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Menopause is more than Hot Flashes: What is Missing in Homeopathic Research? A Narrative Review

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Abstract

Background Menopausal complaints are frequently treated with homeopathy in daily practice worldwide. Recently, vasomotor symptoms have been understood to have implications as predictors of other important and long-term outcomes, causing increased risk of mortality and/or disability.

Methods A comprehensive search of the literature was conducted to investigate whether homeopathic treatments for menopausal women with vasomotor symptoms have a positive effect on other important health outcomes associated with menopause, such as cardiovascular disease, neurocognitive impairment, metabolic and mood disorders, or osteoporosis.

Results Though observational studies have shown encouraging results in reducing the severity and frequency of hot flashes in women treated with homeopathy, few randomized controlled trials have shown positive results. In most of the studies using homeopathy, the primary outcome is reduction in the frequency and severity of hot flashes, and other menopausal complaints are assessed secondarily as a part of the symptoms evaluated in the menopausal scales. Quality of life improves with homeopathic treatments for hot flashes, but there is scarce evidence of the effect of homeopathy on other health outcomes associated with menopause. Limited evidence exists in the case of menopausal women treated with individualized homeopathy for depression and metabolic disorders.

Conclusion A more comprehensive approach for treating menopause in routine homeopathic practice constitutes a valuable opportunity to increase knowledge and high-quality research in this field. Future homeopathic research for menopause should be focused on well-designed, double-blind, placebo-controlled, randomized trials as well as on pragmatic trials to show whether homeopathic treatments for vasomotor symptoms can also improve outcomes that are well-known to increase the risk of mortality and/or disability.

Keywords
- homeopathy
- menopause
- climacteric
- hot flashes
- vasomotor symptoms
- cardiovascular disease
- metabolic disorders
- depression

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Introduction

During the last decades, women's life expectancy has increased worldwide. Consequently, more women can expect to spend a more significant portion of their lives in the postmenopausal stage. Climacteric is the stage around menopause in which women experience significant biological,

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psychological and social changes.[1] Currently, the latest Stages of Reproductive Aging Workshop (STRAW + 10) classifies the transition from the reproductive to the non-reproductive period based on the changes in the menstrual cycle as the principal criterion, with endocrine parameters as supportive criteria. Therefore, this classification provides a more comprehensive basis for assessing reproductive aging in research and clinical contexts.[2]

The hormonal fluctuations as a result of the neuroendocrine changes introduce the risk of both intermediate and long-term health outcomes associated with menopause.[3] Approximately 70% of midlife women experience vasomotor symptoms (VMS: hot flashes and night sweats) and, for a third of them, these are very severe, frequent, and can affect their quality of life. VMS are considered among the most common symptoms during the climacteric stage and can last many years.[4,5] Based on longitudinal studies, women might follow one of four distinct patterns of VMS: (a) starting to experience them at the early transition and observing a decline when the menstrual cycles stop; (b) starting after the menopause and continuing through the post-menopause years; (c) witnessing few or no VMS; and (d) starting VMS well before the final menstrual period and continuing well into the post-menopause.[6]

While VMS have been linked to women's mental health, sleep and quality of life, recently they (mainly the early-occurring VMS) have been understood to have implications as predictors of sub-clinical cardiovascular disease (CVD). Results from hormone replacement therapy (HRT) trials have shown a difference in the underlying vasculature of women with VMS relative to their counterparts without them.[7,8] The SWAN Heart Study examined associations between VMS and women's vascular health, controlling for multiple CVD risk factors as well as sex hormones, especially among overweight or obese women.[9] Participants without clinical CVD underwent multiple measurements of sub-clinical CVD (endothelial function, aortic and coronary calcification, and carotid intima media thickness [IMT]). Results showed that women reporting VSM had poorer endothelial function as well as greater aortic calcification and IMT relative to women without VMS. Additionally, more frequent VMS are related to higher blood pressure and greater subsequent hypertension,[10] dysregulation in the lipid profile (higher LDL and triglycerides),[11] greater insulin resistance[12] and increased risk of diabetes.[13]

Vasomotor symptoms may also be relevant in the women's neurocognitive health. Observations from the vasculature of the brain show that VMS are related to small vessel disease[14] and hyperconnectivity of the default mode network (DMN). The DMN is an organized network in the brain that is active during rest. Suppression of the DMN is associated with better memory formation; by contrast, hyperconnectivity is associated with poorer attention to tasks and also with psychiatric conditions such as depression.[15] Menopausal transition has been considered as a window of vulnerability to depression because some women have an increased sensitivity to changes in the hormonal milieu experienced during this stage.[16] Longitudinal studies have suggested an increased risk (1.5 to 3.0-fold) for depressive symptoms during menopausal transition and the early post-menopausal years, even among women with no previous episodes.[17,18] It is also important to consider other risk factors that may influence depression in menopausal women: poor education, obesity, chronic medical conditions, and stressful life events.[19]

It has been reported that the peak prevalence of VMS coincides with the time period of accelerated bone loss at the hip and spine, increasing the risk of osteoporosis, characterized by reduced bone mineral density (BMD), impaired bone quality, and a propensity to fractures.[20,21] Data analysis from the Women's Health Initiative (WHI), a large cohort of post-menopausal women in the United States, examined associations of baseline VMS with subsequent BMD and fracture incidence.[22] Women with moderate to severe VMS had lower BMD and increased hip fracture rates over an average of 8.2 years' follow-up.[23] The genitourinary syndrome of menopause (GSM) is another highly prevalent condition associated with estrogen deficiency. It is characterized by bothersome symptoms and changes in the labia, introitus, clitoris, vagina, urethra and bladder, and by vulvovaginal atrophy.[24] Principal symptoms include vaginal dryness (100%) and dyspareunia (78%).[25] GSM often contributes significantly to midlife sexual problems.[26]

In regard to cancer, a later age at menopause has been associated with a higher prevalence of hormone-related cancers such as breast, endometrial (uterine) and ovarian.[27] Breast cancer is the most common malignancy in women worldwide,[28] mostly diagnosed during the post-menopausal stage, with approximately two-thirds experiencing VMS, half of whom report them as severe.[29] For many years, HRT has been prescribed for menopausal symptoms.[30] Nevertheless, in 2002 and 2004, the WHI reported an increased risk of breast cancer with the use of combined HRT, but not with estrogen alone.[31,32] The Collaborative Group on Hormonal Factors in Breast Cancer[33] reported that if women initiate HRT shortly after menopause, there is a significantly increased risk of invasive breast cancer. The hazard ratio (HR) associated with 1 to 4 years of use is 1.17 (95% confidence interval [CI], 1.10 to 1.26) for estrogen alone and 1.60 (95% CI, 1.52 to 1.69) for combination therapy. Moreover, obesity is very frequent in menopausal women and, as for HRT, is a risk factor for post-menopausal breast cancer, but it seems that the effects are not additive.[30] Endometrial cancer it is the second most common female malignancy in the developed world.[34] Several non-genetic risk factors have been associated with an increased risk of endometrial cancer, which include obesity, physical inactivity, excess exogenous estrogen, insulin resistance, and tamoxifen use after breast cancer.[35] Regarding other types of cancer, 55% of women who use HRT can develop ovarian cancer. The risk is increased even with less than 5 years of use (relative risk, 1.43; 95% CI, 1.31 to 1.56; $p < 0.0001$).[36] Early-stage ovarian cancer is difficult to diagnose because presenting symptoms are vague and non-specific, and so screening is mandatory.

