were level II [36,38,39,41,43–45,50] and 42.9% were level III evidence [40,42,46–49].

As shown in Table 2 and Supplement A, in most articles, hormonal agents showed treatment benefit in relation to baseline but not necessarily in relation to placebo or other comparators [38,39,41,42,45–47,49]. When hormonal agents were compared to other interventions, various forms of hormonal agents were equally beneficial, but hormonal agents were not superior to isoflavone [38]. When hormonal agents were combined with psychological treatment, benefits were superior to hormonal agents alone in one study [36], yet in another study, hormonal agents alone was less efficacious than counseling [46]. In two studies, neither hormonal agents or placebo showed benefit [44,50]. In two uncontrolled trials [40,48] shown in Supplement A, severity decreased from pre- to post-treatment with 3 or 6 months of hormonal agents. However, in one report, most women (73.7%) reported unchanged or worsened palpitations [40]. Based on the evidence, hormonal agents should be recommended with caution for menopausal palpitations.

Non-hormonal drug therapies (n=4)

SSRI/SNRI.: As shown in Table 1, palpitations were studied as an adverse effect in three articles [51–53]. One [51] focused on postmenopausal women and two [52,53] on peri- and postmenopausal women reporting depressive symptoms. Of the three articles, two [51,52] had less than 40 women, while one [53] had about 800 women. Palpitations were assessed as a self-reported adverse effect by a checklist or a scale for adverse effects. Palpitations were reported following treatment with vortioxetine (3.7% [51], 25.0% [52]), and desvenlafaxine (3.5%) [53] but not paroxetine (0%) [51]. Although all articles used an outcome measure that included palpitations, none reported the number of participants with palpitations at baseline. Thus, it is unclear whether palpitations were present at baseline or truly an adverse effect of treatment. Given that there is no efficacy data for these medications on palpitations, they cannot be recommended at this time.

Antihypertensives.: As shown in Table 1, one article compared moxonidine and atenolol in 112 postmenopausal women in Finland [54]. Palpitations were an outcome measured by a single self-reported item in a questionnaire. Both medications showed benefit over baseline on decreasing palpitations severity, but there was no placebo group [54] (Table 2, Supplement A). Based on this single article of level III evidence, moxonidine and atenolol are not recommended for menopausal palpitations.

Assessment of bias in articles of drug therapies—All articles of drug therapies (100%) had a critical risk of bias, defined as bias in three or more categories. Article bias was from: no confounders included in the analysis (93.3% articles, 14/15), participant selection bias present or unclear (94.7%, 18/19), no palpitations-specific inclusion criteria (100%), no treatment adherence assessment or analysis (94.7%, 18/19), no dropout analysis among five trials with dropout (100%), and/or no specified measurement recall period (100%) (Supplement B).

Non-drug therapy options (n=18)

Non-drug therapies (n=18) for menopausal symptoms included: supplementary treatments (n=15), psychological intervention (n=2) and auricular acupressure (n=1). Each category is discussed below.

Supplementary treatments – isoflavones and other phytoestrogens (n=5)—As shown in Table 1, five articles evaluated isoflavones and other phytoestrogens and were conducted in four countries, including Italy, India, Austria, and Brazil [55–59]. Four articles compared an intervention to another intervention or placebo [55,57–59], while one was a single-group design [56]. Four articles (80%) included 100 or fewer peri- or postmenopausal women. In all studies, the sample mean age ranged from 42.3 to 55 years. Palpitations were measured as an outcome using a single self-reported item in a survey, MRS, and Blatt-Kupperman index. Of the five articles, three were level II [57–59], and two were level III evidence [55,56].

As shown in Table 2 and Supplement A, the effects of isoflavones/other phytoestrogens were equivocal. One uncontrolled trial of isoflavones showed positive effects on palpitations [56], and another controlled trial showed an isoflavone together with resveratrol was beneficial over placebo [59]. However, in controlled trials, phytoestrogens from pomegranate seed oil showed no benefit over placebo [57], and isoflavone plus exercise showed no benefit over exercise plus placebo [58]. One comparative study showed no differences between two isoflavone supplementary treatments, one of which also contained magnolia bark extract [55]. Based on this evidence, isoflavones and other phytoestrogens are not recommended for menopausal palpitations.

Supplementary treatments– Rheum rhaponticum (n=3)—Three randomized controlled trials compared *Rheum rhaponticum* extract (ERr 731) to placebo for menopausal symptoms [60–62] (Table 1). All had about 100 perimenopausal Ukrainian women with a mean age of about 49 years old. Palpitations as an outcome were measured using a single self-reported item, “heart complaints” in the MRS. All women in Hasper et al. [60] were from a sample who previously participated in the trial by Heger et al. [61]. Hasper et al. [60] measured palpitations for every 12 weeks from baseline to 48 weeks and the other two measured every 28 days from baseline to 84 days [61,62]. All the articles were level II evidence, except a sub-study from Hasper et al., which was level IV [60]. As shown in Table 2 and Supplement A, results were positive in two trials [61,62] but not another trial [60]. Based on the evidence, *Rheum rhaponticum* is not recommended for menopausal palpitations.

