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Management of menopausal hot flushes. Recommendations from the Spanish Menopause Society

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ABSTRACT

This project aims to develop recommendations for treating vasomotor symptoms (VMS) based on the Cervantes short-form scale score (menopausal domain) using the best available evidence. A total of 166 studies were selected: 108 randomized controlled trials, 23 systematic reviews, 3 reviews, 3 meta-analyses, 11 case-control studies, 9 observational studies, and 12 transversal studies. To achieve this objective, a series of PICO (Patient, Intervention, Comparison, and Outcome) questions have been established for the treatment of VMS. We evaluate the quality of the scientific evidence and, with the findings, create a decision framework to treat hot flashes based on the Cervantes short-form scale score.

1. Introduction

Vasomotor symptoms (VMS) are common during menopause and are the main reason women seek medical advice at this stage of life. They are also the most characteristic symptom of climacteric syndrome. The frequency and severity of VMS vary, but they can lead to sleep disturbances, fatigue, anxiety, and irritability. This, in turn, affects their health-related quality of life (HRQoL) making it challenging to maintain normal routines and enjoy daily activities. Effective management of VMS is crucial for improving the HRQoL during menopause [1,2]. To support healthcare professionals involved in women's health care (not for women) we have developed the Spanish guideline for hot flushes.

We created a series of PICO (Patient, Intervention, Comparison, and Outcome) questions for each significant VMS treatment. We then assessed the quality of the scientific evidence and used our findings to develop a treatment decision framework for hot flushes based on the Cervantes Scale Short Form (C-SF).

2. Methods

2.1. Bibliographic review

We conducted thorough literature searches, covering research from the past 20 years in the following databases: PubMed®/MEDLINE

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(NCBI), ScienceDirect (Elsevier), and Cochrane Library (Wiley Online). We developed a tailored search strategy for each database, using a combination of controlled vocabulary and search terms related to hot flushes. These terms included (Climacteric [MeSH Terms]), (climacterics [MeSH Terms]), (menopause [MeSH Terms]), (menopause, premature [MeSH Terms]), (post- menopause [MeSH Terms]), (post menopauses [MeSH Terms]), and (pre-menopause [MeSH Terms]); ("Hot Flashes/diagnosis"[Mesh] OR "Hot Flashes/diet therapy"[Mesh] OR "Hot Flashes/drug therapy"[Mesh]; MeSH descriptor: [Hot Flashes] explode all trees and with a qualifier(s): [therapy - TH, epidemiology - EP, etiology - ET, diagnosis - DI, diet therapy-DT]. We also used validated filters as necessary to retrieve the appropriate study designs. (Flowchart 1)

2.2. Inclusion and exclusion criteria

The search was conducted openly to identify all publications in Spanish and English related to VMS during peri-post menopause over the last 20 years. The objective was to identify publications with relevant information about the treatment of VMS, the experience, and Health-Related Quality of Life (HRQoL) of women in peri or post menopause who report VMS, and the available treatments. In the review we do not include articles in women with ovarian insufficiency that suffer VMS because the position statement about the treatment in this woman is HRT with or without VMS.

We used the references obtained from the database review to create a search strategy tailored to the requirements of each database. This strategy involved using a combination of search terms related to each clinical question defined by the group of experts. We, initially screened the titles, abstracts, and study types, following specific inclusion and exclusion criteria. After that, we evaluated the selected studies more thoroughly and prepared summary tables with the most relevant data for each clinical question. Once these tables were completed, the review team shared them and performed a narrative synthesis and analysis of the evidence for each clinical question to issue corresponding grades of recommendation.

Inclusion criteria: The publication should present information on the experience of women suffering from VMS, the HRQoL of these women, and validated Quality of Life (QoL) scales to measure VMS. The publication should present information on treatments for VMS included in systematic reviews (SR), meta-analyses (MT), randomized clinical trials (RCTs), and observational studies (OE) (case-control studies (CCE); prospective and retrospective cohort studies (PCS-RCS) that include a control group without treatment.

Exclusion Criteria: Studies that do not involve peri-postmenopausal subjects. Studies conducted on animals or in vitro. Editorials, notes, comments, letters, opinion articles, and summaries of conference communications. Studies that do not provide information about VMS, treatments for VMS, women's experiences, and HRQoL. Studies not published in Spanish or English.

2.3. Data extraction

After confirming that the publications met at least one of the inclusions and none of the exclusion criteria, we extracted relevant information in a standardized manner. To accomplish this, we prepared to compile the appropriate information from the selected articles for review.

2.4. PICO development questions

The review team has outlined five PICO questions to address the following clinical and research queries:

1. Should healthy lifestyle habits be recommended for postmenopausal women for treating VMS?
2. Should natural therapies be used in postmenopausal women for treating VMS?
3. Should menopausal hormone therapy (HRT) be used in postmenopausal women for treating VMS?
4. Should neurokinin antagonists be used in postmenopausal women for treating VMS?
5. Should non-hormonal drugs be used in postmenopausal women for treating VMS?

2.5. Quality of evidence and Grade of recommendation [3]

All decisions were made based on the level of evidence from the type of study, with an additional vote from the expert group that developed the guideline.

The quality of evidence was defined as follows:

HIGH: It is very unlikely that new research will alter our confidence in the effect estimate; MODERATE: New studies are likely to have a significant impact on our confidence in the effect estimate and may modify this estimate;

LOW: New studies are very likely to have a significant impact on our confidence in the effect estimate, and this estimate is likely to be modified;

VERY LOW: Any effect estimate is highly uncertain.

The types of studies used to establish the grade of recommendation were as follows: Meta-analysis, Systematic Reviews, Randomized Clinical Trials: High quality evidence-Strong recommendation for or against; Cohort or Case-Control Studies: Moderate or low-quality evidence-Weak recommendation for or against; Non-Analytical Studies, Case Series: Low or very low-quality evidence-Weak recommendation for or against.

2.6. Instruments to measure HRQoL

Among the most important HRQoL scales are the Blatt-Kupperman Index [4], the Women Health Questionnaire (WHQ) [5], the MENCAV questionnaire [6], the Menopause Rating Scale (MRS) [7], the Menopause Quality of Life (MENQOL) [8], the Utian Quality of Life Score (UQOL) [9], the Greene Climacteric Scale [10], the Cervantes Scale (CS) [11] and the Cervantes Scale in its short version (C-SF) [12–16]. The C-SF has been used to establish the decision algorithms in this Spanish guide.

2.6.1. Cervantes scale short form (C-SF)

The CS is a specific HRQoL questionnaire that was originally developed in Spanish to be used in Spain for women through and beyond menopause. The CS can be reduced to a 16-item abridged version (C-SF) that maintains the original dimensional structure and psychometric properties [14]. This abridged questionnaire has four main dimensions: Menopause and Health (VMS, Health, and Aging), Psychology, Sexuality, and Relationship. The questionnaire is scored from 0 to 100, with 0 indicating no impact from menopause symptoms and 100 indicating the greatest possible impact. The C-SF has been used to establish

Table 1
Healthy living habits, alternative therapies, and VMS.

