Gynecological Endocrinology

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/igye20

Efficacy and safety of visnadine in the treatment of symptoms of sexual dysfunction in heterosexual women: a systematic review of randomized clinical trials

Brenda Caira-Chuquineyra, Daniel Fernandez-Guzmán, Humberto Garayar-Peceros, Vicente A. Benites-Zapata, Faustino R. Pérez-López, Juan E. Blümel & Edward Mezones-Holguín

To cite this article: Brenda Caira-Chuquineyra, Daniel Fernandez-Guzmán, Humberto Garayar-Peceros, Vicente A. Benites-Zapata, Faustino R. Pérez-López, Juan E. Blümel & Edward Mezones-Holguín (2024) Efficacy and safety of visnadine in the treatment of symptoms of sexual dysfunction in heterosexual women: a systematic review of randomized clinical trials, Gynecological Endocrinology, 40:1, 2328619, DOI: 10.1080/09513590.2024.2328619

To link to this article: https://doi.org/10.1080/09513590.2024.2328619

© 2024 The Author(s). Published by Informa UK Limited, trading as Taylor & Francis Group

Published online: 25 Mar 2024.

Submit your article to this journal

Article views: 617

View related articles

View Crossmark data

Full Terms & Conditions of access and use can be found at
https://www.tandfonline.com/action/journalInformation?journalCode=igye20

GYNECOLOGICAL ENDOCRINOLOGY
2024, VOL. 40, NO. 1, 2328619
https://doi.org/10.1080/09513590.2024.2328619

Taylor & Francis
Taylor & Francis Group

RESEARCH ARTICLE

OPEN ACCESS Check for updates

Efficacy and safety of visnadine in the treatment of symptoms of sexual dysfunction in heterosexual women: a systematic review of randomized clinical trials

Brenda Caira-Chuquineyra[a], Daniel Fernandez-Guzmán[b], Humberto Garayar-Peceros[c], Vicente A. Benites-Zapata[d], Faustino R. Pérez-López[e], Juan E. Blümel[f] and Edward Mezones-Holguín[g]

[a]Faculty of Human Medicine, Universidad Nacional San Agustín, Arequipa, Perú; [b]Faculty of Health Sciences, Universidad Científica del Sur, Lima, Perú; [c]Faculty of Medicine, Universidad Nacional San Luis Gonzaga, Ica, Perú; [d]Research Unit for the Generation and Synthesis of Health Evidence, Universidad San Ignacio de Loyola, Lima, Peru; [e]Faculty of Medicine, Universidad de Zaragoza, Zaragoza, Spain; [f]Faculty of Medicine, Universidad de Chile, Santiago de Chile, Chile; [g]Centre of Excellence for Social and Economic Studies in Health, Universidad San Ignacio de Loyola, Lima, Perú;

ABSTRACT

Objective: To synthesize the primary evidence on the efficacy and safety of visnadine on symptoms of sexual dysfunction (SD) in heterosexual women.

Methods: We conducted a systematic review of randomized clinical trials (RCTs) with a primary search without language restriction in PubMed/Medline, Scopus, Embase, Web of Science, Cochrane Library, and international clinical trial registries. Trials reporting the use of visnadine by any route in women with SD were eligible. We performed screening, data extraction, and risk of bias assessment in a double-blind approach. The primary outcomes were the Female Sexual Function Index (FSFI) and its domains. Secondary outcomes were safety, arousal, lubrication, pleasure, orgasm, negative sensations, duration, and overall satisfaction.

Results: Initially, 242 records were retrieved. We selected nine papers for full-text reading and finally included two RCTs: one with a parallel design and one with a crossover design with a total of 96 patients. One study compared visnadine aerosol with a placebo, while the other compared different frequencies of visnadine aerosol use. Visnadine use showed a statistically significant improvement ($p < 0.05$) in overall FSFI scores, regardless of the frequency of use. A meta-analysis was not possible due to the high clinical and methodological heterogeneity between available studies.

Conclusion: RCTs regarding the use of visnadine for the Female SD are scarce and methodologically limited. This preliminary evidence shows visnadine as a potentially effective and safe option to alleviate some of the clinical symptoms of SD in heterosexual women. However, future better-designed randomized studies with larger sample numbers are required.

ARTICLE HISTORY
Received 29 January 2024
Accepted 4 March 2024
Published online 26 March 2024

KEYWORDS
Female sexual dysfunction; female sexual function index; FSFI; sex dysfunction; systematic review; visnadine; women's health

Introduction

The treatment and management of female sexual dysfunction (FSD) requires an appropriate diagnosis; however, treatment options validated by high-quality scientific evidence are scarce [1,2]. Sexual dysfunction has been classified into problems of desire, arousal, orgasm, lubrication, vulvodynia, and dyspareunia, which may have an organic [3] or psychological basis and affect the quality of life of individuals [4]. The frequency of FSD varies according to the studied population, the coexistence of comorbid conditions, and the role of the partner [5]. In this context, it is of great interest to study therapies for the management of FSD.

Therapies for FSD can be non-pharmacological or pharmacological [2]. The former includes herbal products, physiotherapy, and psychological therapy, which show heterogeneous effects on various types of female sexual disorders [1,6–9]. On the other hand, modest results have been reported for the use of pharmacologic therapies, including hormone therapy with testosterone, estrogen, intravaginal dehydroepiandrosterone (DHEA), phosphodiesterase type 5 inhibitors, botulinum toxin A, flibanserin, and others [10]. Among the most studied pharmacological approaches are those that seek to improve genital microcirculation, where signals from different neuropeptides and hormones interact to promote vasodilatation and increased blood flow [10], which under physiological conditions would promote increased vaginal lubrication and clitoral and vulvar engorgement [3]. However, there are controversial reports on the clinical effects of these drugs, and the potential biochemical mechanisms they exert [10,11]. Among drugs proposed as alternatives, visnadine is a novel therapy with an efficacy and safety that deserves appropriate evaluation.