Supplementary treatments – Salvia officinalis or sage (n=3)—Three articles used Salvia officinalis or sage for menopausal symptoms in postmenopausal women from Switzerland or Iran [63–65] (Table 1). Palpitations were an outcome measured by a single item in the MRS from baseline to post-treatment with a range of 2 to 12 weeks. One article was level II [65] and two were level III evidence [63,64]. As shown in Table 2 and Supplement A, one controlled trial [65] found Salvia officinalis to be more effective than placebo for reducing palpitations severity. In two uncontrolled trials [63,64], severity was decreased from pre- to post-treatment after 4-week and 8-week treatments with Salvia officinalis. Because of the level of evidence, Salvia officinalis cannot be recommended for menopausal palpitations.

Supplementary treatments – other (n=4)—As shown in Table 1, four articles evaluated other miscellaneous supplementary treatments, including *Tribulus Terrestris* L.

(fruits) powder, ayurvedic agents, homeopathic agents, and *Schisandra chinensis* [66–69]. Three articles were from India [66–68] and one from South Korea [69]. The majority (75%) had small sample sizes of 36 to 60 peri- or postmenopausal women. Palpitations were assessed using a single self-reported item differently across articles, such as “heart discomfort” [66,67] and “heart palpitations” [69]. Half were level II [66,69] and half were level III evidence [67,68].

Compared to placebo, *Tribulus terrestris* [66] significantly reduced palpitations prevalence and severity [66], and *Schisandra chinesis* reduced severity [69] (Table 2, Supplement A). In uncontrolled trials, ayurvedic agents decreased palpitations severity over a 3-month period, and [67] and homeopathic agents decreased palpitations prevalence and severity over one year [68]. Based on only one level II/III evidence article of each supplementary treatment, none of these agents can be recommended for menopausal palpitations.

Psychological intervention (n=2)—Two articles evaluated psychological interventions for menopausal symptoms [70,71] (Table 1, Table 2, Supplement A). In an uncontrolled trial (level III evidence) in 30 women, palpitation severity significantly decreased from pre- to post-treatment after 7 weekly 1.5-hour group cognitive-behavioral sessions [70]. In a partial factorial trial (level II evidence) in 164 women, a psychological intervention plus Chinese herbals were significantly more beneficial in reducing palpitations severity compared to either intervention alone [71]. Based on limited level II evidence, a psychological intervention cannot be recommended for palpitations at this time.

Auricular acupressure (n=1)—One article evaluated 4-week auricular acupressure in 45 postmenopausal Taiwanese women reporting insomnia [72] (Table 1). Palpitations were measured at baseline and 4 weeks post-treatment using a single self-report item in the MRS. Although severity decreased over time (Supplement A), based on this single article of level III evidence, auricular acupressure cannot be recommended for palpitations at this time.

Assessment of bias in articles of non-drug therapies—All non-drug therapy articles (100%) had a critical risk of bias, defined as bias in three or more categories. Article bias was from: no confounders in the analysis (94.4%, 17/18), participant selection bias present or unclear (88.9%, 16/18), no palpitations-specific inclusion criteria (100%), no treatment adherence assessment or analysis (94.4%, 17/18), no dropout analysis among nine trials with dropout (100%), and/or no specified measurement recall period (100%) (Supplement B).

Discussion

This is the first review of treatments for palpitations occurring during the menopause transition. The major findings from this review were the relative scarcity of articles, the heterogeneity in treatments, design, and outcome measures, and the poor quality of articles. Only 37 articles were identified, which pales in comparison to the number of intervention articles related to other menopausal symptoms such as hot flashes or sleep disturbances. In addition, articles varied in terms of intervention (category, agent, dose, treatment length), design, and outcome measures, thus preventing comparisons and meta-analysis. All articles

showed a critical risk of bias when being evaluated for efficacy on palpitations. Finally, there was no level I evidence for any intervention, and level II evidence was not always positive. Thus, based on this review, no treatments can be fully recommended. Only hormonal agents can be recommended with caution, and all other treatments in the reviewed articles cannot be recommended given the existing evidence [35].

