v. 4, n. 47, 2024

International Journal of Health Science

USE OF VENLAFAXINE IN THE TREATMENT OF VASOMOTOR SYMPTOMS IN WOMEN IN MENOPAUSE: SYSTEMATIC REVIEW AND META-ANALYSIS

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Abstract: During menopause, hormonal levels, especially estrogen and progesterone, gradually decrease, which can trigger a series of physical and emotional symptoms. Some of the most common symptoms of menopause include hot flashes, night sweats, mood changes, difficulty sleeping, vaginal dryness, decreased libido, weight gain, and changes in skin and hair. Not all women experience all of these symptoms, and their severity can range from mild to severe. A low-dose antidepressant for managing hot flashes may be helpful for women who cannot take estrogen for health reasons or for women who need an antidepressant for a mood disorder. This is a systematic review study that was designed based on the criteria established in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guide, considering the flow diagram and the PRISMA checklist. The use of oral estradiol in low doses and venlafaxine show good results in relieving vasomotor symptoms in middle-aged women, which included 546 peri- and post-menopausal female patients, divided into two groups, where one of the groups received escitalopram 10 -20 mg/day and another group is administered venlafaxine XR 75 mg/day compared with cognitive behavioral therapy for insomnia. It is clear that the intervention supports current recommendations for CBT-I as first-line treatment for healthy middle-aged women with insomnia symptoms and moderately bothersome VMS. This review confirms that there is a benefit to venlafaxine in the treatment of patients who have vasomotor symptoms, even if they are not significant. However, venlafaxine has shown excellent results associated with low-dose oral 17-beta estradiol for symptoms of hot flashes and mood disorders in perimenopausal and postmenopausal women.
Keywords: Venlafaxine; Menopause; Antidepressant.

INTRODUCTION

Menopause is a natural phase in a woman's life that marks the end of menstruation and reproductive capacity. It usually occurs around the age of 45-55, but can vary from woman to woman. During menopause, hormone levels, especially estrogen and progesterone, gradually decrease, which can trigger a range of physical and emotional symptoms. Some of the most common symptoms of menopause include hot flashes (hot flashes), night sweats, mood changes, difficulty sleeping, vaginal dryness, decreased libido, weight gain, and changes in skin and hair. Not all women experience all of these symptoms, and their severity can range from mild to severe. (REED et al., 2014; ZHOU et al., 2021).

Certain antidepressants related to the class of medications called selective serotonin and norepinephrine reuptake inhibitors may decrease hot flashes in menopause. A low-dose antidepressant for managing hot flashes may be useful for women who cannot take estrogen for health reasons or for women who need an antidepressant for a mood disorder (BORGES et al., 2022; MITCHELL et al., 2018).

According to the Brazilian Institute of Geography and Statistics (IBGE). Estimates based on census data also indicate that 29 million Brazilian women may be in menopause and the number of people aged 65 or over grew by 57.4% in 12 years, according to the latest Census by the Brazil Institute. In addition to physical symptoms, menopause can also have a significant emotional impact. Many women experience feelings of sadness, anxiety or irritability during this transition phase, directly impacting their quality of life.

Recently, research on women's health in the general population has come to the fore. However, this review aims to highlight this process, as it supports the development of more effective actions and treatments aimed at communities. In this context, the objective of this study was to compile the literature on the impact of treating vasomotor symptoms with the use of venlafaxine, to elucidate risk factors and possible interventions.

METHODOLOGY

This is a systematic review study that was designed based on the criteria established in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guide, considering the flow diagram and the PRISMA checklist. Thus, based on the guiding question: "Does venlafaxine have a better therapeutic effect compared to hormonal therapy and placebo in women with vasomotor symptoms of menopause?" The articles were searched.

Keywords were defined according to the PICOS model as follows:

1. Population: Menopausal women with vasomotor symptoms;
2. Intervention: use of venlafaxine;
3. Comparative: control (placebo or hormonal therapy);
4. Results (variables): improvement in the clinical picture of vasomotor symptoms;
5. Study design: clinical trial studies.

LITERATURE SEARCH

The search for articles was carried out in the following databases: Medline/VHL and Medline/Pubmed. The following descriptors and their combinations in Portuguese and English were used to search for articles: "Menopause AND Vasomotor Symptoms AND Venlafaxine // Menopause AND Vasomotor symptoms AND Venlafaxine".

INCLUSION AND EXCLUSION CRITERIA

The selection of articles was guided by inclusion and exclusion criteria. The inclusion criteria defined for the selection of articles were: articles published in Portuguese,

English; original articles in full that portray the theme related to the review and articles published and indexed in the aforementioned databases in the last 10 years.