AUTHOR	N	STUDY	COMPARATOR GROUPS	RESULTS	RECOMMENDATION GRADE
Berin E et al. [17]	65	RCT	Resistance training 3 v/ week/ 15 week	Improvement in HRQoL in menopause	**STRONG IN FAVOR**
Berin E et al. [18]	65	RCT	Resistance training 3 v/ week/ 15 week	Decrease in the frequency of moderate and severe VMS	**STRONG IN FAVOR**
Baena-García L. et al. [19]	112	RCT	59 multicomponent exercise versus 53 tips	Positive effect on menopause symptoms and psychological state	**STRONG IN FAVOR**
Capel-Alcaraz AM et al. [20]	817	SR	Effects of strength exercises versus other types of interventions	Strength exercises are beneficial for menopause symptoms Unclear evidence on types of strength exercise.	**WEAK IN FAVOR**
Daley AJ et al. [21]	762	SR	2 groups Exercise+menopause-specific information vs Exercise + social support groups Interventions 6 months.	Insufficient evidence to demonstrate PE as an effective treatment of VMS	**STRONG AGAINST**
Daley AJ, et al. [22]	261	RCT	3 groups 87 women, one with recommendations, another attendance at PE classes, another control	PE is not effective for HF or NS	**STRONG AGAINST**
Luoto R et al. [23]	176	RCT	88 vs 88 Unsupervised aerobic exercise 50 min/ 4 times a week/6 month. Telephone questionnaire	Aerobic training decreases the frequency of VMS and improves HRQoL in overweight women.	**STRONG IN FAVOR**
Mansikkamäki K, et al. [24]	176	RCT	88 vs 88 Unsupervised aerobic exercise 50 min/ 4 times a week/ 6 months. Telephone questionnaire	Aerobic training for 6 months improves sleep quality and reduces VMS in symptomatic women	**STRONG IN FAVOR**
Aiello EJ et al. [25]	173	RCT	Overweight postmenopausal women: 87 moderate intensity exercise vs 86 control with stretching for 12 months	Significant increase in the intensity of VMS and a decrease in the risk of memory problems	**WEAK AGAINST**
Lindh-Astrand L et al. [26]	75	RCT	Sedentary postmenopausal women: 15 PE vs 15 E2 vs 45 control for 12 weeks	PE improves VMS and HRQoL	**WEAK IN FAVOR**
Herber-Gast GC et al. [27]	6040	PCS	Six dietary patterns were identified from factor analysis: cooked vegetables, fruit, Mediterranean style, meat and processed meat, dairy, and high fat and sugar.	Consumption of a Mediterranean diet or fruits reduces the risk of VMS. High fat and sugar consumption increases risk of VMS.	**WEAK IN FAVOR**
Flor-Alemany M et al. [28]	172	TS	A food frequency questionnaire	Mild symptoms of menopause benefit from lower consumption of poultry and low-fat dairy products and higher consumption of vegetables and soy milk.	**WEAK IN FAVOR**
Kroenke CH et al. [29]	1747	PS	Diet intervention versus control	Weight loss decreases VMS in postmenopausal patients	**STRONG IN FAVOR**
Barnard ND et al. [30]	84	RCT	Changes in diet with increased consumption of fruits, vegetables and whole grains compared to the control group	Reduces frequency and severity of VMS and associated symptoms	**STRONG IN FAVOR**
Jenabi E and J. Poorolajal [31]	27054	MT	Effect of former smoking and current smoking on the risk of hot flushes in midlife women.	Ex-smokers are associated with a higher risk of VMS	**STRONG IN FAVOR**
Gallicchio L et al. [32]	732	TS	Pre and perimenopausal	Smoking and depressive symptoms were associated with the risk of suffering from VMS.	**WEAK IN FAVOR**
Herber-Gast et al. [33]	10454	OBS	45–50 years in 1996. Follow-up 15 years/ questionnaires every 3 years	HF and NS less frequent in highly educated women and more frequent in obese women, current smokers, drinkers, perimenopausal, postmenopausal, weight gain, premenstrual tension, with diabetes and early age at first pregnancy.	**STRONG IN FAVOR**
Gjelsvik B et al. [34]	2229	PCS	40–44 years	Daily smoking and (low) educational level were independent risk factors for experiencing VMS.	**WEAK IN FAVOR**
Hunter MS et al. [35]	10418	TS	54–65 years	Hysterectomy, being a former smoker, and alcohol consumption predict VMS and NS. Anxiety, depressed mood, years since menopause, and education predicted current prevalence of VMS. HRT users who discontinued treatment had more VMS.	**STRONG IN FAVOR**
Kwon R et al. [36]	2394	PCS	Alcohol consumption categories included lifetime abstainer, former or current drinker, categorized as light, moderate, high and very high.	Increased alcohol consumption showed increased risk of early-onset VMS. Abstaining from alcohol consumption may help prevent VMS in premenopausal women	**STRONG IN FAVOR**
Jay Kandiah and Valerie Amend [37]	196	TS	Questionnaire	Aerobic PA, caffeine, and alcohol consumption are predictors of VMS severity. There is a positive relationship between the intake of caffeinated soft drinks and the frequency and severity of VMS.	**STRONG IN FAVOR**

(*continued on next page*)

Table 1 (*continued*)

AUTHOR	N	STUDY	COMPARATOR GROUPS	RESULTS	RECOMMENDATION GRADE
Moreno-Frías C et al. [38]	85 perimenopausal 75 postmenopausal	TS	Diaries	Depressed mood, age, and menopausal status are the main factors associated with sleep disorders.	**WEAK IN FAVOR**
Hyde Riley E et al. [39]	287 postmenopausal 468 perimenopausal	TS	Survey	VMS in perimenopausal women was related to BMI ≥ 25 and alcohol consumption of 1–5 drinks per week. In postmenopausal women, high fat intake was related to VMS	**WEAK IN FAVOR**
Anderson DJ et al. [40]	21460	TS	Pooled data on 21,460 midlife women from 8 studies	BMI ≥ 25 and smoking increased the risk of VMS in a dose-related manner. Maintaining a normal weight before the menopausal transition and quitting smoking before age 40 mitigates the excess risk of VMS in midlife.	**STRONG IN FAVOR**
Smith RL et al. [41]	761	TS	Using data from 761 women aged 45–54 years of age at baseline followed for 1–7 years.	Ex-smoking women have a lower risk of suffering from VMS than those who continue smoking, but a higher risk than those who have never smoked. Women who had been smokers for more than 5 years had a lower probability of VMS than those who continued smoking or had quit in the previous 5 years.	**STRONG IN FAVOR**
Schwingl PJ el al. [42]	334	TS	A cross-sectional sample of 334 black and white, naturally menopausal women was selected from a control group in a population-based study of reproductive cancers in central North Carolina.	Natural menopause < 52 years, low educational level, and lean women who smoked in the premenopausal period were more likely to experience VMS. Among non-smokers, BMI has no effect on VMS. Alcohol consumption has a positive relationship with VMS. Menarche < 12 years and a history of irregular cycles were related to a decrease in VMS.	**WEAK IN FAVOR**
Staropoli CA et al. [43]	233 45–65 years	TS	Self-administered questionnaire assessing selected demographic factors, reproductive history, and behavioral factors	VMS is associated with maternal history of VMS and tobacco use	**WEAK IN FAVOR**
Green SM et al. [44]	71	RCT	CBT versus no treatment Follow-up at 12 weeks and 3 months	Effective in improving VMS, depressive symptoms, sleeping difficulties and sexual concerns.	**WEAK IN FAVOR**
Ye M et al. [45]	1618	MT	Studies from 1977 to 2021	Psychological treatment is effective for mild-moderate VMS. Efficacy was greater for VMS than for other menopausal symptoms induced by oncological treatment.	**WEAK IN FAVOR**
Ayers B et al. [47]	140	RCT	Group CBT vs PCB CBT group: weekly 2-hour sessions,	CBT improves VMS and SN in women during the menopause and postmenopause transition. The findings suggest that CBT is brief and effective in treating VMS.	**STRONG IN FAVOR**
Saensak S et al. [48]	281	SR	Cochrane Database of Systematic Reviews	There is no evidence of the effectiveness of relaxation techniques in the treatment of VMS.	**STRONG AGAINST**
Elkins GR et al. [49]	187	RCT	12 weeks/ 5 sessions hypnosis/week vs control	VMS reduction in the hypnosis group	**STRONG IN FAVOR**
Barton DL et al. [50]	71	RCT	4 groups: 75 mg venlafaxine+ hypnosis, 75 mg venlafaxine + sham hypnosis, PCB+ hypnosis pill PCB + simulated hypnosis	Hypnosis reduces VMS as much as venlafaxine alone, but the combination of both does not reduce it more.	**WEAK IN FAVOR**
Palma F et al. [53]	75	RCT	3 groups 3 months acupuncture session /week 75 mg isoflavone/12 hours 0.30 mg ECE + 1.5 mg MPA	Greene scale score improvement: 44 % HRT, 41.3 % acupuncture and 17 % isoflavone. In a secondary analysis, acupuncture was more effective than phytoestrogens.	**WEAK IN FAVOR**
Dodin S et al. [54]	1155	SR	Databases	Acupuncture more effective than no treatment but less effective than HRT.	**WEAK IN FAVOR**
Soares JM et al. [55]	100	RCT	50 women in 2 groups: G1 48 weeks acupuncture + 24 weeks simulated acupuncture G2 on the contrary	Acupuncture can mitigate VMS and others menopausal symptoms during the transition menopause.	**WEAK IN FAVOR**
Deng et al. [56]	72 women with CM > 3 HF/day	RCT	Acupuncture vs sham	The frequency of VMS in patients with breast Ca was reduced in the acupuncture group.	**WEAK AGAINST**
Ee C et al. [57]	327 > 40 years > 7 HF/day	RCT	10 sessions in 8 weeks (n = 163) vs sham acupuncture (n = 164)	Acupuncture was not superior to sham acupuncture for women with moderate-severe VMS	**STRONG AGAINST**
Wyon Y et al. [58]	Four. Five	RCT	Electroacupuncture vs superficial needle insertion vs E2/ 12 wk. Follow-up 6 months	Electroacupuncture decreased the number of HF/24 h but less than treatment with E2	**WEAK AGAINST**

VMS: Vasomotor symptoms; HF: Hot flushes; NS: night sweets; E2:estrogens; PE; Physical exercise; PA: Physical activity; RCT: Randomized clinical trial; HRQoL: Health relates quality of life's; SR: Systematic review; TS: Transversal Study; CCS: case and control studies; PS: Prospective Study; OBS: Observational study; MT:

metanalysis; PRS: Prospective randomized study; PCS: prospective cohorts study; RCS; Retrospective cohorts study; FSH: follicle-stimulating hormone; BMI: Body mass index; CBT: cognitive behavioral therapy; PCB: Placebo; Ca: Cancer. OBS studies including retrospective and prospective cohort studies, prospective and retrospective case-control studies, and cross-sectional designs

decision algorithms in this Spanish guide [13].This scale has been used because it is validated and compared with other scales [12–16]. There are no other short and easy-to-use scales in routine clinical practice that have a quantifiable vasomotor domain by score and with cutoff points established through population curves that allow distinguishing those women whose vasomotor symptoms affect their HRQoL. Research has shown that the questionnaire is sensitive to changes in the HRQoL for women after menopause, especially related to treatments for menopause symptoms. It shows that a score of more than 25 points in the Menopause and Health domain has a sensitivity and specificity greater than 80 % in identifying women with moderate to severe VMS who require pharmacological treatment. A change of 6.7 points in the total score indicates a significant increase in disability for work and daily activities, greater economic loss, fewer years of disability-free life, fewer hours of peaceful sleep, and more doctor visits per year due to menopause symptoms. This makes successive scores on the C-SF useful for monitoring treatment effectiveness. The C-SF scale also has predictive value in response to treatment, as it can predict significant improvement in a woman's quality of life when a specific type of treatment is prescribed, based on the initial score. The Statement encourages the establishment of a treatment regimen based on the initial C-SF scores and recommends monitoring the response to treatment with successive C-SF assessments at intervals of no less than three months [15,16].To access the Cervantes SF scale score go to https://aeem.es/calculadora-escala-cervantes-de-calidad-de-vida/.