The second finding in this review was the lack of focus on palpitations as an outcome. In articles where palpitations were assessed as an outcome, measurement tools and statistical power were problematic. For example, palpitations were assessed mainly via a single item on a checklist with response options related to the severity, and the recall period for the measure was commonly unspecified. In addition, because articles focused on menopausal symptoms in general, and only a subset of women reported palpitations at baseline, negative findings in many of the smaller trials could be because studies were not powered on palpitations as the outcome. In addition, in four articles [37,51–53] it was unclear whether palpitations resulted from treatments, including hormonal agents (transdermal estrogen [37]) and non-hormonal SSRI/SNRI (vortioxetine [51,52] and desvenlafaxine [53]), or whether they were present at baseline.

In regard to safety, some of the treatment options studied have been associated with adverse effects. For example, in a Cochrane review, tibolone was associated with vaginal bleeding and recurrent breast cancer in those with a history of breast cancer and may be associated with stroke in women over 60 years old [73]. SSRI/SNRI were associated with risks of bleeding, hyponatremia [74], nausea, headache, insomnia, and sexual dysfunction [75]. Long-term phytoestrogens (e.g., 5-year treatment) were associated with an increased risk of endometrial hyperplasia [76]. Adverse effects of *Rheum rhaponticum* include hypersensitivity or rash, gastrointestinal symptoms, and nervous system effects [77]. Adverse effects of *Salvia officianalis* include mild abdominal pain, mild diarrhea, acneiform skin eruption, and mild gastrointestinal complaints [78]. Herbal dietary supplementary treatments are associated with adverse effects in different physiological systems, such as the central nervous system, hematologic, and cardiovascular [79]. Assessment and documentation of adverse effects may be missing, particularly due to misconceptions that natural products are safe because they come from plants. In future research testing interventions for palpitations, it will be critical to examine intervention efficacy and safety to generate the evidence women and providers need to make informed choices about treatment options.

Results from this review should be considered in light of some limitations. Only articles in English were included, which may have led to the inadvertent omission of some articles or some types of interventions (e.g., Traditional Chinese medicine reported in Chinese language publications). Palpitations do not have a standardized subject search term in any of the databases we searched; therefore, some articles may have been missed in our search. Finally, we did not conduct meta-analysis to quantitatively calculate the overall effect size due to the high heterogeneity across studies, and thus avoided the likelihood of producing a questionable summary [80].

This review contributes to future research and clinical practice in the field of palpitations. None of the reviewed articles used ECG devices to evaluate palpitations and exclude arrhythmias, such as atrial fibrillation. Several wearable ECG devices are approved as clinically diagnostic for accurately capturing heart rate and rhythm disturbances [81]. Future studies should use clinically diagnostic ECG devices to evaluate rhythm and rate disturbances occurring with the felt sensation of palpitations to better understand the symptom and develop treatments. Clinicians should be aware that women reporting palpitations may need referral to a cardiologist to further evaluate the symptoms, any underlying arrhythmia, and determine a best course of treatment. We note that while beta-blockers effectively control heart rhythm when used appropriately [82], there is scant evidence regarding their use for menopausal symptoms [54,83].

Conclusions

This review serves as a call to action for rigorous clinical research evaluating the efficacy and safety of commonly researched menopausal symptom treatment options on palpitations. This review also informs clinicians about the current state of evidence related to menopausal symptom treatment options and palpitations. Based on available evidence, no treatment options can be fully recommended, only hormonal agents can be recommended with caution, and many other treatments cannot be recommended based on currently available evidence.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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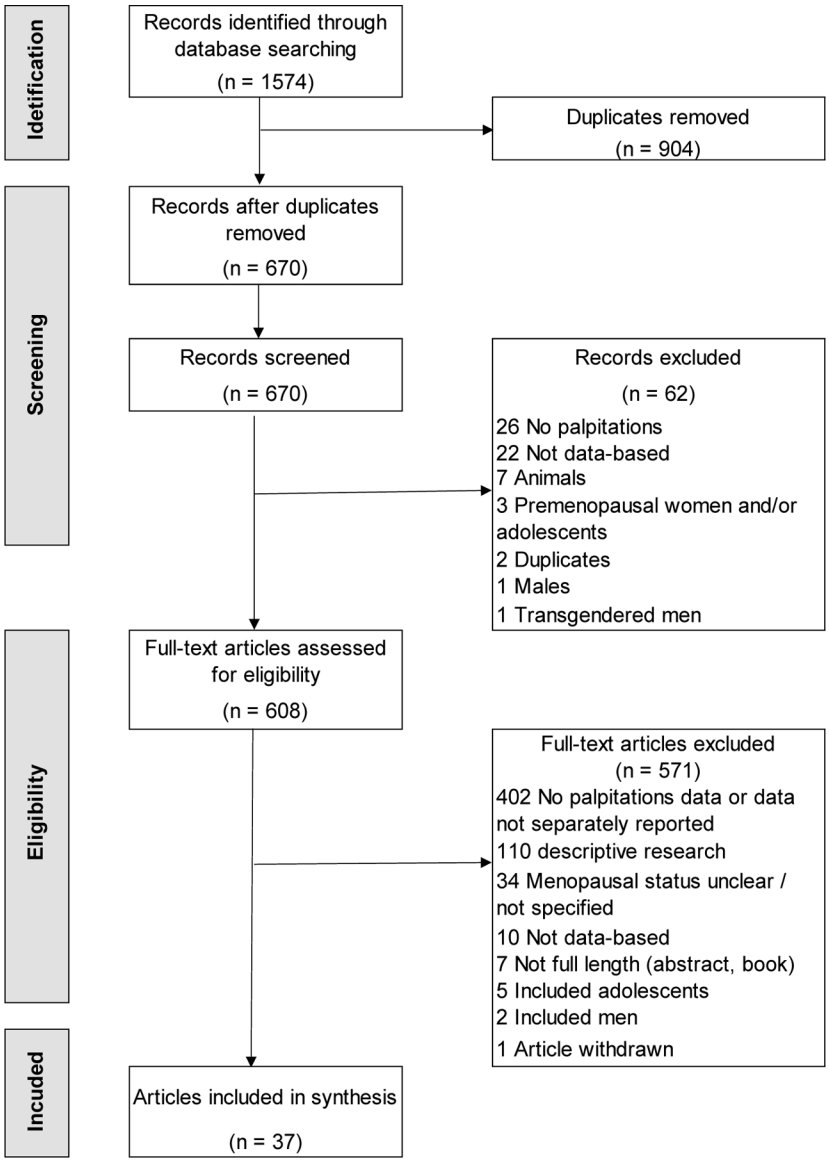