Although the use of visnadine in medicine is not new, scientific evidence of its use in the treatment of FSD began to be published only a few years ago. It is a drug derived from the fruit of the *Ammi Visnaga* plant [12,13], also known as bishop's weed, which has traditionally been used for the relief of renal and digestive colics, asthma, spastic bronchitis, and mild

CONTACT Edward Mezones-Holguín, emezones@gmail.com Universidad San Ignacio de Loyola, Av. La Fontana #750, La Molina, Lima, Perú;
© 2024 The Author(s). Published by Informa UK Limited, trading as Taylor & Francis Group
This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (http://creativecommons.org/licenses/by-nc/4.0/), which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited. The terms on which this article has been published allow the posting of the Accepted Manuscript in a repository by the author(s) or with their consent.

anginal symptoms [12].7 These effects are brought about by visnadine promoting smooth muscle relaxation mediated by its action on L-type calcium (Ca^{2+}) channels [14,15]. The study visnadine as a therapeutic option for FSD is based on the fact that its topical application to the genital region would have an effect on regional blood flow [16], thus improving the sensory threshold of the genital area [17]. According to clinical studies, the administration of visnadine would favor an increase in blood flow to the vulva, lubrication, arousal, orgasm, and the perception of sexual satisfaction, as well as positive effects on vulvovaginal atrophy [17–22]. However, despite the publication of primary studies with visnadine, no synthesis study has yet been published regarding its safety and efficacy in the treatment of FSD.

Our aim was to synthesize the primary evidence on the efficacy and safety of visnadine on symptoms of sexual dysfunction in heterosexual women.

Methods

Reporting, registration, and study design

A systematic review of randomized clinical trials (RCTs) was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement [23]. Each step of the process was performed independently and blindly by at least two investigators. In case of disagreement, consensus was sought, and in case of persistence of disagreement, it was resolved by a third investigator. The protocol was registered in the Prospective International Registry of Systematic Reviews with the code PROSPERO CRD42021243112.

Information sources and search strategy

A search without language restriction was performed until March 2021 with an update on December 2023. A preliminary search strategy was developed for PubMed/MEDLINE using the MeSH terms 'visnadine' and 'female sexual dysfunction', of which we obtained four results. Therefore, we decided to perform a more sensitive search using only the term 'visnadine', adapting the same strategy for Embase, Scopus, Web of Science, Cochrane Library, clinical trials registries of the USA (www.clinicaltrials.gov), Europe (https://www.clinicaltrialsregister.eu), and the World Health Organization (https://trialsearch.who.int). In addition, we searched the Open Grey portal (https://opengrey.eu). Moreover, we performed a secondary search based on the bibliographic references of the selected articles, and authors of the completed trial registries were contacted to identify other potentially eligible reports.

Research question and eligibility criteria

The research question formulation contained the elements: Population, Intervention, Comparison, Outcome, and study design (PICOS):

- Population: Women of any age with global or partial impaired sexual function (desire, arousal, lubrication, orgasm, satisfaction, and pain) as defined with the original 19 item Female Sexual Function Index ([FSFI) [24,25] or the 6-item short version [26–28].
- Intervention: Administration of visnadine orally, topically, or parenterally.
- Comparison: Placebo or other treatments.
- Outcomes: Efficacy and safety.
- Study design: RCTs.

Outcomes and study selection process

The primary efficacy outcomes were improvement in the global FSFI score or of each its domains (desire, arousal, lubrication, orgasm, satisfaction, and dyspareunia). Secondary outcomes were perception of arousal, lubrication, pleasure, orgasm, negative sensations, duration, and overall satisfaction with coital sexual activity. At the safety level, we considered tolerability and reporting of adverse events. Searches in the electronic databases were imported into Rayyan® (Qatar Computing Research Institute, Doha, Qatar), where we removed duplicate records manually. Screening by titles and abstracts was carried out by two pairs of researchers (DFG and BCC, HGP and JTF). We blindly and independently reviewed titles and abstracts. Disagreements regarding selection were resolved by consensus or discussion with one of the adjudicators (VABZ and EMH). The selected studies were reviewed in full text to define their inclusion in the review by the same two pair of investigators; disagreements were addressed using the same mechanism as in the previous stage.

Data extraction, risk of bias, and quantitative synthesis

The two pair of investigators (DFG and BCC, HGP and JTF) independently extracted the predefined data: study characteristics, participant characteristics, specific visnadine intervention, and outcome characteristics from each full-text article directly into previously designed extraction data spreadsheets. Entries were compared for accuracy, and any discrepancies were resolved by consensus or with the involvement of a third-party adjudicator (VABZ, FRPL and EMH). The longest follow-up period was used associated with primary or secondary outcomes for data extraction analysis. The authors of the original studies were contacted *via* email to obtain unpublished information. However, no response was received.

Two pair of investigators (DFG and BCC, HGP and JTF) independently assessed the risk of bias of each included primary study using the Cochrane Collaboration Risk of Bias tool [29]. Similar to the previous phases, any discrepancies were resolved by consensus or by discussion with another investigator (VABZ, FRPL and EMH). We assessed the following domains by categorizing them as low risk of bias, high risk of bias, and other concerns: allocation sequence concealment (selection bias); blinding (detection and performance bias) of participants and staff to outcome assessment; incomplete outcome data (attrition bias); selective reporting of outcomes (information bias); and other biases. We used Review Manager ® Version 1.22.0 software (The Cochrane Collaboration, London, England, 2020) to present these data graphically.