The exclusion criteria defined for the selection of articles were non-original articles, dissertations and theses, articles that addressed the topic, but from a different point of view.

IDENTIFICATION AND SELECTION OF STUDIES

After applying the inclusion and exclusion criteria, the articles were identified. The screening of studies was carried out by reading and analyzing the titles and abstracts of all articles identified in each database, guided by the inclusion and exclusion criteria adopted. In the eligibility phase, after defining the articles to be included in each database, duplicate articles were excluded.

DATA EXTRACTION

Two independent researchers used custom spreadsheets to extract data from all included studies. After data extraction, data conferences, if discrepancies arise, use a third-party investigator.

The data extracted from the article are: (1) Study design; (2) Number Initial participants who participated in the study; (3) Number and characteristics of participants completing the intervention; (4) Results.

STATISTICAL ANALYSIS

Briefly, outcome measures were calculated by sample difference, means and standard deviation. All analyzes were performed using the BioEstat software. Lastly, we define a significance level of P less than 0.05 as statistical significance.

RESULTS

STUDY SELECTION

A total of 103 studies were identified according to our search strategy. Among them, he presented a duplicate. After applying the adopted inclusion and exclusion criteria, 53 studies were excluded from Medline/ VHL reading and 50 studies from Medline/ Pubmed, resulting in a total of 103 articles. Titles and abstracts were then read, 85 of the 103 references were excluded based on the eligibility criteria. Thus, 18 references were selected for full text evaluation. Finally, four articles were eligible for qualitative evaluation. The selection process for identifying eligible studies included in the meta-analysis, shown in Figure 1.

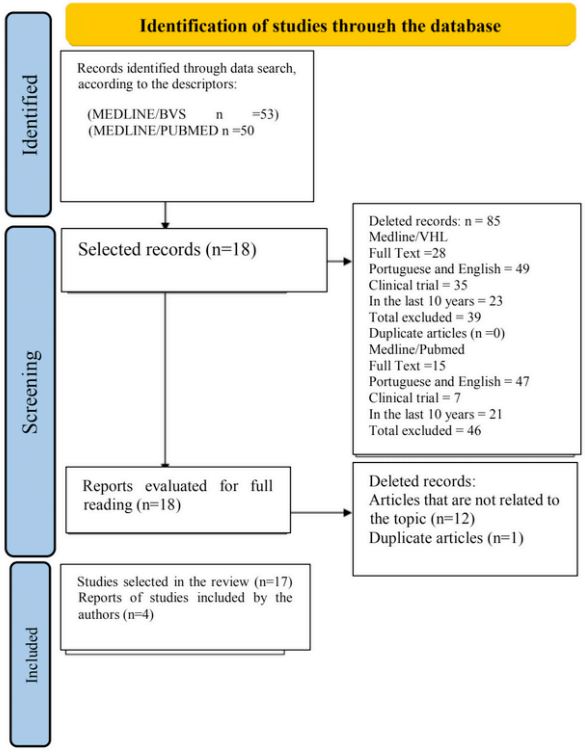

Figure 1: Flowchart for selection, identification, screening, eligibility and inclusion process.

The main characteristics of the included studies are described below. In the study

by Joffe et al.[1] (2014), which involved 2,339 postmenopausal and postmenopausal women patients, the mean and standard deviation of vasomotor symptoms (VMS): 8.1 (5.3), dividing them into three groups based on randomization to be treated with oral 17-beta-estradiol 0.5 mg/day, venlafaxine XR 75 mg/day and placebo.

The use of low-dose oral estradiol and venlafaxine has good results in relieving vasomotor symptoms in middle-aged women. Even though low-dose estradiol appears to have slightly superior efficacy compared to venlafaxine, the difference is minimal and its clinical relevance is uncertain.

It is also worth considering, according to the trial by Guthrier et al.[2] (2015), which involved 899 perimenopausal and postmenopausal women patients, divided between three treatment groups, in which the first received escitalopram 10-20 mg in the second non-aerobic yoga, aerobic exercises, 1.8 g per day of omega-3 fatty acid supplementation, 0.5 mg of low-dose oral 17-beta-estradiol (E2) per day and finally the last group in the which venlafaxine 75 mg/day was administered. Thus, escitalopram, low dose E2 and venlafaxine modestly and comparatively reduce the frequency of vasomotor symptoms and distress in women with moderate hot flashes.