Figure 1.
Flow diagram depicting disposition of the articles.

Table 1.

Descriptive information from interventions articles (N=37).

Author, year, country	Design	Sample size and characteristics	Measure, timepoints	Intervention	O or AE	QR
DRUG THERAPIES (n=19)						
Hormonal agents (n=15)						
Anarte et al., 1998 [36], Spain	2-group RT Unclear masking	• n=73 (IG1 37, IG2 36) • Age IG1 M=50.62 • Age IG2 M=49.83 • With severe and varied psychological sx • Postmeno	• Kupperman Index • Baseline, post-intervention, 6 months	• IG1: HT (transdermal 17 β-estradiol + medroxyprogesterone on days 14 and 25) + 6-month psychological treatment (educational, counselling, behavioral components) of 10–16 sessions x 30 min • IG2: HT alone on days 14 and 25	O	II
Bhattacharya & Jha, 2010 [37], India	2-group single blind RT	• n=76 (Estradiol 38, Tibolone 38) • Age estradiol M=44.5 • Age tibolone M=44.1 • With meno sx • Surgically postmeno	• Not specified • Not specified	• Estradiol: Transdermal estradiol gel (1.5mg/d, 0.06%) for 6 months • Tibolone: Oral tibolone 2.5 mg/d for 6 months	AE	NA
Carmignani et al., 2010 [38], Brazil	3-group double blind RCT	• n=60 (HT 20, Isoflavone 20, CG 20 • Age HT M=53.5 • Age isoflavone M=52.9 • Age CG M=50.9 • With > 8 hot flashes/24 hour • Postmeno	• MRS • Baseline, 16 weeks	• HT: 1mg estradiol, 0.5mg norethisterone acetate) + 2 portion/d of placebo power for 16 weeks • Isoflavone 90 mg + one placebo tablet for 16 weeks • CG: One placebo tablet + 2 portions/d of placebo power for 16 weeks	O	II
Checa et al., 2005 [39], Spain	3-group evaluator blind RT	• n=136 (HT 48, Raloxifene 48, Calcium 40) • Age HT M=56.4 • Age raloxifene M=54.9 • Age calcium M=55.1 • With current HT or osteoporosis	• Modified short form-36 focusing on selected menopausal symptoms • Baseline, 6, 12 months	• HT: Estrogen patches (3.9mg estradiol) / progesterone (100mg/day) for 1 year • Raloxifene: 60mg/day for 1 year • Calcium: 500mg elemental calcium, 400 IU Vitamin D3 daily for 1 year	O	II