We planned to perform meta-analyses with the included studies to estimate the pooled effect size (point estimate and 95% confidence intervals) of the intervention. For dichotomous and continuous data, we proposed the calculation of odds ratios and standardized mean differences, respectively. We also proposed to assess publication bias if enough studies (at least 10) were included in the review.

Results

Selection of studies and characteristics of the included studies

We found 242 records in the database search and three in the clinical trials registries. After removing duplicates, we included 108 records for title and abstract evaluation, from which we examined nine full-text papers. Three clinical trial registries were excluded because they were in the recruitment phase (NCT04579991) [30], did not have a control group (NCT03281655) [22], and were published only as a conference abstract without enough data (NCT04015037) [27]. An attempt was made to contact the authors. Another study by Caputo et al. [31] was also excluded because it did not have a control group. Finally, we included two RCTs: Bernorio et al. [17], and Caruso et al. [19] (Figure 1). Table 1 presents the studies that were not included and the reasons for exclusion after full text review.

Table 2 summarizes the general characteristics of the included studies in the systematic review. In brief, we specify some details about each one of them.

Bernorio et al. [17], *'Efficacy and tolerability of a spray formulation containing visnadine in women self-reporting sexual symptoms: a randomized double-blind placebo-controlled pilot study'*

This study was conducted in three units under the auspices of the Italian Association of Applied Sexology and Psychology (Milano, Italy). The authors enrolled 60 women between the ages

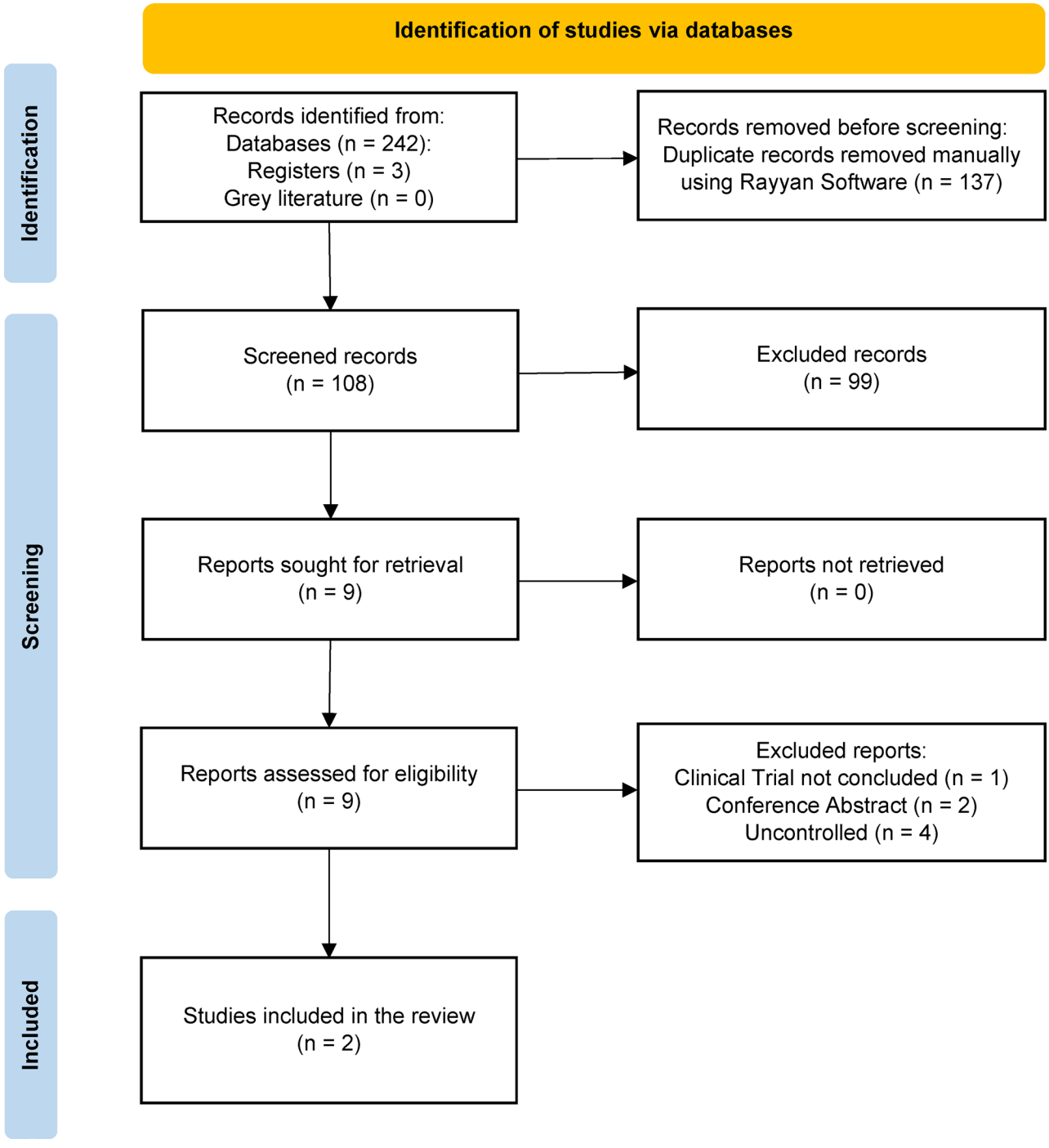

Figure 1. Flow diagram for study selection.

Table 1. Studies excluded after full-text evaluation.