Homeopathy has been used to treat menopausal symptoms in daily clinical practice for more than 150 years,

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especially for VMS, sleep disturbances, mood disorders, and to improve quality of life.[37] Nowadays, it is used worldwide in many clinical settings with positive results.[38–42] Results of a survey of German menopausal women showed that homeopathy was one of the three most popular Complementary & Alternative Medicine (CAM) interventions (14.9%), after changes in lifestyle (28.7%) and St. John's wort (18.3%). The women perceived homeopathy as very useful (73.7%) in managing their symptoms.[43] Homeopathy has also been used for chronic diseases in daily practice worldwide. Patients with hypertension, diabetes mellitus, osteoarthritis, depression, insomnia, migraine, and irritable bowel syndrome, among others, have reported improvement with homeopathic treatments.[44,45] However, homeopathic investigation on menopause has been focused on evaluating (with observational studies or randomized controlled trials, RCTs) the effect of different types of homeopathic prescriptions (individualized homeopathic treatment [IHT], combined homeopathic products, or a single homeopathic medicine) primarily on hot flashes and secondarily on other menopausal complaints.

Thus, this narrative review addressed the following research question: *Do homeopathic treatments for menopausal women with vasomotor symptoms have a positive effect on other important long-term health outcomes associated with menopause, such as cardiovascular disease, neurocognitive impairment, metabolic and mood disorders, or osteoporosis?*

Methods

Search Strategy

This narrative review abided by the recommendations of the Scale for the Assessment of Narrative Review Articles (SANRA), a brief critical appraisal tool for the assessment of non-systematic articles, by Baethge et al.[46] A comprehensive search was conducted in the following electronic databases: Medline (Ovid), the Cochrane Library, EBSCO/CINAHL, Web of Science, Google Scholar, PubMed, Science Direct, Scopus, BMJ Best Practice, IMBIOMED; from 1990 to February 12, 2021. The search terms were: (homeopathy AND menopause OR climacteric) AND (diabetes OR cardiovascular disease OR hypertension OR depression OR anxiety OR metabolic disorders OR dyslipidemia OR osteoporosis OR neurocognitive impairment OR cancer).

Inclusion and Exclusion Criteria

Both observational prospective and retrospective designs, as well as case reports/series, were acceptable. In addition, interventional studies (RCTs) and non-randomized studies were included. The inclusion criteria were: published English- and Spanish-language clinical studies of menopausal women treated with any type of homeopathy prescription for menopausal complaints and/or for any other chronic condition in menopausal women with menopausal complaints. Studies with any other CAM, with or without adjuvant homeopathy, were excluded. References cited in included studies were also reviewed for additional relevant articles that met the inclusion criteria.

Data extraction

In order to answer the research question, the extracted information was summarized focusing on the study design, the author, year, setting, country, population characteristics, sample size, follow-up, outcomes, assessment tools, interventions, type of homeopathy, homeopathic medicines most frequently prescribed, and relevant results.

Results

Though women worldwide frequently seek homeopathic treatments for menopause complaints, to date few studies have been conducted to demonstrate the efficacy of homeopathy for menopause. Only nine RCTs, six observational studies and two case reports met the inclusion criteria. ►**Table 1** summarizes the key data from these studies. Though observational studies have shown encouraging results in reducing the severity and frequency of hot flashes in women treated with homeopathy, few RCTs have shown positive results; some have small sample sizes, most of them do not use a homogeneous classification of women according to international standards (STRAW + 10),[47] and the longest follow-up is two years (a case report by Mahesh and colleagues).[48]

An open, multi-national, prospective, pragmatic and non-comparative observational study by Bordet et al[49] included 438 menopausal women and concluded that 50% of the patients who had had daily hot flashes at baseline no longer suffered them at the final homeopathy visit. The number of diurnal and nocturnal hot flashes fell significantly between baseline and follow-up visits ($p < 0.001$). Another observational study, by Ruiz-Mandujano and coworkers, concluded that there was a significant reduction of the Menopause Rating Scale total mean score (16.71 ± 8.1 to 10.94 ± 4.95, $p < 0.001$) after three months of homeopathic treatment.[50]

Overall there is scarce evidence of the effect of homeopathy on cardiovascular, neurological, metabolic, or other chronic diseases associated with menopause in menopausal women with VMS. There is also lack of scientific evidence of its potentially positive long-term effects in preventing or reducing the risk of fatal outcomes associated with menopause. Recently, Gupta et al conducted a multi-center RCT using one single medicine (*Sepia*), in which routine systemic and gynecological examinations as well as a homeopathic consultation were performed, including assessment of laboratory parameters. The effect, if any, of *Sepia* on lipid profile or glucose was not reported. However, the total score on the Greene Climacteric Scale was reduced from 30.23 ± 8.1 to 7.86 ± 4.6 in the *Sepia* group (improvement of 73.9%) and from 30.05 ± 8.9 to 12.73 ± 8.3 in the placebo group (improvement of 57.63%) ($p = 0.001$).[51] Another RCT, by Macías-Cortés et al of IHT for menopausal women with moderate to severe depression, showed that in the homeopathy group, response rate was 54.5% compared with 41.3% and 11.6% in a fluoxetine and a placebo group respectively ($p < 0.01$). An assessment of laboratory parameters was also included, but only the association between metabolic disorders and response to homeopathic treatment for depression was evaluated.[52]

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Table 1 Summarized data of clinical studies of homeopathy for menopause

Author, year, setting & country.	Population characteristics & sample size	Study design & follow-up	Outcomes & assessment tools	Interventions, type of homeopathy & homeopathic medicines	Results
RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIALS					
Jacobs et al, 2005.[56] Private medical clinic, Seattle, USA.	n = 83 History of breast cancer in remission, ≥3 flashes per day for the previous month.	Randomized, double-blind, placebo-controlled trial. Every two months for one year.	Primary outcome: Hot flash severity score. Secondary outcomes: 1. Total number of hot flashes. 2. KMI. 3. SF-26 Quality of Life Score. 4. FSH level.	Individualized homeopathic single medicine, homeopathic combination medicine (*Sanguinaria canadensis* 3X, *Lachesis* 12X, *Amyl nitrate* 3X) or placebo.	No significant difference in the primary outcome measure among groups, but a positive trend in the single remedy group during the first three months of the study ($p = 0.1$). Positive trend toward a lower KMI score in the single remedy group compared with placebo in all subjects ($p = 0.1$). No differences among groups in the individual symptoms of the KMI. A statistically significant improvement in general health score in both homeopathy groups ($p < 0.05$) on the SF-36 after one year. No differences in FSH level before or after treatment.
Thompson et al, 2005.[79] The outpatient department of the Glasgow Homeopathic Hospital, UK.	n = 53 Symptoms of estrogen withdrawal in breast-cancer survivors (≥3 hot flashes per day); not taking HRT; no severe concurrent illnesses.	Pilot double-blinded, placebo-controlled study. Baseline and four visits at 4-week intervals (16 weeks).	Primary outcomes: Activity and profile scores of MYMOP. Secondary outcomes: 1. Daily hot flash frequency and severity. 2. Menopausal Symptom Questionnaire. 3. EORTC QLQ-C30; plus breast module. 4. HADS. 5. FAQ. 6. GHHOS.	Individualized homeopathy using CH or LM potencies or placebo. *Sulphur, Sepia, Carcinosin, Natrum muriaticum, Belladona* and *Arnica.*	No evidence of a difference between groups for primary or secondary outcomes: MYMOP activities of daily living and profile scores (adjusted difference: −0.4, 95% CI −1.0 to 0.2, $p = 0.17$ and −0.4, 95% CI −0.9 to 0.1, $p = 0.13$, respectively). Both groups showed large and clinically important improvements over time. Some evidence of an interaction between time of follow-up and trial arm for overall health (EORTC) ($p = 0.03$): homeopathy group continued to increase at both follow-up visits, whereas placebo group decreased.