2.7. Guideline development steps

This structure outlines the development process of the Statement, from assembling the development group to finalizing the document with a comprehensive review.

1. **Integration of the Development Group**
   - o Assemble a multidisciplinary team of experts to guide the development of the Statement.
2. **Definition of the General Statement Framework**
   - o Establish the overall structure, goals, and scope of the Statement.
3. **Patient, Intervention, Comparison, and Outcome (PICO) Question Formulation**
   - o Should healthy lifestyle habits be recommended in postmenopausal women for the treatment of VMS?
   - o Should natural products be used in postmenopausal women for the treatment of VMS?
   - o Should menopause hormonal therapy (HRT) be used in postmenopausal women for the treatment of VMS?
   - o Should neurokinin antagonists be used in postmenopausal women for the treatment of VMS?
   - o Should non-hormonal drugs be used in postmenopausal women for the treatment of VMS?
4. **Identification and Evaluation of Evidence**
   - o Conduct a comprehensive literature review to gather and assess the quality of evidence related to the PICO questions.
5. **Drafting of recommendations**
   - o Develop evidence-based recommendations based on the evaluated evidence.
6. **Preparation of the Final Document (Internal and External Review)**
   - o Compile the Statement document, incorporating feedback from internal and external reviewers to ensure accuracy and comprehensiveness.

3. Results

Recommendations for each PICO question based on evidence:

3.1. Should healthy lifestyle habits be recommended in postmenopausal women for treating VMS? (Table 1)

3.1.1 **Exercise and Healthy Lifestyle Habits.** The evidence regarding the use of exercise as a treatment for VMS in menopause is inconclusive. However, due to the additional benefits exercise provides, it is recommended during this stage of life [17–26].

3.1.2 **Mediterranean-Style Diet**: A Mediterranean-style diet that includes weight control has a beneficial effect on VMS [27–30].

3.1.3 **Reduction of Tobacco, Alcohol, and Caffeine Consumption**: There is a strong correlation between tobacco consumption, alcohol consumption, caffeine consumption, and the occurrence of VMS in postmenopausal women. Reducing the consumption of these substances is advisable to prevent the onset or worsening of VMS [31–43].

3.1.4 **Cognitive behavioral therapy (CBT)** shows a reduction in vasomotor symptoms, myalgia, anxiety, and depression, thereby increasing the quality of life [44–48]

3.1.5 **Hypnosis** has consistently shown clinically significant reduction in VMS. However, its use in clinical practice is limited by the lack of accessibility to trained professionals [49,50].

3.1.6 There is insufficient evidence to recommend acupuncture or yoga to treat VMS [51–58].

3.1.7 Although more studies are needed, it is recommended to maintain an adequate weight, avoid smoking, and practice regular exercise to alleviate VMS

3.2. Should natural products be used in postmenopausal women for treating VMS? (Table 2)

3.2.1 Given that the benefits outweigh the risks and are accompanied by a good safety profile in estrogen-sensitive tissues, without side effects, black cohosh can be recommended in the treatment of VMS. It can be safely used in women with natural menopause and in patients with estrogen-dependent tumors who have VMS [59–63].

3.2.2 The available evidence regarding the use of soy dietary supplements and red clover extracts for the treatment of VMS is contradictory. However, use of soy preparations standardized to contain at least 15 mg/day of genistein is recommended [64–88].

3.2.3 The Hop extract containing 100 μg of 8-PN (8-prenylnaringenin) balances effectiveness and side effects, making it a potential treatment for HRT [89–91].

3.2.4 Preparations made from fresh leaves of Sage officinalis have

Table 2
Natural products and VMS.

AUTHOR	N	Study	Comparator groups	Conclusions	Recommendation
BLACK COHOSH					
Castelo-Branco et al. [60]	901	MT Includes 6 RCTs	PCB THM tibolone	Similar efficacy in VMS to tibolone and low doses of E2-TDM. The greatest effectiveness is observed with iCR Can be administered to patients with estrogen-dependent cancer	**STRONG IN FAVOR**
Charandabi SMA et al. [61]	84	RCT	PCB	Improves HRQoL	**STRONG IN FAVOR**
Henneicke-von Zepelin HH [62]	9669	SR 16 RCTs	PCB Tibolone THM	Superior to PCB and equal to low doses of E2 TDM and tibolone. Improves HRQoL	**STRONG IN FAVOR**
Castelo-Branco et al. [63]	991	AEEM position statement SR 7 RCTs	PCB Tibolone	Efficacy in women with natural menopause and in patients treated with GnRH analogues.	**STRONG IN FAVOR**
Soy dietary supplements with isoflavones					
Albertazzi P et al. [64]	104	Parallel RCT	Supplementation of 60 g/day of soy protein with 76 mg of IF in the form of aglycone versus PCB (casein 60 g)	VMS reduction greater than PCB	**STRONG IN FAVOR**
Kotsopoulos D et al. [65]	94	Parallel RCT	Soybean powder with 118 mg/day of IF vs casein (PCB)	VMS reduction greater than PCB	**WEAK IN FAVOR**
Knight DC et al. [66]	24	Parallel RCT	Soybean powder with 134.4 mg IF versus isocaloric preparation without IF (PCB)	VMS reduction in both groups	**WEAK IN FAVOR**
Lewis JE et al. [67]	99	Parallel RCT	Soy flour muffin (42 mg/day of IF) (soy group) or flax seed flour muffin (50 mg/day of secaisolariciresinol) (flax group) vs wheat flour muffin (PCB)	VMS reduction in all groups	**WEAK IN FAVOR**
Cheng G et al. [68]	60	Parallel RCT	Soy drink (60 mg/day of IF) vs oat drink (PCB)	VMS reduction greater than PCB	**WEAK IN FAVOR**
Soy extracts with isoflavones					
Upmalis DH et al. [69]	175	Parallel RCT	Soybean extract tablets (50 mg/day IF: 25 mg GEN, 25 mg DAID) vs PCB	Reduction in number and intensity of VMS compared to PCB	**STRONG IN FAVOR**
Han KK et al. [70]	82	Parallel RCT	Soy extract capsules (100 mg/day IF: 69.9 mg GEN, 18.6 mg DAID) vs soy protein capsules (150 mg) without IF (PCB)	Kupperman index improvement compared to PCB	**STRONG IN FAVOR**
Faure ED et al. [71]	75	Parallel RCT	Soybean extract tablets (70 mg/day IF: 5 mg GEN) vs PCB	Reduction of VMS in the group treated with PCB	**WEAK IN FAVOR**
Penotti M et al. [72]	62	Parallel RCT	Soybean extract tablets (72 mg/day IF: 11 mg GEN, 36 mg DAID) vs PCB	Improvement in both groups, NS versus PCB	**WEAK IN FAVOR**
Petri Nahas E et al. [73]	fifty	Parallel RCT	Soybean germ capsules (60 mg/day IF: 5 mg GEN) vs PCB (lactose)	Reduction of VMS in the group treated with PCB	**WEAK IN FAVOR**
Campagnoli C et al. [74]	36 (A) 35 (B)	Cross-over RCT	Soybean extract capsules (60 mg/day IF: 30 mg GEN, 30 mg DAID) vs PCB (study A); Equal + PUFA supplement vs PCB + PUFA capsules (study B)	Reduction of VMS in all groups compared to PCB	**STRONG IN FAVOR**
Nahas EA et al. [75]	80	Parallel RCT	Soy extract capsules (100 mg/day IF; 50 mg GEN, 35 mg DAID) vs PCB (lactose)	Reduction of VMS in all groups compared to PCB.	**STRONG IN FAVOR**
Ferrari A et al. [76]	176	Parallel RCT	Soybean extract capsules (80 mg/day IF: 60.8 mg GEN) vs PCB	Reduction of VMS in all groups compared to PCB.	**STRONG IN FAVOR**
Pure gesnistein					
Crisafulli A et al. [77]	90	Parallel RCT	Pure GEN tablets (54 mg/day) or 1 mg E2 tablets + 0.5 mg NETA vs PCB	Reduction of VMS in all groups compared to PCB.	**STRONG IN FAVOR**
Albertazzi P et al. [78]	100	crossover RCT	Pure GEN Capsules (90 mg/day) vs PCB	Reduction of VMS versus PCB.	**STRONG IN FAVOR**
Evans M et al. [79]	82	Parallel RCT	Synthetic GEN vs PCB 30 mg/day tablets	Reduction of VMS vs. PCB	**STRONG IN FAVOR**
D'Anna R et al. [80]	247	Parallel RCT	Pure GEN 54 mg/day tablets	VMS reduction in GEN group	**STRONG IN FAVOR**
Red clover extracts					
Knight DC et al. [81]	37	Parallel RCT	Red clover extract tablets (160 mg/day IF) (160 mg group), or 40 mg/day IF (40 mg group) vs PCB	VMS reduction vs. PCB	**WEAK IN FAVOR**
Van de Weijer PH et al. [82]	30	Parallel RCT	Red clover extract tablets (80 mg/day IF) vs PCB	Reduction of VMS vs. PCB	**WEAK IN FAVOR**
Jeri AS [83]	30	Parallel RCT	Red clover extract tablets (40 mg/day IF) vs PCB	VMS reduction in treatment group versus PCB	**WEAK IN FAVOR**
Tice JA et al. [84]	252	Parallel RCT	Red clover extract tablets (82 mg/day IF) or 57 mg/day IF vs PCB	HF,NS reduction vs. PCB	**WEAK IN FAVOR**
Hidalgo LA et al. [85]	60	crossover RCT	Red clover extract capsules (80 mg/day IF) vs PCB	Reduction of VMS versus PCB.	**WEAK IN FAVOR**
HOP EXTRACT					
Heyerick A et al. [89]	67	RCT	PCB	Reduction of VMS versus PCB. Acts through estrogen α receptors	**STRONG IN FAVOR**