In addition, according to Caan et al.[3] (2015), 339 symptomatic people were selected for the study aged between 40 and 62 years in the women's transition from menopause or post menopause, which mentioned vasomotor symptoms such as hot flashes and night sweats. The therapeutic proposal for the intervention group was hormonal therapy consisting of venlafaxine 75 mg/day, compared with oral 17-beta-estradiol (EA) 0.5 mg/day compared to the group that was managed with placebo for 8 weeks. It is clear that low doses of E2 and venlafaxine are effective agents to improve menopause-related quality of life in healthy women with SVM.

Finally, according to Guthrie et al.[4] (2018), which included 546 peri- and post-menopausal female patients, divided into two groups where one of the groups received escitalopram 10-20 mg/day and the other group was administered venlafaxine XR 75 mg/day compared with cognitive behavioral therapy for insomnia (CBT-I). It is clear that the intervention supports current recommendations for CBT-I as first-line treatment for healthy middle-aged women with insomnia symptoms and moderately bothersome VMS.

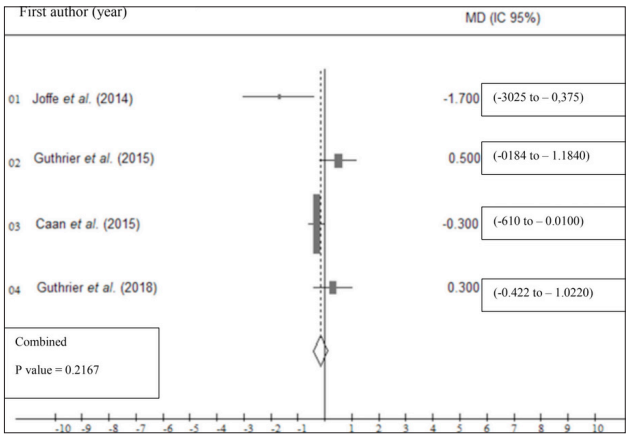

Figure 2: Forest plot treatment relationship of venlafaxine group compared with control group in perimenopausal and postmenopausal patients.

Use of venlafaxine for vasomotor symptoms compared with placebo or hormonal therapies has no association. It is evident that only study [(1)] had a difference between the pre- and post-intervention means, however, it was significant, represented by the mean differences (MD) and confidence interval (-3.025 to -0.375), not passing through the null line. However, the interventions adopted by the authors, in the studies [(2-4)], did not have the desired result, not showing a reduction in vasomotor symptoms with the use of the medication in 8 weeks, with a statistical difference between the means with p-value =

0.2167 > significance level 0.05 (Figure 2). The combinations of results, represented by the diamond, are 95% CI = -0.421 to 0.094 and mean differences (MD w) = -0.163.

DISCUSSION

This study aims to analyze through a meta-analysis continuous fixed effects data that can highlight the most relevant aspects for the proposed topic. Therefore, from the beginning, it was important to repeatedly show that the group receiving venlafaxine had a positive response to the vasomotor symptoms mentioned by the patients. The results of several authors [1-4] showed an association with reduced symptoms of sudden hot flashes in the head, neck and chest, but only in the Joffe study (2014) was it significant. (STEIN et al., 2014)

Regarding venlafaxine against vasomotor symptoms, it can be seen that the studies provide a comprehensive view of different therapeutic approaches associated with a hormone to alleviate vasomotor symptoms (VMS) in perimenopausal and postmenopausal women, highlighting treatment with intervention of oral 17-beta-estradiol (EA) 0.5 mg/day of VMS in the study by Caan (2015), Guthrier (2015) and Joffe (2014). However, these studies revealed relief of vasomotor symptoms, prevention of osteoporosis and osteoporotic fractures, improved sleep and fatigue, mood, ability to concentrate, vaginal dryness, quality of life with this therapy.

Overall, the results of this study provide strong evidence for the efficacy of low-dose oral 17-beta estradiol and venlafaxine in the treatment of menopause-associated VMS (CAAN et al., 2015; REED et al., 2014; ZHOU et al., 2021). Low doses of oral estradiol and venlafaxine are effective and well-tolerated treatments for perimenopausal and postmenopausal women with bothersome vasomotor symptoms. Treatment decisions must consider the risk profile of each medication for each woman and take into consideration, her risk factor status and personal preferences for treatment options. (BARTON et al., 2017; GUTHRIE et al., 2018)

CONCLUSION

This review confirms that there is a benefit to venlafaxine in the treatment of patients who have vasomotor symptoms, even if they are not significant. However, venlafaxine has shown excellent results associated with low-dose oral 17-beta estradiol for symptoms of hot flashes and mood disorders in perimenopausal and postmenopausal women. Therefore, it is necessary to more closely investigate the risk factors associated with this class of drugs to obtain a possible effective intervention.

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