Author [reference]	Title	Exclusion reasons
Aquino et al. [27]	PNM-12 Double-blind randomized study on the effect of non-hormonal gel application to the genital area of women in the Menacme with Sexual Dysfunction Trial (NCT04015037).	Wrong publication type: conference abstract.
Lagana et al. [21]	Effects of a new vaginal cream containing visnadine, prenylflavonoids and bovine colostrum on Vaginal Health Index Score and Female Sexual Function Index in post-menopausal sexually active women affected by vaginal dryness: A pilot study.	Uncontrolled study. Wrong publication type: conference abstract and no further information could be obtained from the authors.
Caputo et al. [18]	Efficacy of an intimate oil solution containing visnadine in women self-reporting sexual symptoms.	Uncontrolled study.
Laganà et al. [22]	Preliminary results of a single-arm pilot study to assess the safety and efficacy of visnadine, prenylflavonoids and bovine colostrum in postmenopausal sexually active women affected by vulvovaginal atrophy (NCT03281655).	Uncontrolled study.
Sparavigna et al. [20]	A randomized single-blind placebo-controlled study of a visnadine emulgel formulation on healthy postmenopausal women.	Wrong outcome.
Caputo et al. [31]	An open trial of a visnadine emulgel topical application in postmenopausal superficial dyspareunia: daily vs. on-demand use.	Uncontrolled study.
Chaikittisilpa et al. [30]	Effects of visnadine, ethyl ximeninate, Coleus Barbatus and Millet in Emulgel on Sexual Function in Postmenopausal Women (NCT04579991).	Clinical trial not concluded.

Table 2. General characteristics of the clinical studies included in the systematic review.

Author (year)	Country	Study Design	Population	Age (years) Mean ± SD	Total FSFI score at baseline	Follow-up period	Intervention Groups details	Outcomes	Funding
Bernorio et al. (2018) [17]	Italy	Randomized, double-blind placebo controlled-pilot study	Women with female sexual dysfunction (self-reported sexual symptoms)	38.3 ± 7.9 (intervention) 39.6 ± 6.8 (control)	25.0 ± 3.8 (intervention) 25.4 ± 5.0 (control)	T_1: 30 days	**Intervention** Two puffs of visnadine spray for a minimum of six times per month **Control** Two puffs of placebo spray for a minimum of six times per month	FSFI scores, visnadine questionnaire	Not Reported
Caruso et al. (2018) [19]	Italy	Randomized, crossover study	Women with female sexual dysfunction (as defined by DSM-IV criteria)	32.5 ± 4.2	21.0 ± 3.0 (sequence A) 21.2 ± 2.9 (sequence B)	T_1: 30 days T_2: 60 days	**Sequence A (on demand → washout → daily).** Each woman had to apply two sprays on her clitoral area 15 min before starting sexual activity following her sexual desire on-demand phases, or every night during the daily phases. **Sequence B (daily → washout → on demand).** Each woman had to apply two sprays on her clitoral area 15 min before starting sexual activity following her sexual desire on-demand phases, or every night during the daily phases.	FSFI, FSDS	Not reported

SD: Standard deviation.
FSFI: Female Sexual Function Index.
FSDS: Female Sexual Distress Scale.

of 18 and 60 with self-reported symptoms of lack of desire, arousal, or orgasm for at least 6 months. By parallel randomization, 30 women received placebo and 30 women received visnadine spray, two puffs applied to the vulvar area 10 min before sexual stimulation (at least six times for 30 days). Most women were premenopausal, except for three postmenopausal women in the placebo group and four in the visnadine group. There were no significant differences between the groups at baseline. The FSFI scores were recorded at baseline (T0) and at 30 days (T1). During follow-up, two women in the placebo group withdrew

from the study, leaving a total a 58 for analysis (28 placebo group and 30 intervention group). An *ad hoc* 12-item questionnaire was also administered at follow-up to measure the efficacy and tolerability of the used product.

Caruso et al. [19], *'Randomized crossover study investigating daily versus on-demand vulvar Visnadine spray in women affected by female sexual arousal disorder'*

This study had a crossover design and was conducted at the Family Planning Center of the Sexology Research Group of the Department of General Surgery and Medical-Surgical Specialties, Faculty of Medicine, University of Catania, Italy. The authors included 38 women aged 25–40 years affected by sexual dysfunction according to DSM-IV criteria (Symptomatology of Sexual Dysfunction). Nineteen participants were randomly assigned to each of two possible sequences: on-demand, washout, daily (Sequence A); and daily, washout, on-demand (Sequence B). Administration for on-demand use was two puffs 15 min before the initiation of sexual activity, according to their sexual desire, and for daily use was two puffs each night. There were no significant differences between the groups at baseline. The FSFI and the Female Sexual Distress Scale (FSDS) were applied at baseline (T0), before crossover, at 30 days (T1), and at 60 days (1 week after the last application) (T2). During follow-up, four subjects dropped out of Sequence A and three dropped out of Sequence B.

Risk of bias assessment

The study by Bernorio et al. [17] had a better profile (better total and domain FSFI scores at baseline) than the one by Caruso et al. [19]. This study had one domain rated as some concerns and did not have any domains rated as high risk of bias; whereas the study of Caruso et al. had three domains rated as high risk of bias and two domains rated as some concerns. Figure 2 shows the risk of bias assessment of the studies included in the systematic review.

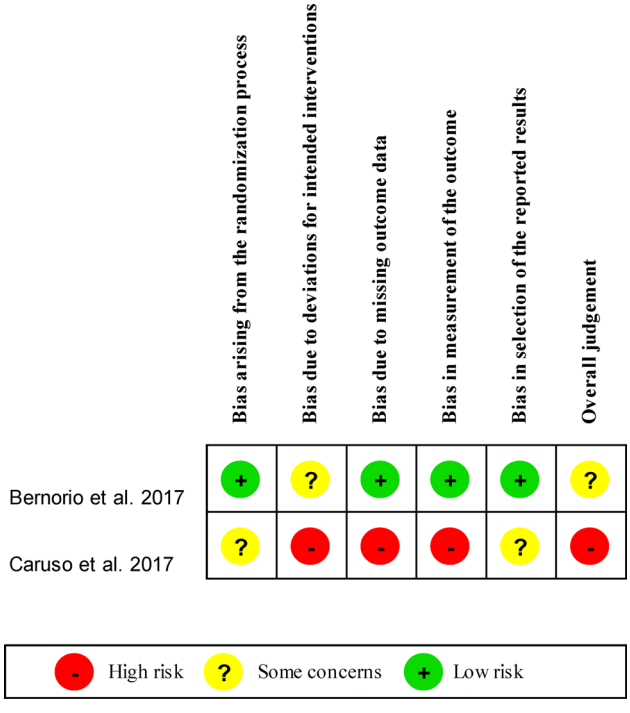

Figure 2. Risk of bias assessment for the included studies.