(*continued on next page*)

Table 2 (*continued*)

AUTHOR	N	Study	Comparator groups	Conclusions	Recommendation
Erkkola R et al. [90]	36	crossover RCT	PCB	Improvement in HRQoL	**WEAK IN FAVOR**
Aghamiri V et al. [91] SAGE	120	RCT	PCB	Reduction of VMS versus PCB.	**STRONG IN FAVOR**
Zeidabadi A et al. [92]	66	RCT	PCB	Reduction of VMS versus PCB.	**STRONG IN FAVOR**
Wilfried et al. [93] Cytoplasmatic pollen extract	80	RCT	PCB	Reduction of VMS compared to PCB.	**STRONG IN FAVOR**
Winther K et al. [94]	64	RCT	PCB	Reduction of VMS versus PCB.	**STRONG IN FAVOR**
Genazzani A et al. [95]	1004	2 RCTs 4 POE	PCB	Reduction of VMS vs. PCB Indicated in patients with breast cancer.	**STRONG IN FAVOR**
Fait et al. [96]	104	POBS	No comparator group Evaluation by comparison with VAS at days 0, 30, 60 and 90 of treatment	VMS reduction.	**WEAK IN FAVOR**

VMS: Vasomotor symptoms; PCB: Placebo; HF: hot flushes; E2-TDM: transdermal estrogens; RCT: Randomized clinical trial; HRQoL: Health relates quality of life's; SR: Systematic review; AEEM: Spanish menopause society; Ca: Cancer; IF: isoflavones**;** NS: night sweets; GEN: genistein; DAID: Daizcein; IF: isoflavones; PUFA: unsaturated fatty acids; E2: Estrogens; NETA: norethisterone acetate; POBS: Prospective Observational study; PG: progestins; VAS: visual analogic scale.

been proven to alleviate VMS. The recommended dosage of the extract is 300–400 mg/day. [92,93].

3.2.5 Cytoplasmic pollen extract is a safe and effective non-hormonal option for treating VMS. It also improves other HRQoL parameters. The recommended dose is 160 mg/day for the first two months, followed by 80 mg/day [94–96].

3.3. Should HRT be used in postmenopausal women for treating VMS? (Table 3)

3.3.1. Both transdermal and oral HRT routes are effective in treating VMS and are better than a placebo [97–101]. The current recommendation is to start with lower doses, such as 0.025 mg of transdermal estradiol or 0.5 mg/day of oral estradiol, and increase as needed to relieve symptoms [102–104].

3.3.2. Oral HRT leads to a more favorable bleeding pattern than transdermal HRT [105–108].

3.3.3. Oral micronized progesterone (MPG) with estradiol, estradiol with norethisterone acetate (NETA), and estradiol with Levonorgestrel intrauterine device (LNG-IUD) have better rates of amenorrhea compared to other formulations [109–111].

3.3.4 The patient profile for LNG-IUD plus natural estrogen typically includes perimenopausal women with heavy bleeding, VMS, and the need for contraception [112–117].

3.3.5 To minimize the risk of thrombosis, it is recommended to use transdermal HRT, estradiol plus NETA, or estradiol plus oral MPG [118–120].

3.3.6 Tibolone could be an alternative for women experiencing breast tenderness caused by classic HRT [121,122].

3.3.7. Tissue Selective Estrogen Complex (TSEC) could also be an alternative for women with breast tenderness caused by classic HRT and severe osteopenia/osteoporosis [123].

3.3.8. The use of 300 mg of oral MPG shows improvement in VMS compared to placebo [124,125].

3.3.9. Therapies composed of bioidentical hormones are currently not regulated and do not comply with safety standards set by the FDA (Food and Drug Administration), EMA (European Medicines Agency), or AEMPS (Spanish Agency for Medicines and Medical Devices). Therefore, their use is not recommended [126].

3.3.10. Reviewing the literature, there is not a minimum period, HRT is given to treat symptoms and should be stopped when symptoms are no longer evident. Furthermore there is agreement that HRT should be started before 60 years old or <10 years since entering menopause (generally before is better, "window of opportunity"), but there is not an established maximum period after which it must be stopped. Generally, a decreased dose can be given or another route of administration considered for older women who have already started HRT during the correct frame.

3.3.11. Both sudden and gradual discontinuations of HRT have been reported, but there is no evidence to suggest that one method is better than the other [127–129].

3.3.12. It would be sensible to evaluate patients 12 weeks after starting treatment to assess the effectiveness of HRT, monitor for side effects and, improve adherence [15].

3.4. Should neurokinin antagonists be used in postmenopausal women for treating VMS? (Table 4)

3.4.1 Fezolinetant 45 mg once daily has shown effectiveness and safety compared to placebo and was well tolerated for treating moderate to severe VMS associated with menopause. Improvement was observed as early as week 1, with continued progress up to week 4, and sustained benefit throughout the 12-week double-blind period. The efficacy was noted to persist over 52 weeks of treatment [130–138].

3.4.2. Fezolinetant 45 mg also demonstrated effectiveness versus placebo in reducing sleep disturbances and impairment during the treatment of VMS due to menopause [139].

3.4.3. Fezolinetant 45 mg is effective in treating moderate-to-severe VMS caused by menopause, regardless of various intrinsic and extrinsic factors [140].

Table 3
Hormonal replacement therapy and VMS.

Study	DESIGN	N	PCB	Type of treatment	Conclusion	Recommendation
Route of administration Santoro N et al. [97]	RCT 3 groups, 4 years	727	Yes	ECE+PG E2 TSD+MPG cyclic	ECE and E2 TSD both effective in VMS v PCB	**STRONG IN FAVOR**
ROUTE OF ADMINISTRATION Shulman LP et al. [98]	OBS, 2 groups, 12 months	22	No	E2 TSD low dose	E2 TSD effective	**STRONG IN FAVOR**
DOSE Bachmann GA et al. [99]	RCT, 3 groups, 4 years	425	Yes	E2 0.025 +LNG E2 0.014 +LNG	E2 0.014mgr/day effective	**STRONG IN FAVOR**
DOSE Utian WH et al. [100]	RCT, 4 groups, 3 doses, 3 years	176	Yes	E2 0.025 E2 0.05 E2 0.100	Improvement of VMS in all group's vs PCB. Low doses just as effective and fewer side effects	**STRONG IN FAVOR.**
DOSE Simon JA et al. [101]	RCT, 4 groups, 4 doses, 12 weeks.	484	Yes	E2 gel various doses	Lower doses, greater adherence after 12 weeks with fewer side effects	**STRONG IN FAVOR**
DOSE Kaunitz AM et al. [110]	RCT, 4 groups, 12 months, 3 years	647	Yes	E2 + 100 mg MPG	Improvement at all doses vs PCB	**STRONG IN FAVOR**
ENDOMETRIAL PROTECTION Saure A et al. [102]	RCT, 2 groups, 2 doses, 12 weeks	310	No	E2 + DG/E2 + NETA	NETA less bleeding than DG Both relieve VMS	**STRONG IN FAVOR**
ENDOMETRIAL PROTECTION Utian W.H. et al. [104]	RCT, 5 groups, 3 doses, 12 months	2673	Yes	ECE+MPA	Low doses = effective High doses + abandonment due to side effects.	**STRONG IN FAVOR**
ENDOMETRIAL PROTECTION Baerug U et al. [103]	RCT	119	Yes	E2 + NETA 3 doses	NETA 0.5 less bleeding All doses more effective than PCB	**STRONG IN FAVOR**
ENDOMETRIAL PROTECTION Mattson LA et al. [107]	PCS, 52 weeks	111	No	E2 0.5 mg +NETA 0.1 mg	High rate of amenorrhea	**WEAK IN FAVOR.**
ENDOMETRIAL PROTECTION von Holst T et al. [105]	RCT, 2 groups, 9 months	446	No	E2 1 mg+NETA continuous EEC 0.025 +MPA 5 mg cyclic	Better continuous NETA bleeding rates than sequential MPA	**STRONG IN FAVOR**
ENDOMETRIAL PROTECTION Pickar JH et al. [108]	SR 45 articles (most RCTs)		No	E2 1 mg+MPG ECE 0.025 +NETA 0.5	Greater amenorrhea E2 + MPG or ECE+NETA Low doses Oral better than TSD	**STRONG IN FAVOR**
TIBOLONE Mendoza N et al. [122]	AEEM position statement				Infrequent bleeding (+ in young people)	**STRONG IN FAVOR**
TIBOLONE Swanson SG et al. [121]	RCT	396	Yes	Tibolone 2.5 mg and 1.25 mg + PCB	2.5 mg more effective Tibolone = E + PG or E alone	**STRONG IN FAVOR**
TSEC SMART 1 Levine JP. [123]	RCT, 12 and 24 months		Yes	BZA 40 mg or 20 mg /ECE 0.45 mg or 0.625 mg	Endometrial hyperplasia < 1 % Protection all doses	**STRONG IN FAVOR**
TSEC SMART 2 Levine JP et al. [123]		332	Yes	BZA 40 mg or 20 mg +ECE 0.45 mg or 0.625 mg	Both doses better than PCB BZA all doses endometrial protection	**STRONG IN FAVOR**
ORAL MPG ALONE Dolitsky SN et al. [125]	SR 892 studies 1980–2020	601	Yes	5–60 mg MPG TDM 10.20 mg oral MPA 300 mg oral MPG 21 days- 12 months (average: 12 weeks)	Beneficial effect of oral MPG in higher doses (300 mg) in the treatment of VMS	**STRONG IN FAVOR**
ORAL MPG ALONE Hitchcock CL et al. [124]	RCT 2003–2009	133	Yes	300 mg MPG PCB	300 mg oral MPG is effective in the treatment of VMS	**STRONG IN FAVOR**
THROMBOSIS Canonico M. [118]	CCS, 3 groups,	186	Yes	E2 TSD+MPG E2 TSD+norpregnane	MPG does not alter parameters. Norpregnanes can activate protein C and coagulation E2 TSD+MPG safer	**STRONG IN FAVOR**
THROMBOSIS Oliver-Williams C [106]	SR, 33 studies				E2 TSD safer and less thrombotic	**STRONG IN FAVOR**
THROMBOSIS Shufelt CL et al. [119]	R			Various doses of E and PG and various routes	Oral E2 more thrombotic than TSD MPG and pregnanos derivatives safer than norpregnanos	**WEAK IN FAVOR**