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Table 1 (*Continued*)

Author, year, setting & country.	Population characteristics & sample size	Study design & follow-up	Outcomes & assessment tools	Interventions, type of homeopathy & homeopathic medicines	Results
von Hagens et al, 2012.[58] University Women's Hospital, Heidelberg, Germany	n = 102 MRS II score ≥3, normal Pap smear, no prior HRT or CAM treatment, or past surgery, chemotherapy, or endocrine therapy for cancer.	Randomized, placebo-controlled, double-blind, three-arm study. Twelve and twenty-four weeks.	Primary outcome: Change in total score of MRS II from baseline to 12 weeks, comparing patients pooled from groups 1 and 3 taking remedy with group 2 receiving placebo. Secondary outcomes: Changes in the somatic, psychological and genitourinary sub-scores.	A complex anthroposophic remedy (*Apis regina tota* GLD4, *Argentum metallicum* D5, *Ovaria bovis* GL D4) 3 × 10 globuli daily (2 × 12 weeks) and placebo (12 weeks) in different orders of remedy (R) and placebo (P). Group 1 R/R/P; 2:P/R/R; 3: R/P/R	Reduction of symptoms after 12 weeks did not differ between remedy and placebo (total score MRS II: −1.4, 95% CI −2.8 to 0 vs −2.3, 95% CI −4.4 to −0.3 $p = 0.441$), with no clinical relevance (defined as reduction in MRS II ≥ −3.5). Comparison of secondary outcomes at 12 weeks between R and P or between groups after the 2nd or 3rd period compared with previous periods did not differ. Treatment with R for 24 consecutive weeks did not reach clinical relevance either. Total reduction of symptoms after three periods in Group 1 (R/R/P) (−5.0, 95% CI −7.5 to −2.5) and Group 2 (P/R/R) (−5.9, 95% CI −8.7 to −3.1) reached clinical relevance, whereas almost no decrease of symptoms after three periods was seen in Group 3 (R/P/R) (−0.5, 95% CI −2.9 to 1.9)
Colau et al, 2012.[59] 35 private outpatient gynecological clinics, France.	n = 108 Menopause for <24 months and ≥5 hot flashes per day, with a significant negative effect on quality of life; with no HRT or any other treatment for hot flashes.	Multicenter, randomized, double-blind, placebo-controlled study. Twelve weeks.	Primary outcome: HFS. Secondary outcomes: 1. HFRDIS. 2. MRS. 3. Effect of hot flashes on professional and personal life.[a] 4. Morisky-Green score.	BRN-01 (Acthéane®) tablets (*Actea racemosa* 4C, *Arnica montana* 4C, *Glonoinum* 4C, *Lachesis mutus* 5C and *Sanguinaria canadensis* 4C), 2 to 4 tablets per day, vs identical placebos.	The global HFS over twelve weeks, assessed as area under the curve (AUC) adjusted for baseline values, was significantly lower in BRN-01 group vs placebo over twelve weeks (88.2 ± 6.5 vs 107 ± 6.4; $p = 0.041$), which translates as a decrease in HFS of 21.5% in favor of women treated with BRN-01. There was a significant reduction in the HFRDIS and MRS score in each group after twelve weeks, but HFRDIS score was not significantly lower in the BRN-01 group than in the placebo group (2.3 ± 1.9 vs 2.8 ± 2.4 respectively, $p = 0.243$). After twelve weeks, MRS score did not differ significantly between groups (5.1 ± 5.9 [95% CI, 3.1 to 7.2]) for BRN-01, vs 7.8 ± 9.5 [95% CI, 4.7 to 10.8]) for placebo. Placebo group had poorer compliance with treatment.

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Table 1 (*Continued*)

Author, year, setting & country.	Population characteristics & sample size	Study design & follow-up	Outcomes & assessment tools	Interventions, type of homeopathy & homeopathic medicines	Results
Macías-Cortés et al, 2017.[52] Juarez of Mexico Hospital, Mexico.	n = 133 Menopausal women with moderate to severe depression, with no prior treatment for menopause or depression.	Randomized, placebo-controlled, double-blind, double-dummy, three-arm trial. Four and six weeks.	Hamilton Rating Scale for Depression.[b] Laboratory parameters: lipid profile, fasting glucose, insulin, glycosylated hemoglobin.	Individualized homeopathy or fluoxetine or placebo. *Natrum muriaticum, Sepia officinalis, Pulsatilla nigricans, Lachesis trig, Staphysagria, Ignatia amara, Nux vomica,* and *Sulphur*	Overall prevalence of obesity and overweight was 86.5%; 52.3% had hypertriglyceridemia; 44.7% hypercholesterolemia; 46.7% insulin resistance; 66.6% dyslipidemia and 39.3% hyperglycemia. In homeopathy group response rate was 54.5% vs 41.3% and 11.6% in fluoxetine and placebo groups respectively, $p < 0.01$. There was no statistically significant association between dyslipidemia, overweight, insulin resistance, hypertriglyceridemia, hypercholesterolemia, or hyperglycemia, and non-response in the homeopathy group [OR (95% CI), 1.57 (0.46 to 5.32), $p = 0.467$; 0.37 (0.003 to 1.11), $p = 0.059$; 0.67 (0.16 to 2.7), $p = 0.579$; 1.44 (0.43 to 4.75), $p = 0.545$; 1.07 (0.3 to 3.76), $p = 0.907$; 0.93 (0.27 to 3.12), $p = 0.910$, respectively].
Macías-Cortés et al, 2018.[42] Juarez of Mexico Hospital, Mexico.	n = 133 Menopausal women with moderate to severe depression, with no prior treatment for menopause or depression.	Randomized, placebo-controlled, double-blind, double-dummy, three-arm trial. Four and six weeks.	Hamilton Rating Scale for Depression.[b] Four questions asking if they have or do not have history of depression, sexual abuse, domestic violence or marital dissatisfaction at any time in their life.	Individualized homeopathy or fluoxetine or placebo. *Natrum muriaticum, Sepia officinalis, Pulsatilla nigricans, Lachesis trig, Staphysagria, Ignatia amara, Nux vomica,* and *Sulphur*	Homeopathy versus placebo had a statistically significant association with response to depression treatment after adjusting for sexual abuse [OR (95% CI), 11.07 (3.22 to 37.96), $p < 0.001$], domestic violence [OR (95% CI), 10.30 (3.24 to 32.76), $p < 0.001$], marital dissatisfaction [OR (95% CI), 8.61 (2.85 to 25.99), $p < 0.001$], history of depression [OR (95% CI), 9.01 (2.98 to 27.20), $p < 0.001$]. Fluoxetine versus placebo also had a statistically significant association with response to depression treatment after adjusting for sexual abuse, marital dissatisfaction, history of depression, and domestic violence.