Assessed outcomes of the included studies and adverse effects

Overall, two comparisons were made with variations in the frequency of visnadine use. Bernorio et al. compared the efficacy of visnadine against placebo through topical spray application for 30 days. Caruso et al. compared the frequency of use of visnadine spray on-demand versus daily overnight use for 30 and 60 days. Details of these studies are provided in Table 3.

Together, the two included studies reported results from 96 participants. Bernorio et al. reported higher total FSFI scores after visnadine application (intervention group, T0 vs T1) and as compared to placebo at T1. Similarly, Caruso et al. found a significant increase of total FSFI scores with daily application of visnadine compared to on-demand application (Table 3). In addition to the outcomes pre-specified in our review, Bernorio et al. reported women's sexual satisfaction with the product and assessment of its tolerability, while Caruso et al. evaluated the FSDS scores and clitoral blood flow.

Bernorio et al. reported adverse effects, such as itching (2/30 patients) and warmth (7/30 patients) in the intervention group, and burning (1/28 patients) and warmth (6/28 patients) in the placebo group. Caruso et al. reported spotting (1/19 patients) in the intervention group.

Quantitative synthesis

The two analyzed studies showed clinical (different age groups, different definitions of intervention groups) and methodological heterogeneity (different designs, different control group, different outcome measurements) reason why meta-analysis was not performed.

Discussion

Main findings and their significance

The evaluation of the evidence from the two RCTs shows that visnadine (i) improves symptoms related to sexual dysfunction in heterosexual women, and (ii) it is well tolerated with no higher incidence of adverse events compared to placebo. In the two RCTs, topical visnadine increased the total FSFI score and in one RCT it also increased the arousal FSFI domain score [19]. However, the analyzed studied were highly heterogeneous at the clinical and methodological level, had small sample sizes and, one had a high risk of bias.

While our results suggest that topical application of visnadine may be an effective and safe therapeutic option for the management of symptoms of sexual dysfunction in heterosexual women, the evidence was too limited to allow the extrapolation of the findings to all women with FSD.

Plausibility of findings

Visnadine is an active ingredient extracted from the *Ammi Visnaga* fruit [12], which has both peripheral and coronary vasodilator activity [32] *via* inhibition of L-type Ca^{2+} channels that are involved in the contractile response of blood vessels [14]. At high concentrations, visnadine also appears to interfere with other mechanisms involved in the contraction of vascular smooth muscle related to inhibition. Thus, the administration of a

Table 3. Effects of visnadine on FSFI global and domain scores.

Author (year)	Comparisons	n	*FSFI Global score*		*Desire (FSFI)*		*Arousal (FSFI)*		*Lubrication (FSFI)*		*Orgasm (FSFI)*		*Satisfaction (FSFI)*		*Dyspareunia (FSFI)*	
			Mean ± SD	*p-value*	Mean ± SD	*p-value*	Mean ± SD	*p-value*	Mean ± SD	*p-value*	Mean ± SD	*p-value*	Mean ± SD	*p-value*	Mean ± SD	*p-value*
Bernorio et al. (2018) [17]	Intervention vs. placebo (T_0)	IG: 30 CG: 28	25.0 ± 3.8 vs. 25.4 ± 5.0	NS	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Placebo (T_1 vs. T_0)	CG: 28	25.6 ± 4.7 vs. 25.4 ± 5.0	NS	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Intervention (T_1 vs. T_0)	IG: 30	27.9 ± 2.4 vs. 25.0 ± 3.8	<0.001	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Intervention vs. placebo (T_1)	IG: 30 CG: 28	27.9 ± 2.4 vs. 25.6 ± 4.7	<0.001	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Caruso et al. (2018) [19]	Sequence A (T_1 vs. T_0)	T_0: 19 T_1: 15 T_2: 15	21.4 ± 2.8 vs. 21.0 ± 3.0	NS	5.3 ± 0.9 vs. 5.4 ± 0.2	NS	2.9 ± 0.6 vs. 2.7 ± 0.4	NS	3.1 ± 0.5 vs. 2.9 ± 0.3	NS	3.6 ± 0.4 vs. 3.5 ± 0.2	NS	3.8 ± 0.8 vs. 3.4 ± 0.6	NS	4.0 ± 0.9 vs. 3.1 ± 0.9	0.007
	Sequence A (T_2 vs. T_0)		32.4 ± 4 vs. 21.0 ± 3.0	0.001	5.6 ± 0.8 vs. 5.4 ± 0.2	NS	5.3 ± 0.7 vs. 2.7 ± 0.4	0.001	5.8 ± 0.4 vs. 2.9 ± 0.3	0.001	5.1 ± 0.6 vs. 3.5 ± 0.2	0.001	5.4 ± 0.7 vs. 3.4 ± 0.6	0.001	5.1 ± 0.5 vs. 3.1 ± 0.9	0.001
	Sequence A (T_2 vs. T_1)		32.4 ± 4.0 vs. 21.4 ± 2.8	0.001	5.6 ± 0.8 vs. 5.3 ± 0.9	NS	5.3 ± 0.7 vs. 2.9 ± 0.6	0.001	5.8 ± 0.4 vs. 3.1 ± 0.5	0.001	5.1 ± 0.6 vs. 3.6 ± 0.4	0.001	5.4 ± 0.7 vs. 3.8 ± 0.8	0.001	5.1 ± 0.5 vs. 4.0 ± 0.9	0.001
	Sequence B (T_1 vs. T_0)	T_0: 19 T_1: 18 T_2: 16	32.5 ± 3.5 vs. 21.2 ± 2.9	0.001	5.6 ± 0.9 vs. 5.3 ± 0.3	NS	5.5 ± 0.8 vs. 2.7 ± 0.4	0.001	5.8 ± 0.4 vs. 2.9 ± 0.4	0.001	5.1 ± 0.6 vs. 3.0 ± 0.4	0.001	5.4 ± 0.5 vs. 3.4 ± 0.6	0.001	5.1 ± 0.4 vs. 3.1 ± 0.4	0.001
	Sequence B (T_2 vs. T_0)		24.0 ± 2.5 vs. 21.2 ± 2.9	0.005	5.3 ± 0.9 vs. 5.3 ± 0.3	NS	3.3 ± 0.9 vs. 2.7 ± 0.4	0.010	3.5 ± 0.4 vs. 2.9 ± 0.4	0.010	3.7 ± 0.8 vs. 3.0 ± 0.4	0.002	4.0 ± 0.7 vs. 3.4 ± 0.6	0.010	3.6 ± 0.9 vs. 3.1 ± 0.4	0.030
	Sequence B (T_2 vs. T_1)		24.0 ± 2.5 vs. 32.5 ± 3.5	0.001	5.3 ± 0.9 vs. 5.6 ± 0.9	NS	3.3 ± 0.9 vs. 5.5 ± 0.8	0.001	3.5 ± 0.4 vs. 5.8 ± 0.4	0.001	3.7 ± 0.8 vs. 5.1 ± 0.6	0.001	4.0 ± 0.7 vs. 5.4 ± 0.5	0.001	3.6 ± 0.9 vs. 5.1 ± 0.4	0.001