Author, year, country	Design	Sample size and characteristics	Measure, timepoints	Intervention	O or AE	QR
		• Postmeno				
Chittacharoen et al., 2004 [40], Thailand	1-group open-label pre-post trial	• n=39 • Age M=52.3 • Peri and postmeno	• MRS II • Baseline, 3, 6 months	• Oral Estradiol valerate (EV) and levonorgestrel (LNG): 2 mg EV and then 2 mg EV plus 0.15 mg LNG for 6 months	O	III
Elfituri et al., 2005 [41], Libya	2-group RT, unclear masking	• n=100 • Age HT M=44.8 • Age tibolone M=43.8 • With meno sx • Postmeno	• Green Climacteric Scale • Baseline, 3, 6, 12 months	• HT: 2mg 17 β-estradiol+10mg dydrogesterone for 12 months • Tibolone: 2.5mg for 12 months	O	II
Fluck et al., 2002 [49], United Kingdom	Follow-up from 2-group open-label trial	• n=50 (IG 25, CG 25) • Age IG M=61 • Age CG M=61.2 • With anxiety and depression • Postmeno	• Visual analog scales • 10 years post-treatment follow-up	• IG: Tibolone 2.5mg daily for 10 years • CG: Untreated	O	III
Kim et al., 2019 [42], Korea	2-group open-label trial	• n=57 • Age estrogen M=50.52 • Age tibolone M=51.23 • With meno sx • Postmeno	• MRS • Retrospective record review before treatment and 6 months later	• Estrogen: Transdermal estrogen gel mixed with progestogen 1.5 mg daily for 6 months • Tibolone: 2.5 mg daily for 6 months	O	III
Moyer et al., 2018 [43], USA	3-group RCT, unclear masking	• n=100 (pills 33, patch 33, CG 34) • Age M=52.7 • With meno sx • Postmeno	• Menopausal symptoms checklist • Baseline, 6, 12, 24, 36 and 48 months	• HT pills: oCEE 0.45mg/d + micronized progesterone 200mg/d for first 12 days of the month • HT patch: Transdermal 17 β-estradiol 50ug/d with micronized progesterone 200mg/d for first 12 days of the month • CG: Placebo pills and patch • All for 48 months	O	II
Nevinny-Stickel, 1983 [50], Germany	2-group single blind crossover RT	• n=35 • Age 48–69	• Not specified • Baseline, 6, 12 weeks	• IG: Tibolone (Org OD 14) 2.5mg for 6 weeks for each period, no washout, the patients were switched over to the second 6-week treatment period	O	II

Author, year, country	Design	Sample size and characteristics	Measure, timepoints	Intervention	O or AE	QR
		• With hot flashes • Postmeno		• CG: Placebo		
Polo-Kantola et al., 1998 [44], Finland	2-group double blind crossover RCT	• n=71 • Age M=56.4 • With sleep sx • Peri and postmeno	• Daily record for 14 days at baseline and last 14 days of each treatment period • Baseline, 3 months, 1 month washout, 3 months later	• Patch or gel: Estrogen patch (Evorel 50 ug) or Estrogen gel (Estrogel 2.5 gm) dependent on age • CG: Placebo • Three periods: 3-month estrogen/ placebo, 1-month placebo washout, and then switched to 3-month placebo/ estrogen	O	II
Pornel 1996 [45], United Kingdom, Australia, New Zealand, Italy, Belgium, France, Netherlands	1st trial: 2-group double blind RT 2nd trial: 2 group open label RT	1st trial: • n=214 • Age 40–65 • With ≥ 21 hot flashes/week for the last 2 weeks • Peri and postmeno 2nd trial: • n=205 (Menorest 102, Estraderm 102) • Age 40–65 years • With ≥ 21 hot flashes/week for the last 2 weeks • Peri and postmeno	• Severity rating • Baseline, 12 weeks	1st trial: • Menorest: 50 twice weekly • Premarin: 0.625mg/d • All women received 10mg/day dydrogesterone on the last 21 days of each 28-day cycle • All for 12 weeks 2nd trial: • Menorest 50 • Estraderm TTS 50 • Both applied twice weekly for 25 out of 28-day cycle for 12 weeks	O	II
Takamatsu et al., 2001 [46], Japan	2-group open-label trial	• n=67 (HT 23, Counseling 44) • Age HT M=53 • Age counseling M=51.4 • With climacteric sx • Postmeno	• Keio modified menopause index • Before and after counseling, 6 months after HT	• HT: 0.625 mg of conjugated estrogen and 2.5 mg of medroxyprogesterone acetate daily for 6 months • Counseling: Interview emphasis on psychodynamics, average counseling sessions of 2.9 (1.5) per patients for 6 months	O	III
Tit et al., 2017 [47], Romania	3-group open label trial	• n=324 (IG1 95, IG2 124, CG 105) • Age IG1 M=49.14 • Age IG2 M=49.2 • Age CG M=49.71	• MRS • Baseline pre-treatment and 6- and 12-month of treatment	• IG1: HT 1mg estradiol and 0.5mg norethisterone acetate po daily for 12 months • IG2: Isoflavones 40mg po daily for 12 months	O	III