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Table 1 (*Continued*)

Author, year, setting & country.	Population characteristics & sample size	Study design & follow-up	Outcomes & assessment tools	Interventions, type of homeopathy & homeopathic medicines	Results
Heudel et al, 2018.[57] Three cancer centers, five hospitals and one private clinic, France	n = 138 ≥18 years old, non-metastatic breast cancer, treated for at least 1 month with adjuvant endocrine therapy, with no chemotherapy or radiotherapy.	Multicenter, randomized, double-blind, placebo-controlled, phase III study (2 to 4-week run-in period before randomization). Four and eight weeks.	Primary outcome: HFS change at week 4. Secondary outcomes: 1. HFS change at week 8. 2. Compliance and tolerance. 3. Quality of life: HFRDIS. 4. Satisfaction.[c]	Acthéane® (*Actea racemosa* 4C, *Arnica montana* 4C, *Glonoinum* 4C, *Lachesis mutus* 5C, *Sanguinaria canadensis* 4C) vs placebo.	No statistical difference was observed in the median (range) HFS variation at week 4 (homeopathy group, −2.9 [16.9–16.5]; placebo, −2.5 [−21.8–19.4] points, $p = 0.756$) and a relative decrease (homeopathy −17%; placebo −15%, $p = 0.629$). HFS was reduced for 75% of the patients in homeopathy group and 68% in the placebo group ($p = 0.323$). HFS decreased for 75% in homeopathy group vs 68% in placebo group at week 4, QoL was stable or improved for respectively 72% vs 74% of patients ($p = 0.47$) at week 4. No statistical difference was observed in median HFS variation at week 8 (homeopathy −3.9 [−27.3–17.3]; placebo −3.3 [−30.4–17.7] points, $p = 0.77$), nor relative risk of 28%. vs 25%, respectively. QoL was stable or improved in 72% (homeopathy) vs 74% (placebo) at week 4 ($p = 0.47$).
Andrade et al, 2019.[47] A private outpatient clinic, Brazil.	n = 40 Hot flashes as major complaint; not receiving any treatment for menopause within the previous 6 months.	Randomized, placebo-controlled, double-blind, phase-2 trial. Baseline, and after one, two, four and eight weeks.	Primary outcome: Intensity of hot flashes measured by MYMOP. Secondary outcomes: 1. Level of activity and well-being measured by MYMOP. 2. Menopausal Vasomotor Symptoms questionnaire at baseline.	*Capsicum frutescens L. (Malagueta)* 30C vs placebo: 5 drops, by mouth, three times/day, for 4 weeks, and then stop taking the medicine for another 4 weeks.	The effect of *Capsicum frutescens* on the intensity of hot flashes assessed by MYMOP was superior to that of placebo over the 4 weeks of treatment ($p < 0.001$). Treatment response (reduction of at least three MYMOP categories) was 0R 2.78 (95% CI, 0.77 to 10.05, $p = 0.20$). *Capsicum frutescens* vs placebo reduced the intensity of the secondary symptoms ($p = 0.001$) and improved level of activity ($p = 0.025$) and well-being ($p = 0.008$).

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Table 1 (*Continued*)

Author, year, setting & country.	Population characteristics & sample size	Study design & follow-up	Outcomes & assessment tools	Interventions, type of homeopathy & homeopathic medicines	Results
Gupta et al, 2019.[51] Four research centres of the Central Council for Research in Homeopathy, India.	n = 88 With menopausal symptoms for at least one month; with indications for *Sepia*; withdrawal of HRT for at least two months.	Multicenter, randomized, double-blind placebo-controlled study. Baseline and each month for six months.	Routine systemic, gynaecological and homeopathic consultations. Haemogram; fasting glucose; lipid profile; kidney and liver function tests; urine and stool tests. Ultrasonography of whole abdomen. Papanicolaou test smear and mammography. Primary outcome: GCS. Secondary outcome: UQOL scale.	One single homeopathic medicine in patients with symptoms corresponding to *Sepia*, prescribed in 200C or identical placebo at monthly interval.	Total score of GCS was reduced from 30.23 ± 8.1 to 7.86 ± 4.6 in *Sepia* group (improvement of 73.9%) and from 30.05 ± 8.9 to 12.73 ± 8.3 in placebo group (improvement of 57.63%) ($p = 0.001$). The total UQOL score was 59.09 ± 7.74 for *Sepia* group vs 57.39 ± 7.80 for placebo at baseline and 62.43 ± 7.71 for *Sepia* group vs 63.48 ± 7.53 for placebo group after treatment. The most frequent symptoms on which *Sepia* was prescribed were hot flashes (75%), irritability (59%), anxiety (36.4%), indifference (54.5%), weeping tendency (31.8%), decreased sexual desire (31.8%), decreased sleep (48.9%) and weakness (41%).
PARTIAL PILOT OF THE COHORT MULTIPLE RCT					
Relton et al, 2012.[62] Sheffield NHS Menopause Clinic, UK.	Hot flash cohort ($n = 48$). ≥14 hot flashes/night sweats per week, no HRT, immune-suppressants, chemotherapy or homeopathic treatment.	Partial pilot of the cohort multiple RCT (cmRCT) Thirty-six weeks.	Primary outcome: Hot Flash Frequency and Severity Scale. Secondary outcomes: 1. GCS. 2. MYMOP. 3. Cost effectiveness: EQ-5D. 4. Medication Change Questionnaire. 5. Visits to hospital 6. Visits to GP surgery. 7. Visits to other health professionals. 8. Days off work.	Offer Group: Individualized homeopathy. *Sepia officinalis* and *Lachesis mutus*. Some prescriptions were a one-off single dose whereas other prescriptions were to be taken twice daily every day.	There was variability of the primary outcome between the Offer and the No Offer control group (16.58 ± 15.18 vs 8.30 ± 5.74 respectively) at baseline, which compromised any comparison of clinical outcomes between groups, though the majority of the data for all measures were in the direction of favoring the Offer Group. The mean change in Hot Flash Frequency severity score was −6.89 ± 13.7 in Offer Group vs −1.16 ± 3.9 in the No Offer Group; GCS, −1.95 ± 7.16 vs 1.83 ± 6.19; MYMOP primary symptom score, −0.5 ± 1.25 vs 0.09 ± 0.90; MYMOP wellbeing score, 0.05 ± 1.51 vs −0.22 ± 1.48 in Offer Group vs No Offer Group respectively.

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Table 1 (*Continued*)