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Table 3 (*continued*)

Study	DESIGN	N	PCB	Type of treatment	Conclusion	Recommendation
					E2 TSD less coagulation effect, stroke and DVT vs oral	
THROMBOSIS Vinogradova Y et al. [120]	CCS	5790 DVT 21670 controls		HT 90 days oral /TSD, various doses	Oral E2 more risk of DVT ECE more risk than E2 ECE+PG more risk ECE+MPA more risk E2 + NETA or DG lower risk E2 TSD less risk Tibolone no risk More DVT in oral and more doses of E2	**WEAK IN FAVOR**
LNG IUD Joo JK et al. [112]	R	200			Perimenopause: more effective in bleeding IUD plus E2 safe endometrial protection	**WEAK IN FAVOR**
LNG IUD Boon J et al. [113]	RCT	200		oral LNG+E2 IUD E2 2 mg/NETA1 mg cyclic (13−22) E2 2 mg/NETA1 mg cyclic (1−21) E2 2 mg/NETA1 mg cyclic (22−28)	All endometrial protection IUD decreased bleeding	**STRONG IN FAVOR**
LNG IUD Anderson K et al. [114]	RCT	40		oral LNG+E2 IUD E2 2 mg/NETA 1 mg cyclic (13−22) E2 2 mg/NETA 1 mg cyclic (1−21) E2 2 mg/NETA 1 mg cyclic (22−28)	IUD+E2 2 mg oral daily prevents endometrial proliferation and reduces bleeding Group with cyclic NETA, regular bleeding	**STRONG IN FAVOR**
LNG IUD Depypere H et al. [115]	SR 6 pivotal studies	554		397 IUD 157 oral sequential PG	IUD non-endometrial proliferation. PG sequential proliferation 11.1 % at 2 years	**STRONG IN FAVOR**
LNG IUD Suhonen S, et al. [116]	Open, uncontrolled study			IUD+E2 (oral, TSD, subdermal)	76 and 79 % amenorrhea 20 and 34 months Spotting 1–2 days/month	**WEAK IN FAVOR**
LNG IUD Boon J, et al. [117]		200		E2 2 mg+NETA 1 mg 13–22 (n100) E2 2 mg+IUD (n100)	IUD 38 % amenorrheic VS NETA 0 %	**WEAK IN FAVOR**
COMPOSED OF BIOIDENTICAL HORMONES Stanczyk et al. [126]	SR				They do not meet FDA profiles Saliva/serum steroid concentration correlation inconclusive Individualized preparations are not standard, not regulated	**STRONG AGAINST**

IUD: Intrauterine device; ECE: Equine conjugated estrogens; PG: progestins; TSD: transdermal; LNG; LNG: levonorgestrel; MPG: micronized progesterone; NETA: Norethisterone acetate; MPA: Medroxyprogesterone acetate; HF: hot flushes; NS: night sweets; E2:estrogens; PE; Physical exercise; PA: Physical activity; RCT: Randomized clinical trial; HRQoL: Health relates quality of life's; BZA: Bazedoxifene; DG: Dienogest; EH: endometrial hyperplasia; DVT: Deep venous thrombosis; SR: Systematic review; R: Review; TS: Transversal Study; CCS: case and control studies; PS: Prospective Study; OBS: Observational study; MT: metanalysis; RPS: randomized prospective study; PCS: prospective cohorts study; RCS; Retrospective cohorts study;

3.4.4. A meta-analysis revealed that Fezolinetant 45 mg resulted in a significantly higher proportion of $\geq$75 % responders than Desvenlafaxine 50 mg. Additionally, it was found to be non-inferior to HRT in reducing the frequency of moderate to severe VMS [141].

3.4.5. The current evidence supporting Elinzanetant is primarily derived from phase 3 clinical trials [142–144].

3.4.6. Further research in Phase 4 randomized controlled trials (RCTs) and observational studies (OE) is necessary to validate these emerging therapies' long-term efficacy and safety in real-life settings.

3.5. Should non-hormonal drugs be used in postmenopausal women for treating VMS? (Table 5)

3.5.1. The benefits of selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) are promising, particularly due to their safety profile. These would be indicated in cases where HRT cannot be used. However, since the absolute benefit is small, costs and the individual woman's preference should guide recommendations. For all drugs, it is recommended to start treatment with the lowest recommended dose, increasing it if necessary, to minimize possible adverse effects. A gradual withdrawal of the drug over 1–2 weeks is advised to avoid potential withdrawal syndromes [145–165].

3.5.2 Gabapentin reduces the frequency and severity of VMS compared to placebo [166–174].

3.5.3. Clonidine is less effective than venlafaxine in VMS treatment and it has more side effects [175,176].

3.5.4. For women with moderate or severe hot VMS that disturb their HRQoL and for whom HRT is not an option, refused, or ineffective, SSRIs and SNRIs such as low-dose paroxetine, venlafaxine, desvenlafaxine, and gabapentin could be used.

Table 6 compares the dosage, effectiveness, and safety of non-hormonal drugs.

Table 4
Neurokinin inhibitors and VMS.

AUTHOR	N	TYPE OF STUDY	COMPARATOR GROUPS	COMMENTS
Lederman et al. **SKYLIGHT−1** [132]	522	RCT 12 weeks plus 40-week blinded extension phase (Phase 3). (NCT04003155)	Fezoniletant 30 mg: 173 Fezoniletant 45 mg: 174 PCB: 175	Both doses reduce frequency and severity of moderate/ severe VMS vs PCB at weeks 4 and 12
Johnson et al. **SKYLIGHT−2** [133]	500	RCT 12 weeks plus 40-week blinded extension (Phase 3). (NCT04003142)	Fezoniletant 30 mg: 166 Fezoniletant 45 mg: 167 PCB: 167	Both doses reduce frequency and severity of moderate/ severe VMS vs PCB at weeks 4 and 12 Fezolinetant 45 mg reduces sleep disturbances
Neal-Perry G, et al. [134] **SKYLIGHT−4**	1830	RCT 52 weeks (Phase 3). (NCT04003389)	Fezoniletant 30 mg: 611 Fezoniletant 45 mg: 609 PCB: 611	Confirm the longer-term safety and tolerability of Fezolinetant
Ruan X, et al. **MOONLIGHT−1** [135]	302	RCT 12weeks followed by an open label extension phase of 12 weeks (Phase 3). (NCT04234204)	Fezolinetant 30 mg: 150 PCB: 151	Numerically greater reduction in VMS frequency from baseline in East Asian women vs placebo
Yu Q, et al. **MOONLIGHT−3** [136]	150	Open-label study 52 weeks (Phase 3). NCT04451226	Fezoniletant 30 mg: 150	Fezolinetant 30 mg once daily was generally safe and well tolerated in Chinese women .
Schaudig K, et al. DAYLIGHT	452	RCT 24 weeks (Phase 3b) (NCT05033886)	Fezoniletant 45 mg: 226 PCB: 226.	Fezolinetant 45 mg reduces frequency and severity of VMS in a population unsuitable for HRT
IN PROGRESS 2024	540	RCT 52 weeks (Phase 3) (NCT06440967)	Fezolinetant 45 mg PCB	Primary outcome: Change in HT frequency and severity from baseline to weeks 4 and 12 in women with hormone receptor-positive BC who are receiving adjuvant endocrine therapy
Simon JA et al. 2023 **SWITCH−1** [142]	199	RCT 12 weeks (Phase 2b) NCT03596762	Elinzanetant 40 mg: 31 Elinzanetant 80 mg: 17 Elinzanetant 120 mg: 52 Elinzanetant 160 mg: 52 PCB: 47	Elinzanetant improves VMS versus PCB for doses of 120 and 160 mg at week 4 and with 120 mg at week 12.
Pinkerton et al., 2024 Participating countries: Austria, Czechia, Greece, Hungary, Israel, Italy, Netherlands, United States, Spain **OASIS −1** [178]	396	RCT 12 weeks followed by 14-week active-treatment extension (Phase 3) (NCT05042362)	Elinzanetant 120 mg: 199 PCB: 197	Elinzanetant reduced VMS frequency and severity over 12 weeks.
Thurston R, et al. 2024 Participating countries: Canada, Czechia, Germany, Italy, Norway, Poland, Portugal, Slovakia, Switzerland, United States **OASIS −2**	400	RCT 12 weeks followed by 14-week active-treatment extension (Phase3) (NCT05099159)	Elinzanetant 120 mg: 200 PCB: 200	Elinzanetant reduced VMS frequency and severity over 12 weeks
COMPLETED Participating countries: Belgium, Bulgaria, Canada, Denmark, Finland, Poland, Spain, United Kingdom, United States **OASIS−3**	628	RCT 52 weeks. (Phase 3). (NCT05030584)	Elinzanetant 120 mg PCB	Primary outcome: change in moderate-severe VMS from baseline to week 12.
IN PROGRESS Participating countries: Austria, Belgium, Canada, Finland, Hungary, Ireland, Israel, Italy, Kazakhstan, Poland, Portugal, Romania, Spain and the United Kingdom **OASIS 4**	473	RCT 52 weeks. (Phase3) (NCT05587296)	Elinzanetant 120 mg PCB	Primary outcome: change in moderate-severe VMS caused by adjuvant endocrine therapy in women with or at high risk of developing hormone receptor-positive BC from baseline to weeks 4 and 12