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Author, year, country	Design	Sample size and characteristics	Measure, timepoints	Intervention	O or AE	QR
		• With meno sx • Postmeno		• CG: Untreated		
Glaser et al., 2011 [48], USA & Greece	1-group open label trial	• n=300 • Age M=51.7 • With meno sx • Premeno, postmeno	• MRS • Baseline, 3 months	• Testosterone subcutaneous implant varying 75–160mg based on weight	O	III
Non-hormonal drug therapies (n=4)						
SSRI/SNRI (n=3)						
Callegari et al., 2019 [51], Italy	2-group open label trial	• n=39 (IG1 24, IG2 15) • Age IG1 M=54.8 • Age IG2 M=54.8 • With depressive sx • Postmeno	• Antidepressant Side-Effect Checklist • 8, 12 weeks	• IG1: Paroxetine for 12 weeks • IG2: Vortioxetine for 12 weeks	AE	NA
Freeman et al., 2017 [52], USA	1-group open label trial	• n=27 • Age M=52.1 • With MDD • Peri, postmeno	• Patient Report of Incidence of Side Effects checklist • 8 weeks	• Vortioxetine flexible dosing from 5mg/d to 20mg/d for 8 weeks	AE	NA
Kornstein et al., 2015 [53], USA	2-group double blind RCT	• n=798 in two RCTs (IG 147+316, CG 105+230) • Age 40–70 • With MDD • Peri, postmeno	• Treatment emergent adverse events scale • 8 or 10 weeks	• IG: Desvenlafaxine 100–200mg/d flexible dosing for 8 weeks or Desvenlafaxine 50mg/d for 10 weeks • CG: Placebo for 8 weeks or 10 weeks	AE	NA
Antihypertensives (n=1)						
Kujala et al., 2014 [54], Finland	2-group RT Unclear masking	• n=112 (IG1 57, IG2 55) • Age IG1 M=53.4 • Age IG2 M=53.4 • With hypertension and overweight	• Questionnaire • Baseline, 8 weeks	• IG 1: Moxonidine 0.6 mg/d for 8 weeks • IG 2: Atenolol 50 mg/d for 8 weeks	O	III

Author, year, country	Design	Sample size and characteristics	Measure, timepoints	Intervention	O or AE	QR
		• Postmeno				
NON-DRUG THERAPIES (n=18)						
Supplementary treatments – isoflavones and other phytoestrogens (n=5)						
Agosta et al., 2011 [55], Italy	2-group RCT (unclear if open-label or masked)	• n=634 (IG1 300, IG2 334) • Age IG1 M=53.3 • Age IG2 M=53.0 • With meno sx and borderline anxious-depressive sx and/or sleep disorders • Postmeno	• Survey • Baseline, 4, 8, 12 weeks	• IG1: Estromineral supplement containing isoflavones 60mg + Lactobacillus sporogenes + calcium + vitamin D3 for 12 weeks • IG2: Estromineral Serena supplement containing same ingredients as Estromineral (IG1) + Magnolia bark extract for 12 weeks	O	III
Ahsan & Mallick, 2017 [56], India	1-group open-label trial	• n=50 (29 peri, 21 postmeno) • Age M=42.3 peri, M=49.6 post • With meno sx • Peri & postmeno	• MRS • Baseline, 12 weeks	• Isoflavones 100mg daily for 12 weeks	O	III
Auerbach et al., 2012 [57], Austria	2-group double blind RCT	• n=100 (IG 51, CG 49) • Age IG M=54 • Age CG M=55 • With ≥ 5 hot flashes daily • Postmeno	• MRS II • Baseline, 4, 8, 12, 24 weeks	• IG: Pomegranate seed oil 30mg containing 127ug steroidal phytoestrogens per day for 12 weeks • CG: Placebo	O	II
Costa et al., 2017 [58], Brazil	2-group double blind RT	• n=32 (IG1 17, IG2 15) • Age M=54.4 • Age IG1 M=56 • Age IG2 M=52.7 • Postmeno	• MRS, Blatt–Kupperman Menopausal Index, Cervantes scale • Baseline, 10 weeks	• IG 1: Isoflavone 100mg/d + aerobic and resistance exercise 3x/week for 10 weeks • IG 2: Placebo/d +aerobic and resistance exercise 3x/week for 10 weeks	O	II
Davinelli et al., 2017 [59], Italy	2-group double blind RCT	• n=60 • Age 50–55 • With meno sx • Postmeno	• MRS • Baseline, 1, 3 months	• IG: Equopausa (200 mg fermented soy + 25mg resveratrol (*Vitis vinifera*) daily for 12 weeks • CG: Placebo daily for 12 weeks	O	II