Author, year, setting & country.	Population characteristics & sample size	Study design & follow-up	Outcomes & assessment tools	Interventions, type of homeopathy & homeopathic medicines	Results
RANDOMIZED, PLACEBO-CONTROLLED TRIAL (BLINDING NOT SPECIFIED)					
Desiderio et al, 2015.[60] Setting not specified.	n = 45 Non-metastatic breast cancer survivors, suffering from menopausal symptoms.	Pilot, uncontrolled, non-randomized study (3 months: phase A), followed by a randomized, placebo-controlled study (6 months: phase B).	A 5-point numerical scale used to evaluate the severity of the menopausal symptoms (not specified if the tool was validated)	Not specified.	In the pilot study (phase A) a mean reduction in the total score of 2.27 ± 0.59, and a reduction in the severity of hot flashes ($p = 0.01$), vaginal dryness ($p = 0.027$), and headache ($p = 0.015$). In phase B, a statistically significant difference in favor of homeopathy for night sweats ($p = 0.009$), and for the total score ($p = 0.018$).
OBSERVATIONAL STUDIES					
Clover & Ratsey, 2002.[41] Tunbridge Wells Homeopathic Hospital, UK	n = 31 Three groups: no cancer; cancer, no tamoxifen; cancer and tamoxifen.	Pilot uncontrolled, non-randomized study. One year.	Two non-validated questionnaires: 1. Severity and frequency of hot flashes. 2. Patient assessment of benefit.	Not specified. *Amyl nitrosum, Calc carb, Lachesis, Natr mur, Pulsatilla, Sepia.*	Improvement in severity and frequency of hot flashes (73%, 86% and 77% in the 'no cancer', 'cancer, no tamoxifen' and 'cancer, tamoxifen' groups respectively). Overall, 45% felt much better at final consultation and only one person felt much worse.
Thompson & Reilly, 2003.[55] Glasgow Homeopathic Hospital, UK.	n = 45 Breast cancer survivors with symptoms of estrogen withdrawal.	Open, prospective, non-randomized, uncontrolled, observational study. Three to five consultations.	Primary outcome: Effect on daily living score. Secondary outcomes: 1. HADS. 2. EORTC QLQ-C30 3. Overall satisfaction.[d]	Individualized homeopathy given in CH and LM potencies.[e] *Pulsatilla, Sepia* and *Sulphur* were each used on more than three occasions for the first prescription.	Significant improvements in symptom scores and in the primary outcome ($p < 0.001$). Improvements in EORTC QLQ-C30 score. Significant improvements in HADS score in anxiety ($p = 0.013$) and depression ($p = 0.039$). Satisfaction with the treatment: 90% rated their satisfaction as ≥ 7. Homeopathic approach: 67% regarded as helpful, very helpful or extremely helpful for their symptoms.
Relton & Weatherley-Jones, 2005.[80] Sheffield NHS menopause clinic, UK.	n = 102 With distressing menopausal symptoms; not taking HRT.	Data obtained from an audit. Six monthly consultations.	MYMOP Each patient was asked to name the two most bothersome symptoms and score them on a seven-point Likert scale.[f]	Individualized homeopathy. Most frequently prescribed medicines not specified.	Overall improvement: 80%. The mean decrease (improvement) in the score for their primary symptom was 2.0 (95%CI, 1.64 to 2.43, $p < 0.005$). Average MYMOP score change of 1.5 for wellbeing and 2.0 for vasomotor symptoms. Greatest clinical benefit for headaches, tiredness, vasomotor symptoms, locomotor symptoms and sleeping difficulties.

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Table 1 (*Continued*)

Author, year, setting & country.	Population characteristics & sample size	Study design & follow-up	Outcomes & assessment tools	Interventions, type of homeopathy & homeopathic medicines	Results
Bordet et al, 2008.[49] 99 physicians in 8 countries: France, Tunisia, Brazil, Poland, Bulgaria, Portugal, Italy & Morocco.	n = 438 Established menopause, with hot flashes; not taking homeopathic treatment or HRT or raloxifene.	Open, multi-national, prospective, pragmatic and non-comparative observational study. Two to six months.	Non-validated scales. 1. Clinical condition at final visit.[g] 2. Diurnal and nocturnal frequency of hot flashes.[h] 3. Percentage of patients who suffered from daily hot flashes.[i] 4. Quality of life.[j]	Medications were given simultaneously or sequentially depending on the physician's practice. *Lachesis mutus, Belladona, Sepia officinalis, Sanguinaria canadensis, Sulphur.*	Fifty percent of the patients with daily hot flashes at baseline no longer suffered them at the final visit. The number of diurnal and nocturnal hot flashes fell significantly between baseline and follow-up visits ($p < 0.001$). At baseline, 46%, 38% and 16% of patients experienced 0 to 5, 6 to 10 and >10 hot flashes per day, respectively, compared with 90%, 8% and 2% at final visit. At baseline, 69%, 23% and 8% of patients, experienced 0 to 5, 6 to 10 and >10 hot flashes per night, respectively, compared with 93%, 5% and 1% at final visit. Discomfort decreased from 6.1 ± 2.3 to 2.5 ± 2.0 ($p < 0.001$); disturbance to sleep decreased from 6.2 ± 2.6 to 2.4 ± 2.3 ($p < 0.001$).
Nayak et al, 2011.[53] The outpatient services of six Units of Central Council for Research in Homeopathy, India.	n = 222 Peri-menopause (FSH levels) or established menopause; no HRT or history of cancer, or uncontrolled chronic diseases (diabetes, hypertension).	Open, multicenter, prospective, observational study. Every week (one month), every two weeks (three months), and monthly (eight months).	DDCYSS. Levels of FSH and lipid profile baseline and after one year.	Individualized homeopathy in 30C, using repertorization on CARA software. *Sepia, Pulsatilla, Lachesis, Sulphur, Calcarea carb, Lycopodium, Natrum mur.*	The mean total score of DDCYSS reduced from 14.1 ± 4.79 at baseline to 3.30 ± 2.92 at the end of the study ($p = 0.0001$). All symptoms significantly improved at the final visit, except dysuria. Hot flashes, night sweats, anxiety, depression and insomnia mean scores decreased from 1.9 ± 0.84, 1.89 ± 0.84, 1.79 ± 0.78, 1.66 ± 0.78 and 1.3 ± 0.46, respectively, at baseline, to 1.24 ± 0.47, 1.15 ± 0.42, 1.22 ± 0.42, 1.17 ± 0.45 and 1.09 ± 0.29, at the end of the study ($p = 0.0001$). FSH level was reduced in 56% of the patients ($p = 0.86$). There were no significant changes in levels of FSH, HDL and LDL. Levels of cholesterol, triglycerides and VLDL decreased significantly.

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Table 1 (*Continued*)

Author, year, setting & country.	Population characteristics & sample size	Study design & follow-up	Outcomes & assessment tools	Interventions, type of homeopathy & homeopathic medicines	Results
Ruiz-Mandujano et al, 2019.[50] The National Homeopathic Hospital, Mexico.	n = 31 With menopausal complaints, and no history of cancer or cardiovascular diseases or HRT	Open, uncontrolled, non-blinded, non-randomized, prospective study. Every month (three months).	MRS score.	Individualized homeopathy. Repertorization. *Lachesis trig, Pulsatilla nigricans* and *Natrum muriaticum*.	There was a significant reduction of the total MRS mean score (16.71 ± 8.1 to 10.94 ± 4.95, $p < 0.001$) after three months. All symptoms had a significant reduction, except sleep disturbances, cardiac and urinary symptoms and vaginal dryness. Hot flashes mean score decreased from 2.10 ± 1.25 to 1.23 ± 1.02 ($p < 0.001$); depressive mood mean score reduced from 1.87 ± 1.36 to 1.36 ± 1.14 ($p = 0.001$).
CASE REPORTS					
Sharma, 2008.[54] Regional Research Institute for Homeopathy, India.	A 43-year-old with amenorrhoea for 3 months and hot flushes; *Trichomonas vaginalis* discharge and chronic cervicitis.	Case report. One year.	Routine systemic and gynaecological examinations. Homeopathic consultation. Haemogram; fasting glucose; lipid profile; FSH level. Gynaecological ultrasonography. Papanicolaou test smear.	Individualized homeopathy. Repertorization with CARA software. *Crotalus horridus* 30C, *Nux vomica* 6C, Placebo.	FSH level decreased from 54.61 to 15.72 mIU/mL. Lipid profile normal at baseline. DDCYSS score decreased from 18 points at baseline to 1 point after one year of treatment. *Trichomonas vaginalis* discharge, chronic cervicitis, Nabothian follicle and tenderness in the right fornix disappeared completely.