VMS: Vasomotor symptoms; HF: Hot flushes; HRT: Hormone replacement therapy; RCT: Randomized control tried; PCB: placebo; BC: breast cancer.

There are many drugs with VMS as a side effect. You can find more information in the supplementary file in this paper [177].

4. Discussion

Based on the C-SF scale score, this project aimed to establish criteria for using various therapies in treating VMS. Developing a tool that helps clinicians make decisions using these scales could improve clinical practice. Continuous scores on the C-SF scale could assist in monitoring prescribed treatment and evaluating the womanś improvement in HRQoL. The C-SF scale has also demonstrated predictive value in treatment response, as it can anticipate a significant improvement in a

Table 5
Medications for relieving VMS.

AUTHOR	N	TYPE OF STUDY	COMPARATOR GROUPS	CONCLUSIONS	ADVERSE EFFECTS
PAROXETINE					
Nelson et al. [149]	316	SR-MT (2 RCTs)	Comparison between doses of paroxetine • 10 mg • 25 mg Peri and post menopause	There are no differences between doses in the treatment of VMS.	
Shams et al. [150]	1174	SR-MT (2 RCTs)	Paroxetine 7.5 mg/day Sertraline Fluoxetine Escitalopram Citalopram PCB	No more effective than other drugs in the treatment of VMS.	Nausea (3.8 % vs 1.4 % PCB) Fatigue (3.4 % vs 1.5 % PCB) Dizziness (2.0 % vs 0.8 % PCB) Abandonment treatment higher on paroxetine Increased risk of mortality in women with breast cancer treated with tamoxifen (drug interaction)
Rienma et al. [151]	1482	SR-MT (5 RCTs)	Paroxetine 7.5 or 12.5 mg/day PCB Post-menopausal (1 surgical menopause trial) 6–16 months	VMS reduction compared to PCB Not effective in nocturnal awakenings	Sleep disturbances, headache, nausea, dizziness
Stearns et al. [152]	151	Double-blind and crossover RCT	Paroxetine 10 mg/day Paroxetine 20 mg/day PCB BC survivors 6 weeks	Reduces VMS Effective in the first week and maintained until the end Both doses are effective, but 10 mg/day is better tolerated.	17 patients dropped out due to adverse effects, mainly in the 20 mg/day group Dry mouth and nausea
Soares et al. [153]	64	Single and double blind RCT	Paroxetine (controlled release) 12.5 mg/day 25 mg/day PCB Symptomatic women after discontinuation of hormonal therapy 6 weeks	Greater reduction of VMS VS PCB	Similar in all groups Headache and dizziness
Simon et al. [154]	42	RCT	Paroxetine (25 mg/day) Raloxifene (60 mg/day) PCB 16 weeks	VMS decreases in both paroxetine and PCB and not in raloxifene	
FLUOXETINE					
Nelson et al. [149]	316	SR – MT (2 RCTs)	Fluoxetine 20 mg/day Peri and post menopause Women with and without a history of BC	No significant reduction in VMS compared to PCB No more effective than other drugs	
Loprinzi et al. [156]		Double-blind crossover RCT	Fluoxetine 20 mg/day PCB (4 weeks) Women with a history of breast cancer or concerned about the risk associated with HRT	VMS reduction in fluoxetine greater than in PCB	
Suvanto et al. [157]	150	RCT	Fluoxetine 10 mg/day, increasing to 20 mg/day at 1 month and 30 mg/day at 6 months Citalopram PCB Women without history of cancer (9 months of follow-up)	No significant differences compared to PCB	No adverse effects regarding PCB.
Oktem et al. [158]	120	PS	Fluoxetine (20 mg/day) Black Cohosh (4 0 mg/day) 6 months	Decrease in HF and SN better black cohosh. Best Fluoxetine Depression Scale	30 % Interrupt treatment in both groups
VENLAFAXINE AND DESVENLAFAXINE					
Nelson et al. [149]	247	SR – MT (2 RCTs)	Venlafaxine PCB	It did not show effectiveness in reducing frequency, but it did show effectiveness in comparison to PCB.	
Joffe et al. [159]	339	RCT, double blind	Venlafaxine (75 mg/day) Oral 17β-estradiol 0.5 mg/day PCB Peri and postmenopause > 2 episodes/day 8 weeks	Low doses of venlafaxine and 17β-estradiol are more effective than PCB; the second being somewhat more effective than the first	Good tolerability

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Table 5 (*continued*)

AUTHOR	N	TYPE OF STUDY	COMPARATOR GROUPS	CONCLUSIONS	ADVERSE EFFECTS
Sun et al. [160]	1931	SR – MT (6 RCTs)	Desvenlafaxine (100 mg/day) PCB 26 weeks	Efficacy of desvenlafaxine in reducing frequency and intensity	No evidence of increased cardiovascular, cerebrovascular or hepatic risk
Sun et al. [160]	749	3RCT	Desvenlafaxine (150 mg/day) PCB	Efficacy of desvenlafaxine in reducing frequency and intensity	Nausea, constipation, diarrhea, dry mouth, drowsiness, asthenia, dizziness, insomnia, etc.
Pinkerton et al. [161,162]	365	RCT, double blind	Desvenlafaxine (100 mg/day) PCB Postmenopause 12 weeks	Effectiveness of desvenlafaxine in reducing the frequency and intensity of VMS.	
Berhan Y and Berhan A. [163]	2020 tto. 1665 PCB	7 RCTs	Desvenlafaxine: 50 mg/day 100 mg/day 150 mg/day 200 mg/day PCB > 12 weeks	Decrease in frequency and intensity of moderate and severe VMS for doses of 100 and 150 mg/day Reduction of associated nocturnal awakenings.	Adverse effects (asthenia, hypertension, anorexia, constipation, diarrhea, dry mouth, nausea, dizziness, insomnia, drowsiness and mydriasis) that determine the suspension of treatment
CITALOPRAM AND ESCITALOPRAM					
Shams et al. [150]	2069	SR – MT (3RCT)	• Citalopram (20 mg/day) • Fluoxetine • HRT • PCB Peri and postmenopause	Frequency of VMS: No significant differences compared to PCB, fluoxetine, sertraline, paroxetine and escitalopram	
Shams et al. [150]	231	SR – MT (2RCT)	• Escitalopram 10 and 20 mg/day • PCB Peri and postmenopause	The weighted average differences indicate that there are no significant differences compared to PCB	
Carpenter et al. [164]	205	RCT	• Escitalopram (10–20 mg/day) PCB	Improved HRQoL in women	Not reported
GABAPENTIN AND PREGABALIN					
Guttuso et al. [167]	59	Double blind RCT	• Gabapentin 900 mg/day • PCB Postmenopause	VMS vs PCB decreases	Dropout rate due to adverse effects: 13 % in gabapentin and 3 % in PCB.
Pandya et al. [168]	420	Double blind RCT	• Gabapentin 300 or 900 mg/day (in three doses) • PCB Women with BC	VMS intensity decreases; frequency only at the highest dose −900 mg/day-)	More drowsiness and fatigue at higher doses.
Reddy et al. [169]	60	Double blind RCT	• Gabapentin 2400 mg/d • ECE 0.625 mg/day • PCB Postmenopause	Reduces frequency and intensity of VMS with similar efficacy to gabapentin and estrogens and superior to PC	Headache, dizziness and disorientation with a higher incidence in the group treated with gabapentin
Butt et al. [170]	197	Double blind RCT	• Gabapentin 900 mg/d in three doses • PCB 45–65 years	Decreases the frequency of VMS.	Dizziness (18 %), instability (14 %) and drowsiness (12 %) during the first week that disappear after two weeks.
Loprinzi et al. [156]	169	Double-blind phase III RCT	• Pregabalin 150 mg/d or 300 mg/d • PCB 6 weeks	Decreases the frequency and intensity of VMS	Better tolerated dose of 150 mg/d
Aguirre et al. [171]	45	Single-blind RCT	• Gapapentin 600 mg/night • E2 25 µg/d TSD, 1 patch weekly	It reduces the frequency and intensity of VMS with similar effectiveness to E2.	Drowsiness, dizziness, fatigue in the gabapentin group Mastodynia, vaginal spotting in the E2-treated group.
Saadati et al. [172]	60	RCT	• Gabapentin 900 mg/d • PCB Postmenopause	Decreases the frequency and intensity of VMS	Not referenced
Pinkerton et al. [173]	600	Phase III RCT	• Gabapentin 600 mg/morning and 1200 mg/night • PCB	Decreases the frequency and intensity of VMS	More about abandonment of treatment regarding PCB. Dizziness, headache and drowsiness. Adverse effects decrease significantly after several weeks of treatment.
Agarwal et al. [174]	50	Double blind RCT	Gabapentin 900 mg PCB + Ca;	Reduces the frequency and intensity of VMS. Maximum effect after 3 months.	Not referenced
CLONIDINE					
Nelson et al. [149]	444	SR– MT (4 RCTs)	Clonidine: • 0.1 mg/ day) • 0.05–0.15 mg/day • PCB	No decrease in frequency and intensity of VMS vs PCB	Does not affect BP at the doses tested
Loibl et al. [165]	64	Phase III RCT	• Clonidine (0.075 mg/day • Venlafaxine (37.5 twice daily) Women with BC	Venlafaxine is more effective than clonidine in the treatment of VMS	Seniors in venlafaxine group