Author, year, country	Design	Sample size and characteristics	Measure, timepoints	Intervention	O or AE	QR
Supplementary treatments – *Rheum rhaponticum* or false rhubarb (n=3)						
Hasper et al., 2009 [60], Ukraine	2-group double blind RCT	• n=81 of 109 in Heger et al., 2006[61] • n=80 study 1 (IG 39, CG 41) • n=51 study 2, (IG 23, CG 28) • Age IG M=49.5 • Age CG M=49 • With meno sx (hot flash) • Perimeno	• MRS II • Baseline, 12, 24, 36, 48 weeks (study 1), 96 weeks (study 2)	• IG: ERr 731 (400 mg enteric-coated tablet containing 4 mg of *Rheum rhaponticum* dry extract) daily for 12 weeks in both studies • CG: Placebo daily for 12 weeks	O	II, IV
Heger et al., 2006 [61], Ukraine	2-group double blind RCT	• n=109 (IG 54, CG 55) • Age IG M=49.3 • Age CG M=48.6 • With meno sx (MRS II > 22) • Perimeno	• MRS II • Baseline, days 28, 56, and 84	• IG: ERr 731 (250 mg enteric-coated tablet containing 4 mg of *Rheum rhaponticum* dry extract) daily for 12 weeks • CG: Placebo daily for 12 weeks	O	II
Kaszkin-Bettag et al., 2009 [62], Ukraine	2-group double blind RCT	• n=112 (IG 56, CG 56) • Age IG M=49.4 • Age CG M=49.6 years • With meno sx (MRS > 18) • Perimeno	• MRS • Baseline (day 0), and days 28, 56, and 84	• IG: ERr 731 (400 mg enteric-coated table containing 4 mg *Rheum rhaponticum* dry extract) daily for 12 weeks • CG: Placebo	O	II
Supplementary treatments – *Salvia officinalis* or sage (n=3)						
Bommer et al., 2011 [63], Switzerland	1-group open-label trial	• n=71 • Age M=56.4 • With ≥ 5 hot flashes daily • Postmeno	• MRS • 7 days before treatment initiation, baseline, 8 weeks	• Thujone-free Sage spissum extract tablet 280 mg (*Salvia officinalis*) for 8 weeks	O	III
Dadfar & Bamdad, 2019 [64], Iran	1-group open-label trial	• n=30 • Age M=52.6 • With meno sx • Postmeno	• MRS • Baseline, 4 weeks	• Sage extract capsule 100mg (*Salvia officinalis*) daily for 4 weeks	O	III

Author, year, country	Design	Sample size and characteristics	Measure, timepoints	Intervention	O or AE	QR
Zeidabadi et al., 2020 [65], Iran	2-group double blind RCT	• n=59 (IG 33, CG 28) • Age unspecified • With meno sx • Postmeno	• MRS • Baseline, week 2, 4, 6, 8, 10, 12	• IG: 100mg sage x 3 daily (*Salvia officinalis* extract for 3 months • CG: Placebo	O	II
<u>Supplementary treatments – other (n=4)</u>						
Fatima et al., 2017 [66], India	2-group patient blind RCT	• n= 60 (IG 30, CG 30) • Age IG M=43.7 • Age CG M=43.9 • With meno sx ≥ 2 months • Postmeno	• MRS • Baseline, 2, 4, 6, 8, and 12 weeks	• IG: *Tribulus terrestris* L. (fruits) 3g powder twice daily for 8 weeks • CG: Placebo daily for 8 weeks	O	II
Modi et al., 2012 [67], India	1-group open-label trial	• n=52 • Age 40–55 • Kupperman index ≥ 15 • Postmeno	• MRS • Baseline, 1 month after 3-month treatment	• Ayurvedic: *Ashokarishta* (25ml twice daily) + *Ashwagandha Churna* (3g twice daily) + *Praval Pishti* (250mg twice daily) for 3 months	O	III
Nayak et al., 2011 [68], India	1-group open-label trial	• n=223 • Age M=46.7 • Peri and postmeno	• DDCYSS • Baseline, every week x 1 month, every 2 weeks x 3 months, monthly x 8 months	• Individualized homeopathic consultation and medicine	O	III
Park & Kim, 2016 [69], South Korea	2-group double blind RCT	• n=36 (IG 18, CG 18) • Age IG M=51.78 • Age CG M=52.78 • With Kupperman index > 15 • Peri or postmeno	• Kupperman Index • Baseline, 6 weeks, and followed at 12 weeks	• IG: 784mg/day *Schisandra chinensis* for 6 weeks • CG: Placebo	O	II
<u>Psychological intervention (n=2)</u>						
Alder et al., 2006 [70], Switzerland	1-group open-label trial	• n=30 • Age M=52.3 • With meno sx • Peri and postmeno	• MRS • Baseline, 1, 2, 3 months post-intervention	• Weekly 1.5-h group cognitive-behavioral sessions for 7 weeks	O	III