SD: Standard deviation; FSFI: Female Sexual Function Index; NS: Non-significant; NA: Not applicable.
In the study of Bernorio et al. [17] used: IG: Intervention group; CG: Control group;.
In the study of Caruso et al. [19] used: T0: Baseline, T1: Before the cross-over, T2: within one week from the end of the study.
Sequence A presents the following phases: on demand → washout → daily. While Sequence B presents the following phases: washout → daily → on demand.

visnadine emulgel increased the blood flow of the clitoris within 30 min after the application of phosphodiesterases [33]. However, the effect of visnadine on FSD symptomatology could be attributed to these pharmacological properties related to the regulation of vascular relaxation [16,32] and the increase of regional vascularization, affecting the turgor and sensory threshold in the area of application [20]. Therefore, in the randomized crossover clinical trial of Sparavigna et al. [20] it was found that the administration of a visnadine emulgel caused hyperemia and greater vasodilatation of the clitoris within 30 min of application compared to a placebo. Similarly, the pilot study by Laganà et al. [21] found that visnadine application together with prenylflavonoids and bovine colostrum in 15 sexually active postmenopausal women with vaginal dryness improved the elasticity and the type and consistency of vaginal secretions. Visnadine also improved mucosal epithelialization and vaginal moisture in this study [21].

Previous reviews and unpublished studies

A systematic review was conducted to evaluate the efficacy of natural products for the treatment of FSD [8]. Of the 15 included RCTs, the two studies analyzed in our review were described. However, the authors only qualitatively summarized the results of the primary studies, they did not show the effect of visnadine on FSD or FSFI scores in the results and did not assess the risk of bias of the primary studies.[8]

Contrary to the encouraging results found with visnadine spray, Aquino et al. [34] in their randomized double-blind study that evaluated the use of visnadine, ethyl ximeninate, Coleus barbatus, and Panicum miliaceum in a gel form in a sample of 60 women of reproductive age, found no significant differences in changes in FSFI global and domain scores when comparing the active intervention group with the placebo group ($p > 0.05$). Nonetheless, this report was not published as full text and was only presented as a lecture at a Latin American congress on sexual health [34].

Limitations and strengths

Our systematic review has some limitations. First, the evidence was scarce with few included studies with high clinical (age groups, menopausal stage) and methodological (study design, variations in intervention and outcomes) heterogeneity, which made it impossible to perform the pre-specified analyses in the protocol. Second, the sample size in the studies was small, which precluded subgroup analyses, which had a considerable effect on the precision of the results. Third, there was a potential selection bias due to the existence of a registry of completed controlled clinical trials that have not been published in an indexed journal. Fourth, there was a lack of geographic and ethnic variability, which makes it difficult to generalize the results to other populations. Fifth, although FSD was assessed with the FSFI, the study by Bernorio et al. did not report the effect of visnadine on the FSFI domains, limiting the understanding of the effect of visnadine. Finally, adherence to the intervention was reported in more than two-thirds of the participants in the included studies. Therefore, the influence of adherence on study outcomes could not be adequately assessed. Based on the aforementioned points, we acknowledge that no conclusion can be drawn about the appropriate therapeutic scheme, dosage, and routes of administration of visnadine for the management of symptoms of FSD.

Despite the above limitations, one of the strengths of this systematic review is the exhaustive bibliographic search that was performed without language limitations and the inclusion of RCTs conducted in the female population with the preconceived exclusion of women with organic pathology. Furthermore, to the best of our knowledge, ours is the first synthesis study with this research question.