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Table 1 (*Continued*)

Author, year, setting & country.	Population characteristics & sample size	Study design & follow-up	Outcomes & assessment tools	Interventions, type of homeopathy & homeopathic medicines	Results
Mahesh et al, 2020.[48] Setting not specified, India.	A 54-year-old Russian woman with 35 hot flashes per day, total hysterectomy, HRT (8 years); dyslipidemia; chronic pelvic inflammatory disease.	Case report. Forty-four months.	Gynecological and homeopathic consultations. Past medical history. Clinical examination. Laboratory parameters [glucose, lipid profile, TSH[k]]. Ultrasound scan abdomen and pelvis.	Individualized homeopathy starting with *Sepia succus* 21C, and increasing the potency in the following consultations up to 30C and 200C. *Medorrhinum* 200C.	At the end of the follow-up: mood improved, with good energy, better relationship with her husband, without hot flashes, no pain in the pelvic area. Weight loss (14 kg). Lipid parameters:[l] Total cholesterol reduced from 8.32 to 4.07 mmol/L. HDL increased from 1.19 to 1.81 mmol/L. LDL reduced from 5.12 to 2.94 mmol/L. Triglycerides reduced from 2.04 to 1.24 mmol/L. Atherogenicity index reduced from 5.9 to 1.2. TSH[k] reduced from 5.7 to 1.43 μIU/mL.

DDCYSS: Distress during Climacteric Years Symptom Scale (questionnaire assessing 15 pre-defined symptoms of menopause, developed by the Central Council for Research in Homeopathy. Each symptom was quantified considering its frequency, duration and intensity by attributing scores 0 to 4 (0 = not at all, to 3 = worst scenario). The intensity of distress was: mild = 4 to 11; moderate = 12 to 24; severe = 25 to 36). EORTC QLQ-C30: European Organization for Research and Treatment in Cancer–Quality of life Questionnaire–Core 30. FAQ: Final Assessment Questionnaire for overall satisfaction and perception of helpfulness. GHHOS: Glasgow Homeopathic Hospital Outcome Scale for the impact on daily living. GCS: Greene Climacteric Scale. HRSD: Hamilton Rating Scale for Depression. HADS: Hospital Anxiety and Depression Scale. HFRDIS: Hot Flash Related Daily Interference Scale for quality of life [HFRDIS ranging from 0 to 10 (0 = not affected, to 10 = extremely affected)]. HFS: Hot flash Score defined as the product of the daily frequency and intensity of all hot flashes, graded by women from 1 to 4 (1 = mild; 2 = moderate; 3 = strong; 4 = very strong), 2 days after enrollment and 2 days per week until the 11th week of treatment, and daily during the 12th week of treatment. Hot flash Severity Score (frequency times severity), as measured by the symptom diaries. KMI: Kupperman Menopausal Index. MYMOP: Measure Yourself Medical Outcome Profile score (an improvement of 0.8 = clinically significant). MRS: Menopause Rating Scale for severity of symptoms [consists of eleven symptoms that can be rated as 0 (no complaints) up to 4 points (severe symptoms) depending on the severity of the complaints perceived]. Morisky-Green score for compliance to treatment at the end. SF-26 Quality of Life Score for mental and physical health status. Utian Quality of Life (UQOL) scale for quality of life (baseline and at 6 months).

[a]Effect of hot flashes on professional and personal life, using VAS (0 to 100 mm).

[b]17-item version of the Hamilton Rating Scale of Depression (HRSD): scores range from zero to 61; 14 to 24 points were considered as moderate to severe depression. (Response rate: decrease of 50% or more from baseline HRSD score at week 6. Remission rate: HRDS $\leq$ 7 points).

[c]Satisfaction (self-reported patient satisfaction questionnaire, ranging from 1 to 5: 1=very unsatisfied to 5=very satisfied).

[d]Overall satisfaction with the homeopathic approach (0=completely dissatisfied and 10=completely satisfied).

[e]A maximum of three symptoms were targeted and rated by the patient as a problem (0=no problem, 10=tremendous problem).

[f](0='as good as it could be' to 6='as bad as it could be').

[g]A question with four responses: disappearance (no symptom), improvement (lessening of symptoms), no change (same symptoms), or aggravation (deterioration of symptoms).

[h]Diurnal and nocturnal frequency of hot flashes: 0 to 5, 6 to 10, or $\geq$10 hot flashes per day, at each visit.

[i]Percentage of patients who suffered from daily hot flashes (baseline and at the final visit).

[j]Quality of life measured by visual analogue scales (0 to 10) by two questions: a) "When you have a hot flash during the day, how would you describe the discomfort in your life?" (10 indicates the most disturbed daily life); b) "When you have hot flashes at night, how would you describe the consequences on your sleep?" (10 indicates the most disturbed sleep).

[k]TSH: thyroid stimulating hormone (Normal range (N): 0.4 to 4 μIU/mL).

[l]Lipid parameters: Total cholesterol (N: 3.10 to 5.16 mmol/L); HDL: High-density lipoprotein (N: 1.02 to 2.07 mmol/L); LDL: Low-density lipoprotein (N: 1.71 to 3.4 mmol/L); triglycerides (N: 0.45 to 1.60 mmol/L); atherogenicity index (N: 1.5 to 3).

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An observational study by Nayak and collaborators showed an improvement in menopausal symptoms as well as a decrease in levels of cholesterol, triglycerides and very low-density lipoprotein (VLDL) in climacteric women using IHT.[53] Furthermore, for two case reports (Sharma[54] and Mahesh et al[48]), in addition to the routine clinical, gynecological and homeopathic consultations, laboratory parameters (fasting glucose, lipid profile, follicle stimulating hormone [FSH]), gynecological ultrasonography and the Papanicolaou cervical screening test were included. Sharma reported improvement in menopausal symptoms and in chronic cervicitis after the IHT.[54] Mahesh and colleagues reported weight loss and improvement in lipid profile.[48]

Broadly, in most of the studies, the primary outcome is reduction in the frequency and severity of hot flashes; other menopausal symptoms were assessed secondarily as a part of the symptoms evaluated in the menopausal assessment scales (i.e., vaginal dryness, lowered libido, headaches, fatigue, poor concentration, sleep disturbances, mood changes, cardiac symptoms, muscle and joint pain, and so on), with minor attention on their individual improvement. In the best cases, internationally validated scales for menopause or for quality of life have been applied, but in other cases, non-validated self-assessment questionnaires or personal diaries and registries have been used (►**Table 1**).

