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Review Article

Antidepressants & Antiepileptics: An Attractive Alternative for Hot Flushes

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Abstract

Two of the most common complaints about menopause are hot flashes and night sweats. Although menopause hormone therapy (MHT) is considered the gold standard treatment for hot flashes, many women request non-hormonal treatments either because hormonal treatment is contraindicated or due to the patient's refusal to use it. Serotonin-norepinephrine reuptake inhibitors (SNRIs), selective serotonin reuptake inhibitors (SSRIs), pregabalin and gabapentin seem to be an attractive alternative for women to ameliorate the frequency and severity of menopausal vasomotor symptoms (VMS).

Keywords: Hot Flashes; Night Sweats; Nonhormonal Treatment; Antidepressants; Antiepileptics

Introduction

The North American Menopause Society (NAMS) describes hot flashes as a spontaneous sensation of warmth affecting the face, neck and upper chest, and are often associated with palpitation and sweating followed by chills [1]. During perimenopause and post menopause, 40 to 80% of women respectively suffer VMS and report symptoms as being of moderate to severe intensity [2]. Sleep disturbances, irritability, difficulty concentrating and diminished quality of life (QOL) are associated with VMS [3]. Its duration and frequency vary from one woman to another and can often be prolonged for many years. Although the exact pathophysiology is unknown, it is important to understand the underlying physiological changes caused by estrogen deficiency. It has been suggested that estrogen withdrawal affects the neuroendocrine system, resulting in changes in the hypothalamus control of the temperature [4]. This process is regulated by multiple neurotransmitters. Fluctuations in serotonin and norepinephrine levels are responsible for lowering the thermoregulatory set point, triggering the heat loss [5]. Menopause hormone therapy remains the most effective treatment for climacteric symptoms but the interest in alternative pharmaceutical therapies was increased. History of breast cancer, endometrial cancer and thromboembolism, bad response to THM or negative of the patient to use it, are examples why these alternative therapies are necessary. Several non-estrogen options have been evaluated, these include the anticonvulsant gabapentin and pregabalin, selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs).

Summary of The Evidence

Antidepressants

SSRIs and SNRIs are groups of drugs that have been widely studied for the treatment of VMS. It seems to be a class effect; they are all helpful in low dosage. It has been proposed that their mechanism of action is to enhance serotonergic neurotransmission by its selective inhibition of serotonin reuptake, as well as its concentration at the hypothalamic level, through the activation of the 5HT2 receptor. Their benefit on VMS appears independently of their antidepressant effect and much earlier than with other therapies. They have proved to reduce hot flashes with a variability between 25-69% [6]. Although patients inform some side effects, such as headaches, nausea, dry mouth and loss of appetite among other, are a well-tolerated alternative [7]. These events occur less frequently at low doses, which are the recommended dose for manage hot flashes, resulting SSRIs and SNRIs an excellent alternative [8]. Paroxetine, sertraline, citalopram, escitalopram and