Contribution to the literature, clinical relevance, and recommendations for future studies

The need for the effective and safe management of FSD has increasingly been recognized in the clinical setting. In this context, natural product-based therapies are emerging as important potential alternatives [35]. Due to the demand to develop a targeted treatment for FSD in the population of pre- and postmenopausal women, there is a need for research that can generate clear evidence regarding the efficacy and safety of the evaluated products [36]. Our review, addressed visnadine as a potential treatment of FSD, with the evaluation of its efficacy, based on the improvement of clinical symptoms of FSD as assessed with the FSFI, as well as safety through tolerability and low risk of adverse events. Despite the limitations of the available studies, results demonstrated that visnadine is safe and FSFI scores improved, especially with the daily use.

Our systematic review can serve as a basis for the design of new studies and promote the use of visnadine in the comprehensive clinical management of FSD. According to the consolidated clinical data derived from the two available clinical trials, visnadine could be an effective therapeutic option with promising evidence related to its safety and positive effects for the improvement of clinical symptoms related to FSD. However, new evidence is required from controlled clinical or real-world larger sample-sized and longer follow-up studies that assess the therapeutic potential of visnadine and the inclusion of different population groups.

Conclusion

Available clinical trials on the use of visnadine for the treatment of FSD symptoms are scarce and methodologically limited. This preliminary evidence demonstrates that visnadine is a potentially effective and safe option for the treatment of FSD of heterosexual women.

Acknowledgment

None.

Authors' contribution

BCC: investigation, data curation and visualization, drafting, review, editing, and approval of the final version. DFG: investigation, data curation and visualization, drafting, review, editing, and approval of the final version. HGP: investigation, data curation and visualization, drafting, review, editing, and approval of the final version. VABZ: methodology, project management and supervision; drafting, review, editing, and approval of the final version. FRPL: methodology, drafting, review, editing, and approval of the final version. JEB: methodology, drafting, review, editing, and approval of the final version. EMH: idea conceptualization, investigation, methodology, project management, writing, revision, editing, and approval of the final version.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

None.

ORCID

Faustino R. Pérez-López http://orcid.org/0000-0002-2801-416X
Edward Mezones-Holguín http://orcid.org/0000-0001-7168-8613

Data availability statement

Not applicable as this was a systematic review and meta-analysis of publications found in the literature.