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Table 5 (*continued*)

AUTHOR	N	TYPE OF STUDY	COMPARATOR GROUPS	CONCLUSIONS	ADVERSE EFFECTS
Buijs et al. [175]	88	RCT, double blind and crossover	• Clonidine (0.05 mg/day) • Venlafaxine (75 mg/day) Women with BC treated with antiestrogens, aromatase inhibitors or LHRH analogues	Non-significant greater decrease with clonidine than venlafaxine (the latter more immediate effect)	nausea, dry mouth, drowsiness, fatigue, altered taste and loss of appetite.
Boekhout et al. [176]	102	RCT, double blind	• Clonidine (0.1 mg/day) • Venlafaxine (75 mg/day) • PCB Women with BC	Significant differences vs. PCB in the treatment of VMS. (clonidine at the end of treatment; venlafaxine more immediately -first weeks of treatment-)	Nausea, constipation and loss of appetite (greater in the venlafaxine group)

VMS: Vasomotor symptoms; HF: Hot flushes; SR: Systematic review; RCT: Randomized control tried; PCB: placebo; MT: Metanalysis; BC: Breast cancer; BP: Blood pressure; PS: Prospective study; PS: Prospective randomized study; TSD: Transdermal; HRT: Hormonal therapy; ECE: Equine conjugated estrogens; E2: estrogens; Ca: Calcium; HRQoL: Health- related quality of life.

womańs HRQoL based on the initial score when a specific treatment is prescribed.

4.1. Strengths

No studies are addressing HRQoL scales to aid clinicians in choosing the best VMS treatment. We anticipate that the widespread use of this decision tool will benefit clinicians treating VMS during menopause.

4.2. Weakness

An important limitation encountered during this project was the extensive use of treatments for VMS during menopause with minimal evidence. This oversight could have led to avoiding products treating VMS with sufficient evidence.

5. Conclusion

In conclusion, we have developed a decision framework for treating VMS in women based on the C-SF scale score. (See Algorithm 1 Image)

Decision Algorithm for VMS in women.

1. **Initial Assessment**

   Women suffering VMS
   Follow *lifestyle* advice:

   ○ Reduce consumption of tobacco, caffeine, and alcohol.
   ○ Maintain adequate weight.
   ○ Consume a Mediterranean diet and fruits.

2. **Evaluate C-SF Menopausal Domain Scores**

   If Menopausal domain $\leq$ 25 **(Mild)**

   ○ Follow the path for mild symptoms
   ○ If after 12 weeks there is no improvement, move on to the next step (lifestyle changes continue)

   • If Menopausal domain $>$ 25 **(Moderate-severe)**

   ○ Follow the path for moderate-severe symptoms

3. **Mild Symptoms Management**

   • Start with Natural Therapies:
   First Choice: Black cohosh (Isopropanolic Extract) 40 mg/day
   Alternatives
   Isoflavones: Genistein ($\geq$ 15 mg/day)
   Sage: 300–400 mg/day
   Hops: 100 μg of 8-PN (8-prenylnaringenin)
   Pollen Extract: 160 mg/day
   • Reevaluate after 12 weeks using the Cervantes Short form scale

4. **Moderate-Severe Symptoms Management**

   • Assess eligibility for hormone replacement therapy (HRT) or fezolinetant 45 mg
   • Follow criteria for HRT use (refer to the "Criterios de elegibilidad para el uso de la THM")

   ○ If eligible, start HRT and monitor
   ○ If not eligible or have contraindications, consider non-hormonal pharmacological treatment: Fezolinetant 45 mg

5. **Follow-up and Reevaluation**

   • For both mild and moderate-severe cases, perform a follow-up assessment 12 weeks after starting the intervention
   • Use the Cervantes Short form scale to evaluate the effectiveness of the treatment

6. **Next Steps Based on Follow-up**

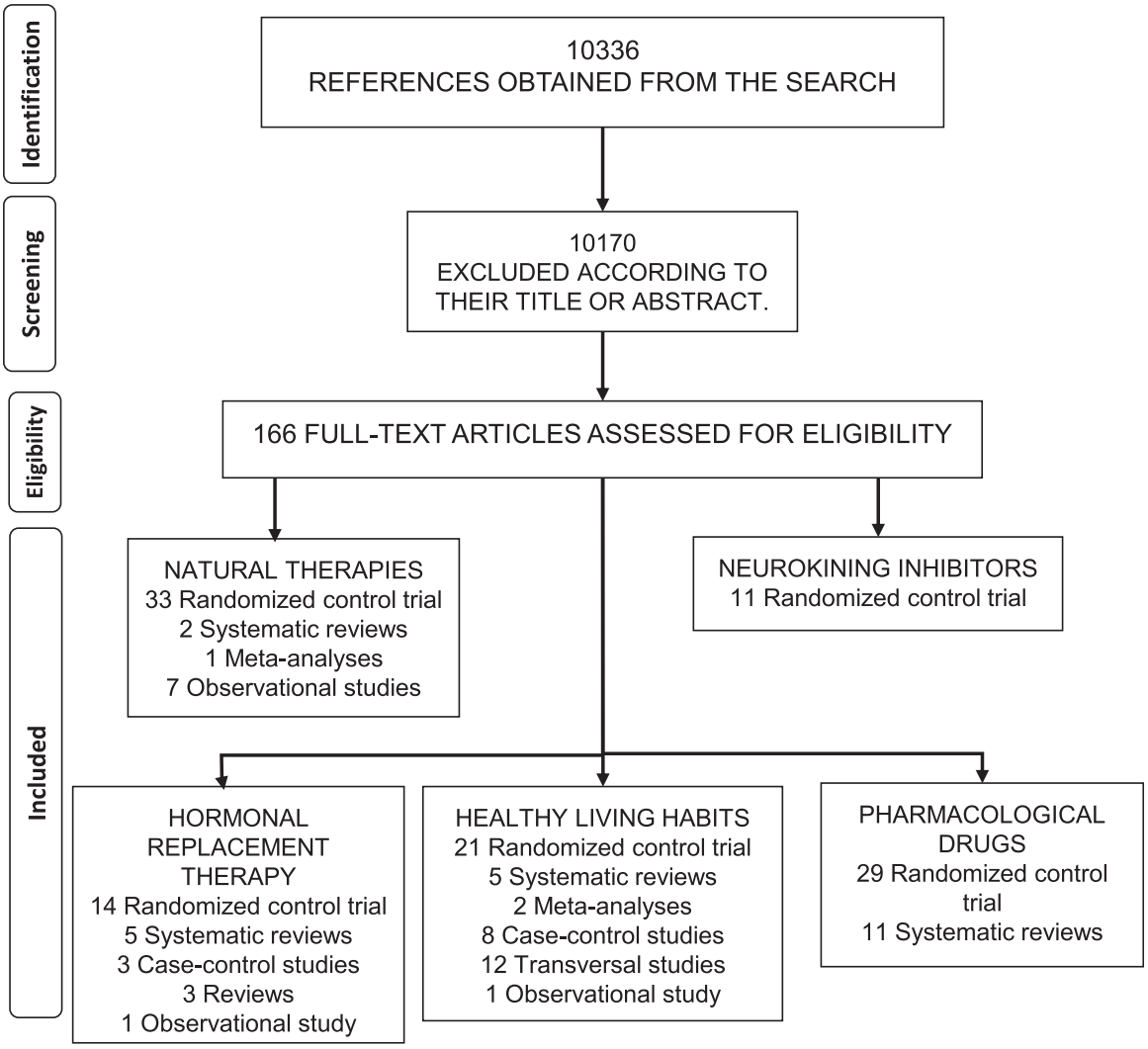
   • If symptoms improve, continue the current management
   • If no improvement, reassess and consider alternative or additional treatments

By following these steps and recommendations, a structured and logical approach to managing VMS in women can be ensured.

Table 6
Comparison of the dosage, efficacy, and safety of non-hormonal drugs in hot flushes.