fluoxetine are antidepressants belonging to the SSRI class of drugs. The International Menopause Society (IMS) does not recommend the use of fluoxetine or sertraline due to the fact that no significant reduction in vasomotor symptoms was found in placebo-controlled studies [9]. Paroxetine was initially studied in breast cancer survivors for relief of hot flashes. Stearns et al. conducted a randomized, controlled, crossover study to assess the effectiveness of paroxetine 10 and 20 mg/day versus placebo in 151 menopausal women. Eighty percent of participants were breast cancer survivors. Both the 10 and 20mg doses significantly decreased the frequency of hot flashes compared with placebo. Adverse effects occurring more frequently with paroxetine for hot flashes than with placebo included headache, nausea, somnolence, insomnia, and dry mouth [10]. Paroxetine is a potent CYP2D6 inhibitor, which interferes with the transformation of tamoxifen into its active metabolite, 4-hydroxy-desmethyl-tamoxifen (endoxifen) [11]. The American Clinical Oncology Society recommends avoiding the use of antidepressants classified as strong inhibitors, like paroxetine, sertraline and fluoxetine, considering venlafaxine and escitalopram as the best option for the treatment of vasomotor symptoms in these patients [12,13]. In the year 2013, the FDA approved the use of paroxetine at 7.5mg doses as the first nonhormonal treatment for hot flashes. The efficacy of paroxetine was established in two randomized, double-blind, placebo-controlled, multicenter clinical trials. Among a total of 1184 menopausal women who had a median of 10 moderate-to-severe hot flushes per day, paroxetine 7.5mg was shown to provide significant relief in comparison to placebo [14]. Escitalopram at increasing doses has shown a 55% reduction in hot flashes in menopausal and perimenopausal women, with 4% of side effects and a 70% satisfaction rate [15]. Our experience in the Climacteric Section of the Hospital Italiano de Buenos Aires with the use of escitalopram at 5mg and 10mg doses in patients with at least 28 moderate and severe hot flashes weekly, a history of breast cancer, or with a contraindication for MHT, was similar or even superior to the percentages of most published studies. Our results have showed a 60% reduction by week 1, which is progressively maintained after one year of use, with good compliance and few side effects. Venlafaxine and desvenlafaxine, are antidepressants belonging to SNRIs. Venlafaxine has been shown to be effective in decreasing hot flashes compared to placebo in several clinical trials, being the first of these antidepressant agents that demonstrated clinical efficacy [16]. Evans et al showed that an extended-release formulation of venlafaxine 75 mg daily is superior than placebo, decreasing hot flashes by 51% compared to 15% respectively [17].In a double-blind, placebo-controlled, randomized trial with venlafaxine, an SNRI, in increasing doses of 37.5, 75 and 150mg/day in patients with breast cancer who took tamoxifen, it was observed that, after four weeks, hot flashes scores had a rapid and significant 37% and 61% decrease, depending on dose[16]. There was no drug interaction in the metabolism of tamoxifen [18]. Our work group at the Climacteric Section of the Hospital Italiano has carried out an experience with 37.5mg of venlafaxine in 30 postmenopausal women with moderate to severe hot flashes, including breast cancer patients. The result was statistically significant, with a 66% reduction in hot flashes scores [19]. On the other hand, desvenlafaxine, the major active metabolite of venlafaxine, at 100mg doses has shown a rapid onset of action, efficacy and to be well tolerated, with a significant reduction of VMS of 64% [20].

Antiepileptics

The anticonvulsant gabapentin also used for neuropathic pain has been studied for hot flash management. A systematic review of 13 randomized controlled trials including 1714 women found that 900mg gabapentin per day, reduced the severity and frequency of vasomotor symptoms in breast cancer survivor [21]. Its mechanism of action involves a direct effect on the hypothalamic thermoregulatory center in the ventromedial hypothalamus [22]. It has no drug interactions and seems to be well tolerated. The recommended dose for the treatment of hot flashes is 900 mg/day. Side effects are dose related and may include somnolence, dizziness, and fatigue [22]. Pregabalin is a gamma-aminobutyric acid (GABA) analogue with the same indications as gabapentin. A randomized placebo-controlled study of 163 women compared 75mg twice daily or 150mg twice daily of pregabalin and placebo. After 6 weeks, hot flashes were reduced by 50%, 65%, and 71%, respectively [23]. As for adverse effects, insomnia, dizziness and weight gain were observed. Our Climacteric Section of the Hospital Italiano de Buenos Aires has carried out an experience to examine the efficacy of pregabalin supplementation on hot flashes in 11 postmenopausal women with at least 21 moderate and severe hot flashes weekly. Patients received an initial dose of pregabalin of 25mg/d increasing to 50mg after the first week. After 8 weeks of follow-up, 77.77% of women reported a decrease by 50% in the frequency of severe hot flashes and 55.55% of night sweats. According to our results, pregabalin could be a nonhormonal therapeutic option for climacteric symptoms. In the year 2015, the North American Menopause Society (NAMS) published their position statement on the nonhormonal management of vasomotor symptoms associated with menopause. The NAMS panel concluded that the recommended therapies for menopausal and postmenopausal hot flashes are paroxetine 7.5-10-25mg/day; escitalopram 10-20mg/ day; citalopram 10-20mg/day; desvenlafaxine 50-150mg/day; venlafaxine XR 37.5-150mg/day; gabapentin 900mg/day and pregabalin 150-300mg/day [24].

Conclusion

For many women, vasomotor symptoms can be severe and debilitating, and sometimes hormone therapy is not an option. It is mandatory that primary care doctors be aware of these alternatives to offer this patients safe and effective therapies to manage menopausal symptoms to improve their quality of life.

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