In most studies there is real evidence of improvement in quality of life in women treated with homeopathy for menopause.[47,49,55–57] Different types of homeopathic prescription have been used: IHT, a single homeopathic medicine, or a combined homeopathic preparation.[58,59] Noticeably, however, not enough information has been reported on how the homeopathic approach was performed, specifically in the case of IHT, nor on the criteria for the selection of potencies and dosage. The same well-known homeopathic medicines for menopause were typically prescribed (*Lachesis mutus, Sulphur, Sepia officinalis, Sanguinaria, Natrum muriaticum,* and so on). In each of only two RCTs was a single homeopathic medicine (*Capsicum frutescens* or *Sepia*) evaluated with positive results.[47,51]

Regarding cancer, there are some studies only in breast cancer survivors with symptoms of estrogen withdrawal[55–57,60] that have shown mixed results, as shown in ►**Table 1**. Both IHT and combined prescriptions were evaluated in these patients. Clover & Ratsey reported improvement in severity and frequency of hot flashes in three groups of women: no cancer (73%); cancer, no tamoxifen (86%); and cancer, tamoxifen (77%).[41] Thompson & Reilly conducted an observational study using IHT in breast cancer survivors and reported significant improvements in the effect on daily living score ($p < 0.001$), significant improvements in anxiety ($p = 0.013$) and depression ($p = 0.039$); 90% of women rated their satisfaction as $\geq$7, and 67% regarded the treatment as helpful, very helpful, or extremely helpful for their symptoms.[55] Jacobs et al conducted an RCT in breast cancer survivors, comparing an individualized homeopathic single remedy, a combined homeopathic medicine, and placebo, and found no significant difference in the Hot Flash Score among groups, but a positive trend in the individualized single remedy group during the first three months of the study ($p = 0.1$).[56] A multicenter, randomized, double-blind, placebo-controlled, phase III study by Heudel et al found no statistically significant difference in the median (range) Hot Flashes Score variation after a four-week follow-up (combined homeopathic medicine group, -2.9 [16.9 to 16.5] points; placebo, −2.5 [−21.8 to 19.4] points; $p = 0.756$) and a relative decrease (combined homeopathic medicine group, −17%; placebo, −15%; $p = 0.629$).[57]

Finally, there have been no clinical studies on the role of homeopathy in menopausal women with osteoporosis or neurocognitive impairment.

Discussion

Daily homeopathic practice faces great challenges and opportunities for treating menopausal women. First, in the case of IHT, the 'gold standard' approach in homeopathy, the consultation itself (i.e., the homeopathic case-taking) requires special training and expertise in classical homeopathy to accurately prescribe the most similar homeopathic medicine to the patient's totality of symptoms.[61] Therefore, homeopathy has been considered as a complex intervention, which includes the consultation with a trained homeopath and the prescription of the homeopathic medicine.[62] Second, though VMS are the most frequent symptoms during menopause, there is a wide range of other complaints that appear with VMS: thus each woman experiences menopause in a unique and individual manner, some with a few mild symptoms, but others with severe complaints. Consequently, IHT is a suitable approach for treating menopausal complaints.

Taking into account that, in 'real world' practice, menopausal women seek homeopathic treatments for hot flashes because they are bothersome and impact their quality of life – and many of them do not want or cannot take HRT – special attention should be centered on detecting, preventing and treating the various health implications that come together with the hot flashes. As stated before, in addition to VMS, many of these women may be suffering other non-diagnosed chronic diseases related to menopause (i.e., CVD, metabolic disorders, osteoporosis, cancer, depression) that have serious long-term health consequences and a high risk of mortality or disability.[11–21] Therefore, while it is important for women to see improvement in VMS, their routine homeopathic care should also be focused on a more comprehensive medical approach, broadening the scope of assessment, prevention and treatment.

Specifically, as the homeopathic case-taking constitutes a very detailed and useful medical evaluation of the patients, some special considerations could be included for treating menopausal women. The National Institute for Health and Care Excellence (NICE) guidelines suggest adopting an individualized approach at all stages of diagnosis, investigation and management of menopause.[63] STRAW + 10 allows a standardized classification in research and clinical contexts.[2] A complete systemic and gynecological examination is mandatory. It is also important to include screening for: breast cancer (mammography), cervical cancer (cytology and

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human papillomavirus test), colon cancer (colonoscopy), lipid profile, fasting glucose, thyroid-stimulating hormone, obesity (weight control), osteoporosis (dual-energy X-ray absorptiometry, DEXA), hypertension (blood pressure measurement), depression, anxiety and sleep disturbances (standardized validated scales), according to international consensus recommendations and the patient's age.[64]

Currently there are several validated scales for the assessment of menopausal symptoms that provide a more strategic measurement for evaluating clinical outcomes and can be easily used in routine homeopathy settings. Screening tools specifically for primary care settings may also be useful. The Menopause Quick 6 (MQ6) questionnaire is a brief and efficient screening tool to identify the presence of menopause-related symptoms that are very common, and could help homeopathic doctors in daily practice.[65] It is also essential to give information to women about the long-term health implications of the menopause, as well as to promote lifestyle changes (diet, exercise, sleep hygiene, meditation techniques).

A more comprehensive approach for treating menopause in routine homeopathic practice constitutes a valuable opportunity to increase and widen high-quality research in this field. Though there is apparent evidence for an improvement of menopausal complaints in observational studies, many of them based in 'real world' practice, homeopathy research has faced difficulties in the conduct of an RCT. Firstly, reproducibility of IHT has been criticized or questioned.[66] Secondly, it is difficult to distinguish a specific effect of the homeopathic medicine on the menopausal symptoms from an effect of the in-depth homeopathic consultation. It has been suggested that what is being tested is the whole package of IHT, i.e., the consultation plus the individualized medicine.[61] Another important problem is the potency and dosage because the criteria for selecting them may be extremely heterogeneous among studies. Most of the published RCTs using homeopathy for menopause do not describe in detail all these above topics. Therefore, all the recommendations of the guidelines for Reporting Data on Homeopathic Treatments (RedHot),[67] which is an important supplement to CONSORT, should be rigorously adhered to when conducting an RCT, including a special detailed description of all these aspects.

Thompson & Relton have suggested that pragmatic RCTs can be an option to evaluate clinical and cost-effectiveness in menopausal women, preserving the integrity of IHT.[61] Though the placebo-controlled RCT is the 'gold-standard' to explore *if an intervention works in an ideal setting*, controlling known biases so that the intervention's effect is really observed, the pragmatic trial is designed to test interventions of daily practice to maximize applicability and generalizability; the research question is now *whether an intervention actually works in a real practice setting*.[68] A double-blind, placebo-controlled, randomized trial design to evaluate homeopathy for menopause should abide by homogeneity for controlling biases, which might be difficult in daily practice. Thus, so as to surmount the problem of heterogeneity, which might limit the measured effect size, Patsopoulos suggests that pragmatic RCTs must include a large sample size (to increase the power to detect small effects) and be simple in design (easy to plan, perform and follow up).[68] Additionally, Relton et al have suggested the cohort multiple RCT (cmRCT) design – recently renamed as Trials within Cohorts (TwiCs)[69] – to address the limitations of the standard pragmatic RCT design.[62] They conducted a pilot study in which a cohort of women with hot flashes was recruited through an observational study of women's midlife health, each woman consenting to provide individual data that could be used comparatively. This 'Hot Flash Cohort' was then screened to identify patients eligible for a trial evaluating the clinical and cost-effectiveness of treatment by a homeopath for women with menopausal hot flashes. The authors concluded that the cmRCT is a feasible design as a *"patient centred approach to informed consent which has scientific and practical advantages"*[62].

The TwiCs design from a Hot Flash Cohort may also allow the collection of long-term data of the effects of homeopathy on the previously described menopause-related outcomes and could be a useful approach for homeopathic research in this field. Menopause is more than hot flashes and night sweats. If there is evidence that VMS improve or, even more, disappear with homeopathic treatment, it is possible that the effect of homeopathy goes further: thus, menopausal women treated with homeopathy might witness decreased severity of CVD, metabolic or mood disorders, for example. Nevertheless, this hypothesis remains unstudied. Given that all these issues may require conducting large, expensive and long-term cohort studies – which is over-ambitious and unattainable at this moment – homeopathic research should be first aimed at: (1) confirming that homeopathy is an efficacious treatment for VMS, ideally with well-designed, double-blind, placebo-controlled, randomized trials or, from a more realistic and achievable point of view, with pragmatic trials; (2) starting to recruit a cohort with hot flashes through an observational study of women's midlife health and then conducting a TwiCs design; (3) including other outcomes that are available in clinical settings. The latter include metabolic parameters (i.e., lipid profile, glucose, insulin resistance, glycosylated hemoglobin), depression and anxiety assessment using internationally validated scales, and measuring blood pressure, with study periods long enough to collect more specific data. ►**Table 2** shows a SMART (Specific, Measurable, Achievable, Relevant, and Time-bound) summary of suggested next steps in homeopathic research in this field.