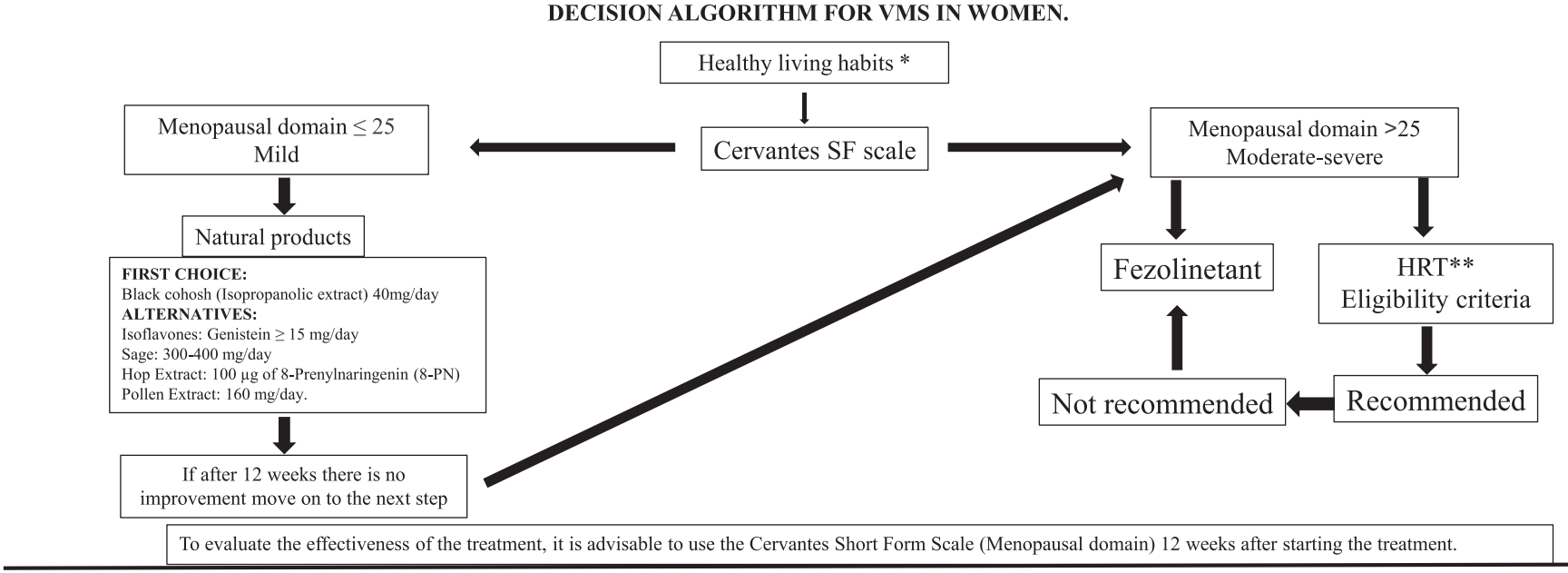
DRUG	VMS REDUCTION	ADDITIONAL BENEFIT	ADVERSE EFFECTS
SELECTIVE SEROTONIN REUPTAKE INHIBITORS			
Paroxetine (7.5–20 mg/day)	41–60 % vs PCB (14–38 %)	Improves sleep. Little effect on sexual function	Dry mouth and upper gastrointestinal tract disorders
Citalopram (10 −20 mg/day)	43–50 % vs PCB (23 %)	Reduces anxiety, does not affect libido	Drowsiness, dry mouth, palpitations
Escitalopram (10 −20 mg/day)	50–60 % vs PCB (30 %)	Improves HRQoL and sleep related to vasomotor disorders Does not affect sexual function	Increase in VMS after cessation of treatment
Fluoxetine (20 mg/day)	50 % vs PCB (36 %)	Improves HRQoL and mood Does not affect libido	
SSRI-SNRI			
Venlafaxine (37.5–150 mg/day) extended release	37–61 % vs PCB (27 %)	Improves HRQoL, sleep and mood	Dry mouth, upper GI tract discomfort, headache, decreased sexual function
Desvenlafaxine (100–150 mg/day)	64 % vs PCB (51 %)	Reduces night awakenings Does not affect sexual function	Upper GI tract discomfort, drowsiness, and severe insomnia in the first week of treatment.
ANTICONVULSANTS			
Gabapentin 900–2400 mg/day divided doses (start with 300 mg/day)	35–38 % more than PCB	Improves HRQoL, sleep and reduces pain	Dizziness, instability, fatigue and drowsiness. Tremors. (at higher doses the incidence and severity are much greater)
Pregabalin (150–300 mg) divided doses ,,,	65–71 % vs PCB (50 %)		
Clonidine (0.1–0.15- mg/day)	26–49 % vs PCB	Improves HRQoL	Hypotension, headaches, dry mouth, weakness, sedation and constipation.

VMS: Vasomotor symptoms; HF: Hot flushes; PCB: placebo; HRQoL: Health- related quality of life; GI tract: gastrointestinal tract.



Chartchart 1. FLOWCHART BIBLIOGRAPHIC REVIEW.

Algorithm 1. : Decision Algorithm for VMS in women.



*Healthy living habits
It is advisable to reduce the consumption of tobacco, caffeine, and alcohol.
It is advisable to maintain an adequate weight.
Consumption of the Mediterranean diet and fruits
Alternative Therapies.: CBT and Hypnosis: Show a reduction in hot flashes. Mindfulness and Acupuncture; The evidence is not enough to affirm their effectiveness in the treatment of HF.

****START** with lower doses, such as: Transdermal E2 (0.025 mg), Oral E2 (0.5 mg/day), Tibolone or TSEC.
EVALUATE AT 12 WEEKS: Re-assess symptoms and side effects.
CONTINUING TREATMENT: HRT should be started < 60 years or < 10 years since menopause, there is not an established maximum period after which it must be stopped.
DISCONTINUATION: Sudden and gradual discontinuations have been described, but there is no evidence that one regimen is better than the other.

SPECIFIC CONSIDERATIONS
Perimenopause: E2 is better than EE; MPG is better than PG; Cyclical oral PG/MPG is better than continuous; maintain PG IUD
LNG IUD plus E2: Suitable for perimenopausal women with HF who experience heavy bleeding and need contraception.
Postmenopause: E2 , PG/MPG continuos better than cyclical ; LNG IUD 52 mg if poor adherence or tolerance and Woman's preference
Minimize Risk of Thrombosis:
Prefer transdermal HRT, estradiol plus NETA, or estradiol plus oral MPG

VMS: Vasomotor symptoms; HF: Hot flushes; HRT: Hormonal Therapy; TSEC: Tissue-Selective Estrogen Complex ; MPG: Micronized progesterone; PG: Progestins; C-SF: Cervantes short form scale; E2: Estradiol; EE: Ethinylestradiol; CBT: Cognitive behavioral therapy ; LNG IUD: Levonorgestrel intrauterine device; NETA: Norethisterone acetate.

Contributors

Maria Fasero contributed to conception and design of the idea, coordination and preparation of manuscript, manuscript editing, and was a coordinator of Menoguide Hot flushes. Laura Baquedano contributed to preparation of manuscript and was a member of menoguide Hot flushes. Maria Teresa sanchez contributed to preparation of manuscript and was a member of menoguide Hot flushes. Isabel Gippini contributed to preparation of manuscript and was a member of menoguide Hot flushes. Danilo Fuentes contributed to preparation of manuscript and was a member of menoguide Hot flushes. Concha Navarro contributed to preparation of manuscript and was a member of menoguide Hot flushes. Estanislao Beltran contributed to preparation of manuscript and was a member of menoguide Hot flushes. Mariella Lilue contributed to preparation of manuscript and was a member of menoguide Hot flushes. Iris Porcel contributed to preparation of manuscript and was a member of menoguide Hot flushes. Carmen Pingarron contributed to preparation of manuscript and was a member of menoguide Hot flushes. Mercedes Herrero contributed to preparation of manuscript and was a member of menoguide Hot flushes. Pablo Romero contributed to preparation of manuscript and was a member of menoguide Hot flushes. Maria Teresa Ortega contributed to preparation of manuscript and was a member of menoguide Hot flushes. Maria Emilia Carretero contributed to preparation of manuscript and was a member of menoguide Hot flushes. Nicolas Mendoza contributed to external review. Santiago palacios contributed to external review. Pluvio Coronado contributed to external review.

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Ethical statement

None

Declaration of Competing Interest

Maria Fasero competing interest: Astellas Pharma, Shionogui, MSD, Organon, Atika Pharma, Dermofarm, Theramex. Mariella Lilue: Shionogi, Novonordisk. Iris Porcel: Theramex, gedeon Richter, Adamed. Carmen Pingarron: Astellas, Pfizer, MSD, Uriach, Shionogi, Arica, Organon, Exeltis, Theramex, NTDs, Faes, Meiji. Mercedes Herrero: Atlantia, Bayer, Bial, Dermofarm, Exeltis, Gedeon Richter, Ibérica, Kern Pharma, MSD, Ordesa, Organon, ProcareHealth, Sysmex, Shionogui, Ther amex y Zambón. Pablo Romero: Astellas, Shionogi, Procare. Maria Teresa Ortega: None declared. Maria Emilia Carretero: None declared. Nicolas Mendoza: Astellas Pharma, Shionogi. Santiago palacios: Arkochim, Bayer Healthcare, Exeltis, Theramex,Gedeon Richter, Novo Nordisk, Procare Health, Serelys, Mithra, Lacer, Sandoz. Pluvio Coronado: Exeltis, Gedeon Richter, Novo Nordisk, Procare Health, Lacer, Theramex; Atika Pharma.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.eurox.2025.100366.

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