Author, year, country	Design	Sample size and characteristics	Measure, timepoints	Intervention	O or AE	QR
Qian et al., 2010 [71], China	3-group RT, partial factorial trial, unclear if masked	• n=164 (Psychological 55, Herbals 53, Both 56) • Age herbals M=51.25 • Age psychological M=52.8 • Age both M=51.43 • With meno sx • Unspecified meno status	• Reformed Kupperman Scale • Baseline, 6 months	• Psych: Psychological intervention and 30–40 min weekly follow-up interview for 6 months • Herbals: Chinese herbals (5g Kunbao Pill+ 6g Modified Xiaoyao Pill) twice a day for 6 months • Both: Combined herbals and psych for 6 months	O	II
Auricular acupressure (n=1)						
Kung et al., 2011 [72], Taiwan	1-group open-label trial	• n=45 • Age M=56.2 • With insomnia • Postmeno	• MRS • Baseline, 4 weeks	• Auricular acupressure for 4 weeks	O	III

O = outcome, AE = adverse event, QR = level of evidence quality rating, R = randomized, C = controlled, T = trial, HT = hormonal therapy, IG = intervention group, CG = control group, M = mean, sx = symptoms, meno = menopausal, premeno = premenopausal, peri = perimenopausal, postmeno = postmenopausal, NA = not applicable, MRS = menopausal rating scale, SSRI = selective serotonin reuptake inhibitor, SNRI = serotonin-norepinephrine reuptake inhibitor, MDD = major depressive disorder, oCEE = oral conjugated equine estrogen, ERr 731 = a special extract of *Rheum rhaponticum*, DDCYSS = Distress During Climacteric Years Symptom Scale.

Table 2.

Palpitations findings from two or three groups articles of drug therapies and non-drug therapies (n=24).

1st author year	Placebo benefit		Treatment benefit		Comparison of treatment and placebo benefit		
	No	Yes	No	Yes	Same	Difference	
DRUG THERAPIES (n=13)							
Hormonal agents (n=12)							
Anarte 1998 [36]				√ √		♦	HT + psychological treatment > HT
Carmignani 2010 [38]		●		√ √	♦		HT = Isoflavone = placebo
Checa 2005 [39]				√ √ √	♦		HT > Calcium or raloxifene at 6 not 12 months
Elfituri 2005 [41]				√ √	♦		Estradiol+dydrogesterone = Tibolone
Fluck 2002 [49]				√		♦	Tibolone > untreated group
Kim 2019 [42]				√ √	♦		Estrogen = Tibolone
Moyer 2018 [43]	●		√ √		♦		oCEE = Transdermal E = placebo
Nevinny-Stickel 1983 [50]	●		√		♦		Org OD 14 = placebo
Polo-Kantola 1998 [44]	●		√		♦		HT = placebo
Pornel 1996 [45]				√ √ √	♦		(HT) Menorest = Premarin = Estraderm
Takamatsu 2001 [46]				√ √		♦	HT < Counseling
Tit 2017 [47]				√ √			HT, isoflavones not reported
Non-hormonal drug therapies (n=1)							
Kujala 2014 [54]				√ √	♦		Moxonidine = Atenolol
NON-DRUG THERAPIES (n=11)							
Supplementary treatments - isoflavones&other phytoestrogens (n=4)							
Agosta 2011[55]				√ √	♦		Estromineral = Estromineral Serena

1st author year	Placebo benefit		Treatment benefit		Comparison of treatment and placebo benefit		
	No	Yes	No	Yes	Same	Difference	
Auerbach 2012 [57]		●		√	♦		Pomegranate seed oil = placebo
Costa 2017 [58]				√ √	♦		Isoflavone + exercise = Placebo + exercise
Davinelli 2017 [59]		●		√		♦	Equopausa (resveratrol) > placebo
Supplementary treatments - *Rheum rhaponticum* (n=3)							
Hasper 2009 [60]		●		√	♦		ERr 731 = placebo
Heger 2006 [61]	●			√		♦	ERr 731 > placebo
Kaszkin-Bettag 2009 [62]	●			√		♦	ERr 731 > placebo
Supplementary treatments - *Salvia officinalis* or sage (n=1)							
Zeidabadi 2020 [65]	●			√		♦	*Salvia officinalis* extract > placebo
Supplementary treatments - other (n=2)							
Fatima 2017 [66]		●		√		♦	*Tribulus terrestris* L. > placebo
Park & Kim, 2016 [69]	●			√		♦	*Schisandra chinensis* > placebo
Psychological intervention (n=1)							
Qian 2010 [71]			√ √	√		♦	Psychological + herbals > single treatment

> indicates that one intervention is superior to another one or placebos; = indicates no effect difference between interventions and/or placebos.

HT = hormonal therapy, oCEE = oral conjugated equine estrogen, ERr 731 = a special extract of *Rheum rhaponticum*.