References

[1] Kingsberg SA, Althof S, Simon JA, et al. Female sexual dysfunction-medical and psychological treatments, committee 14. J Sex Med. 2017;14(12):1–10. doi: 10.1016/j.jsxm.2017.05.018.
[2] Weinberger JM, Houman J, Caron AT, et al. Female sexual dysfunction: a systematic review of outcomes across various treatment modalities. Sex Med Rev. 2019;7(2):223–250. doi: 10.1016/j.sxmr.2017.12.004.
[3] Salonia A, Giraldi A, Chivers ML, et al. Physiology of women's sexual function: basic knowledge and new findings. J Sex Med. 2010;7(8):2637–2660. doi: 10.1111/j.1743-6109.2010.01810.x.
[4] Nappi RE, Cucinella L, Martella S, et al. Female sexual dysfunction (FSD): prevalence and impact on quality of life (QoL). Maturitas. 2016;94:87–91. doi: 10.1016/j.maturitas.2016.09.013.
[5] McCabe MP, Sharlip ID, Lewis R, et al. Incidence and prevalence of sexual dysfunction in women and men: a consensus statement from the fourth international consultation on sexual medicine 2015. J Sex Med. 2016;13(2):144–152. doi: 10.1016/j.jsxm.2015.12.034.
[6] Molkara T, Motavasselian M, Akhlaghi F, et al. The effects of herbal medicines on women sexual dysfunction: a systematic review. Curr Drug Discov Technol. 2021;18(6):e130921186972–16. doi: 10.2174/1570163817666201019130139.
[7] Stein A, Sauder SK, Reale J. The role of physical therapy in sexual health in men and women: evaluation and treatment. Sex Med Rev. 2019;7(1):46–56. doi: 10.1016/j.sxmr.2018.09.003.
[8] Jurado AR, Jouda-Benazouz M, Mendoza-Huertas L, et al. The use of natural products for the treatment of female sexual dysfunction: a systematic review of randomized clinical trials. ASM. 2020;10(02):56–69. doi: 10.4236/asm.2020.102004.
[9] Santos Silva IM, Paula Pinto M, Gonçalves D. Educational programs and sexual counselling for postmenopausal sexual dysfunction: a systematic review and meta-analysis. J Sex Med. 2022;19(1):54–63. doi: 10.1016/j.jsxm.2021.09.017.
[10] Caruso S, Di Pasqua S. Update on pharmacological management of female sexual dysfunctions. Sexologies. 2019;28(2):e1–e5. doi: 10.1016/j.sexol.2019.02.002.
[11] Weinberger JM, Houman J, Caron AT, et al. Female sexual dysfunction and the placebo effect. Obstet Gynecol. 2018;132(2):453–458. doi: 10.1097/AOG.0000000000002733.
[12] Khalil N, Bishr M, Desouky S, et al. *Ammi visnaga* L., a potential medicinal plant: a review. Molecules. 2020;25(2):301. doi: 10.3390/molecules25020301.
[13] Ahmed S, Fahim J, Abdelmohsen U. Chemical and biological potential of ammi visnaga (L.) lam. and apium graveolens L.: a review (1963-2020). J Adv Biomed Pharma Sci. 2021;4(3):160–176.
[14] Rauwald H, Brehm O, Odenthal KP. The involvement of a Ca 2+ channel blocking mode of action in the pharmacology of ammi visnaga fruits 1. Planta Med. 1994;60(2):101–105. doi: 10.1055/s-2006-959426.
[15] Venugopala KN, Rashmi V, Odhav B. Review on natural coumarin lead compounds for their pharmacological activity. Biomed Res Int. 2013;2013:963248–963214. doi: 10.1155/2013/963248.
[16] Duarte J, Pérez-Vizcaíno F, Torres AI, et al. Vasodilator effects of visnagin in isolated rat vascular smooth muscle. Eur J Pharmacol. 1995;286(2):115–122. doi: 10.1016/0014-2999(95)00418-k.
[17] Bernorio R, Piloni S, Mori G, et al. Efficacy and tolerability of a spray formulation containing visnadine in women self-reporting sexual symptoms: a randomized double-blind placebo-controlled pilot study. J Endocrinol Invest. 2018;41(6):729–737. doi: 10.1007/s40618-017-0801-0.
[18] Caputo A, Natoli A, Radice R, et al. Efficacy of an intimate oil solution containing visnadine in women self-reporting sexual symptoms. Minerva Gynecol. 2018;70(4):490–492.
[19] Caruso S, Mauro D, Cariola M, et al. Randomized crossover study investigating daily versus on-demand vulvar visnadine spray in women affected by female sexual arousal disorder. Gynecol Endocrinol. 2018;34(2):110–114. doi: 10.1080/09513590.2017.1354366.
[20] Sparavigna A, Caputo A, Natoli A, et al. A randomized single-blind placebo-controlled study of a visnadine emulgel formulation on healthy postmenopausal women. Minerva Ginecol. 2019;71(5):353–358. doi: 10.23736/S0026-4784.19.04398-3.
[21] Laganà AS, Basile F, Stojanovska L, et al. Effects of a new vaginal cream containing visnadine, prenylflavonoids and bovine colostrum on vaginal health index score and female sexual function index in post-menopausal sexually active women affected by vaginal dryness: a pilot study. Maturitas. 2017;100:123. doi: 10.1016/j.maturitas.2017.03.265.
[22] Laganà AS, Vitale SG, Stojanovska L, et al. Preliminary results of a single-arm pilot study to assess the safety and efficacy of visnadine, prenylflavonoids and bovine colostrum in postmenopausal sexually active women affected by vulvovaginal atrophy. Maturitas. 2018;109:78–80. doi: 10.1016/j.maturitas.2017.12.015.
[23] Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. Published online March doi: 10.1136/bmj.n71.
[24] Rosen R, Brown C, Heiman J, et al. The female sexual function index (FSFI): a multidimensional self-report instrument for the assessment of female sexual function. J Sex Marital Ther. 2000;26(2):191–208.
[25] Wiegel M, Meston C, Rosen R. The female sexual function index (FSFI): cross-validation and development of clinical cutoff scores. J Sex Marital Ther. 2005;31(1):1–20. doi: 10.1080/00926230590475206.
[26] Isidori AM, Pozza C, Esposito K, et al. Development and validation of a 6-item version of the female sexual function index (FSFI) as a diagnostic tool for female sexual dysfunction. J Sex Med. 2010;7(3):1139–1146. doi: 10.1111/j.1743-6109.2009.01635.x.
[27] Chedraui P, Pérez-López FR, Sánchez H, et al. Assessment of sexual function of mid-aged ecuadorian women with the 6-item female sexual function index. Maturitas. 2012;71(4):407–412. doi: 10.1016/j.maturitas.2012.01.013.
[28] Pérez-López FR, Fernández-Alonso AM, Trabalón-Pastor M, MenopAuse RIsk Assessment (MARIA) Research Group., et al. Assessment of sexual function and related factors in mid-aged sexually active spanish women with the six-item female sex function index. Menopause. 2012;19(11):1224–1230. doi: 10.1097/gme.0b013e3182546242.
[29] Cumpston M, Li T, Page MJ, et al. Updated guidance for trusted systematic reviews: a new edition of the cochrane handbook for systematic reviews of interventions. Cochrane Database Syst Rev. 2019;10(10):ED000142.
[30] Chaikittisilpa S, Orprayoon N. Effects of visnadine, ethyl ximeninate, Coleus Barbatus and Millet in Emulgel on Sexual Function in Postmenopausal Women (NCT04579991). Available athttps://classic.clinicaltrials.gov/ct2/show/NCT04579991?term=NCT04579991&draw=2&rank=1.
[31] Caputo A, Sparavigna A, Natoli A, et al. An open trial of a visnadine emulgel topical application in postmenopausal superficial dyspareunia: daily vs. on-demand use. Minerva Ginecol. 2020;72(1):59–60. doi: 10.23736/S0026-4784.19.04402-2.
[32] Campos-Toimil M, Orallo F, Santana L, et al. Synthesis and vasorelaxant activity of new coumarin and furocoumarin derivatives. Bioorg Med Chem Lett. 2002;12(5):783–786. doi: 10.1016/s0960-894x(02)00015-x.
[33] Duarte J, Lugnier C, Torres AI, et al. Effects of visnagin on cyclic nucleotide phosphodiesterases and their role in its inhibitory effects on

vascular smooth muscle contraction. Gen Pharmacol. 1999;32(1):71–74. doi: 10.1016/s0306-3623(98)00083-4.

[34] Aquino J, Parente J, Moreira J, et al. PNM-12 double-blind randomized study on the effect of Non-Hormonal gel application to the genital area of women in the menacme with sexual dysfunction. J Sex Med. 2017;14(Supplement_6):e386–e386. doi: 10.1016/j.jsxm.2017.10.059.

[35] Nappi RE. Why are there no FDA-approved treatments for female sexual dysfunction? Expert Opin Pharmacother. 2015;16(12):1735–1738. doi: 10.1517/14656566.2015.1064393.

[36] Miara MD, Bendif H, Rebbas K, et al. Medicinal plants and their traditional uses in the highland region of Bordj Bou Arreridj (northeast Algeria). J Herbal Med. 2019;16:100262. doi: 10.1016/j.hermed.2019.100262.