Interestingly, common homeopathic medicines for menopause, specifically for VMS, may be useful for cardiovascular or mood symptoms. *Lachesis mutus* is a homeopathic medicine frequently prescribed for menopausal women who suffer mood disturbances and hot flashes, but it is also used for cardiac symptoms during the climacteric stage: palpitations, irregular beats, with dyspnea and vertigo (on falling sleep, with immediate awakening), as well as other menopausal complaints, such as pulsating headaches, sadness, anxiety, poor concentration in the morning, jealousy and suspicion, sleep disturbances, and uterine hemorrhage, with its characteristic modalities.[70] *Lachesis mutus* venom

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Table 2 SMART summary of the suggested next steps for homeopathic research in menopausal women

Element	
Specific	To confirm the efficacy of homeopathic treatments (HTs) for improving vasomotor symptoms (VMS): conducting well-designed, high-quality, double-blind, placebo controlled, randomized studies as well as pragmatic trials (Trials within Cohorts -TwiCs design). To routinely assess other menopause-related outcomes (metabolic parameters, blood pressure, mood, cognitive health, sleep, bone mineral density, screening for gynecological cancer, among others) in women with VMS: in both daily homeopathic practice and clinical research. To show whether homeopathic treatments for VMS can also improve these outcomes (stated above) that are well known to increase the risk of mortality and/or disability.
Measurable	Evaluation of the effect of HTs for women with VMS on: 1. The frequency and severity of VMS using internationally validated scales. 2. Mood disorders, cognitive function, quality of sleep, using internationally validated scales. 3. Metabolic dysregulation, high blood pressure, weight, thyroid changes using clinical and laboratory assessments.
Achievable	Menopause clinics with gynecologists or general/family practitioners as well as trained homeopaths; at least laboratory assessment; special training as to how the validated scales are applied. Menopause clinics able to recruit a cohort with hot flashes through an observational study of women's midlife health and then conducting a TwiCs design, with an adequate sample size, to assess in real life the effectiveness of homeopathy in menopause-related outcomes. If possible, double-blind, placebo-controlled, randomized trials to assess the efficacy of homeopathy for menopause.
Relevant	Well-designed double-blind, placebo-controlled, randomized trials, as the 'gold standard', could provide high-quality scientific evidence of homeopathy for menopause and its health consequences. Results of pragmatic trials using homeopathy for VMS and other menopause-related outcomes would show real-world practice evidence of homeopathy in one of the most frequent conditions treated by homeopaths worldwide; health policy-makers could have a more comprehensive context for taking healthcare decisions based on both scientific evidence and women's choices. If homeopathy shows scientific evidence for menopause and its related conditions, women could benefit from a low-cost and safe treatment for important long-term health outcomes.
Time-bound	At least a 3-months follow-up, with longer study periods preferable (1 or 2 years as minimum).

itself causes systemic bleeding that is strongly associated with a fatal outcome. Its components (serine proteases and metalloproteases) can affect hemostatic mechanisms in different ways by interfering with both clotting factors and/or platelets, affecting their function; it is known that these proteases can also damage the integrity of blood vessel walls.[71]

Another example is *Sanguinaria canadensis*, a well-known homeopathic medicine used for hot flashes. Sanguinarine is one of its six alkaloids and has been found to have a vasodilatory effect. Sanguinarine has also been shown to block angiotensin II in a slow, nearly irreversible and non-competitive manner: thus it probably has implications in blood pressure regulation.[72]

Though a high prevalence of obesity, dyslipidemia and insulin resistance in menopausal women has been demonstrated, only the two case reports,[48,54] one observational study[53] and two RCTs[51,52] in homeopathy have evaluated the lipid profile. Pre-clinical studies of homeopathic medicines have shown positive results in this field. Sampath et al reported that homeopathic preparations of *Syzygium jambolanum* produced anti-diabetic effects in rats.[73] *Helonias dioica* has been used for mood disorders in climacteric women and produced anti-diabetic effects as well.[74] *Fucus vesiculosus* treatment has been shown to prevent rats from becoming obese and to maintain biochemical parameters at normal levels.[75] *Baryta carbonicum* and *Baryta muriaticum* have shown dose-dependent effects in decreasing lipid profile in chickens.[76] Nevertheless, whilst clinical studies in the general population have also reported improvement in dyslipidemia and hypertension treated with homeopathy,[77,78] the evidence is still limited. Based on the health implications caused by the endocrine changes that lead to the end of the reproductive stage, the homeopathic approach cannot be limited to improving hot flashes and quality of life only. Macías-Cortés et al showed that a cohort of Mexican menopausal women, treated in an outpatient service of homeopathy, also had obesity, dyslipidemia, insulin resistance, hypoalphalipoproteinemia, depression, and social problems such as domestic violence, sexual abuse and marital dissatisfaction, which were detected during the clinical assessment. Many of these women were probably unaware of the long-term implications of having VMS.[42,52]

In relation to cancer, though there are studies in breast cancer survivors using homeopathy for menopausal complaints,[41,55–57,60,79] the efficacy of homeopathy in this field is not fully studied. These women may experience a complex group of symptoms, some of them the result of adverse effects of conventional treatments, others a consequence of the illness itself in combination with the estrogen withdrawal and the fact that they cannot use HRT or other non-hormonal treatments. Homeopathy can offer them a safe

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and efficacious treatment, but further research in this field is necessary.

Finally, this review has only included studies in the Spanish and English languages. Taking into account that homeopathy is used worldwide, especially for VMS,[47,49,51,59,62,80] important contributions in homeopathic research for menopause might have been written in other languages. Nevertheless, this review contributes a summary of identified publications to date, together with suggestions for the future direction of homeopathy research in menopause.

In conclusion, there is scarce evidence for an effect of homeopathy on non VMS-related conditions of menopause (metabolic dysregulation, CVD, depression, anxiety, neurocognitive impairment, among others). Clinical studies for depression and metabolic disorders are limited, but cardiovascular diseases, neurocognitive impairment or osteoporosis remain unstudied in menopausal women treated with homeopathy. Based on current evidence about the neurobiology of VMS, their long-term health implications, and the encouraging results of homeopathic treatments for hot flashes in real-world homeopathic practice, further research is necessary to increase knowledge and thus the scope of homeopathy for menopausal complaints and for associated serious chronic conditions.

Highlights

- Vasomotor symptoms of the menopause have implications as predictors of other long-term outcomes, such as cardiovascular disease, metabolic and mood disorders, neurocognitive impairment and osteoporosis.
- Though observational studies have shown encouraging results in reducing the severity and frequency of hot flashes in women treated with homeopathy, few RCTs have shown positive results.
- Further research is necessary to increase the knowledge and scope of homeopathy for menopausal complaints and for other associated chronic conditions that are known to increase mortality and/or disability.

Conflict of Interest

None declared.

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